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Olle Ekberg *Editor*

Dysphagia

Diagnosis and Treatment

Second Edition

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Preface to the Second Edition

The goal of the second edition continues to be a single-volume presentation of deglutology with focus on the symptom dysphagia: its causes and management. The target readers are the large and growing healthcare professionals who deal with patients with swallowing problems.

The continued rapid advances in diagnostics have prompted extensive revision of many chapters as well as inclusion of new chapters. Of pivotal importance for the understanding of dysphagia is the clinical history, carefully obtained and used to triage the instrumental evaluation and specific treatments. The clinical history is crucial for understanding the result of the examinations. A new chapter on high-resolution manometry clarifies how it is performed and its potential as a problem solver. Abundant and diverse treatment options are now available. Each is described by world leading experts. As care of the dysphagic patient may be fraught with ethical and moral issues, a closing chapter on this theme has been added. Crucial for the compilation of new material for this second edition is the prosperous activities in the European Society for Swallowing Disorders (ESSD). A rapidly growing organization led by Professor Pere Clavé who with skills and enthusiasm is guiding and fostering us to become better deglutologists. To achieve this he has by his side Jane Lewis, executive officer of ESSD, who with grace and patience has developed our society. It has been a pleasure working together with the authors of this book. Please enjoy!

Malmö, Sweden — Olle Ekberg

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Part V: Complications

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Anatomy and Physiology

Olle Ekberg and Göran Nylander

Contents

Abstract

The oral cavity, pharynx, and esophagus constitute three anatomically and functionally integrated areas that are involved in swallowing. They are made up of muscular tubes surrounded by cartilages and bones. Swallowing is controlled by the brain stem in the central nervous system where the swallowing center is located.

1 Introduction

The swallowing apparatus is made up of three anatomically and functionally separated, but integrated, areas, namely, the oral cavity, the pharynx, and the esophagus. These are tubular structures with muscular walls, in certain areas containing bone and cartilage. Each compartment functions independently, but for a successful swallowing process a finely tuned coordination between the compartments is necessary. Each compartment acts as a hydrodynamic pump. Between these pumps are interconnected valves.

To interpret the findings of the radiological examination, detailed knowledge of anatomy and physiology in this area is mandatory. In this context it is also important to understand that the larynx, both anatomically and physiologically, is an integrated part of the pharynx during swallowing. The nomenclature used in this chapter corresponds to anglicized Latin commonly in use (Williams et al. 1989). The description below

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refers to the adult individual. Those interested in newborns and infants are referred to works by Bosma (1973, 1976).

2 Anatomy of the Pharynx and Larynx

2.1 Cartilages of the Larynx and Pharynx

Several of the important swallowing muscles insert on the inside of the mandible (Fig. 1). On the inside and medial surface of the mandible there is a centimeter-sized crest called the mylohyoid line, where the mylohyoid muscle inserts. Anteriorly in the midline on the posterior surface of the mandible there are a couple of eminences (mental spines) on which the geniohyoid and genioglossus muscles insert. These muscles then also insert within the tongue and on the hyoid bone, respectively. The hyoid bone is made up of a body and four horns, two on each side (Fig. 2). The upper two are called the lesser cornu of the hyoid bone, and the lower ones are called the greater cornu of the hyoid bone. From the lesser cornu there is a ligament that connects the cornu with the styloid process of the skull base. This ligament is called the stylohyoid ligament.

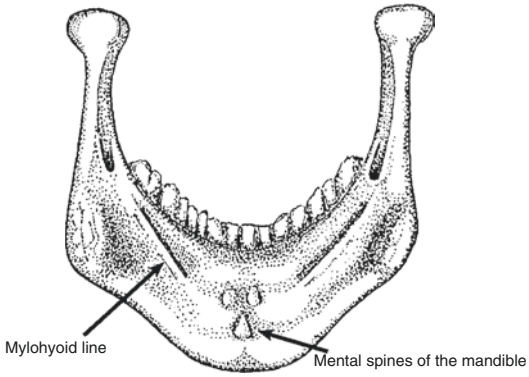

Fig. 1 The mandible seen posteriorly

The thyroid cartilage is made up of two quadrilateral laminae, their anterior borders fused inferiorly and with a convexity superiorly and anteriorly. It also has a notch in the midline and superiorly. Posteriorly the cartilage has four horns (cornu). Two of these have a superior direction (superior cornu of the thyroid cartilage) and two have an inferior direction (inferior cornu of the thyroid cartilage; Fig. 3).

The superior cornu is connected via the thyrohyoid ligament with the greater cornu of the hyoid bone. The inferior cornu articulates directly against the cricoid cartilage. The hyoid bone and the thyroid cartilage are connected not only with the median and lateral thyrohyoid ligaments but also by the thyrohyoid membrane (Fig. 4). There is a lateral opening in the thyrohyoid membrane through which the laryngeal artery, vein, and nerve pass. There is also a small cartilage in the posterior and lateral part of the thyrohyoid ligament. This is called the triticeal cartilage.

The cricoid cartilage has the shape of a signet ring and is made up of a thin anterior part called the arcus of the cricoid cartilage and a posterior thicker portion called the lamina of the cricoid cartilage (Fig. 5). On its lateral margin the cricoid cartilage has an articulate facet for the inferior

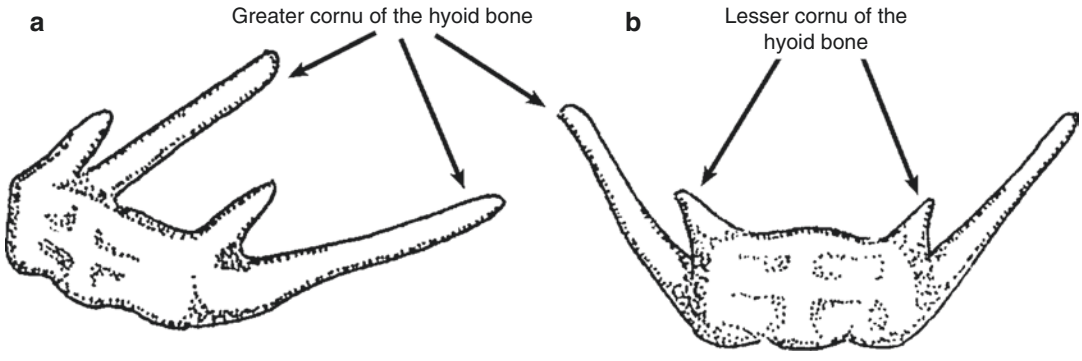

Fig. 2 The hyoid bone seen superiorly and from the *left* (**a**) and anteriorly (**b**)

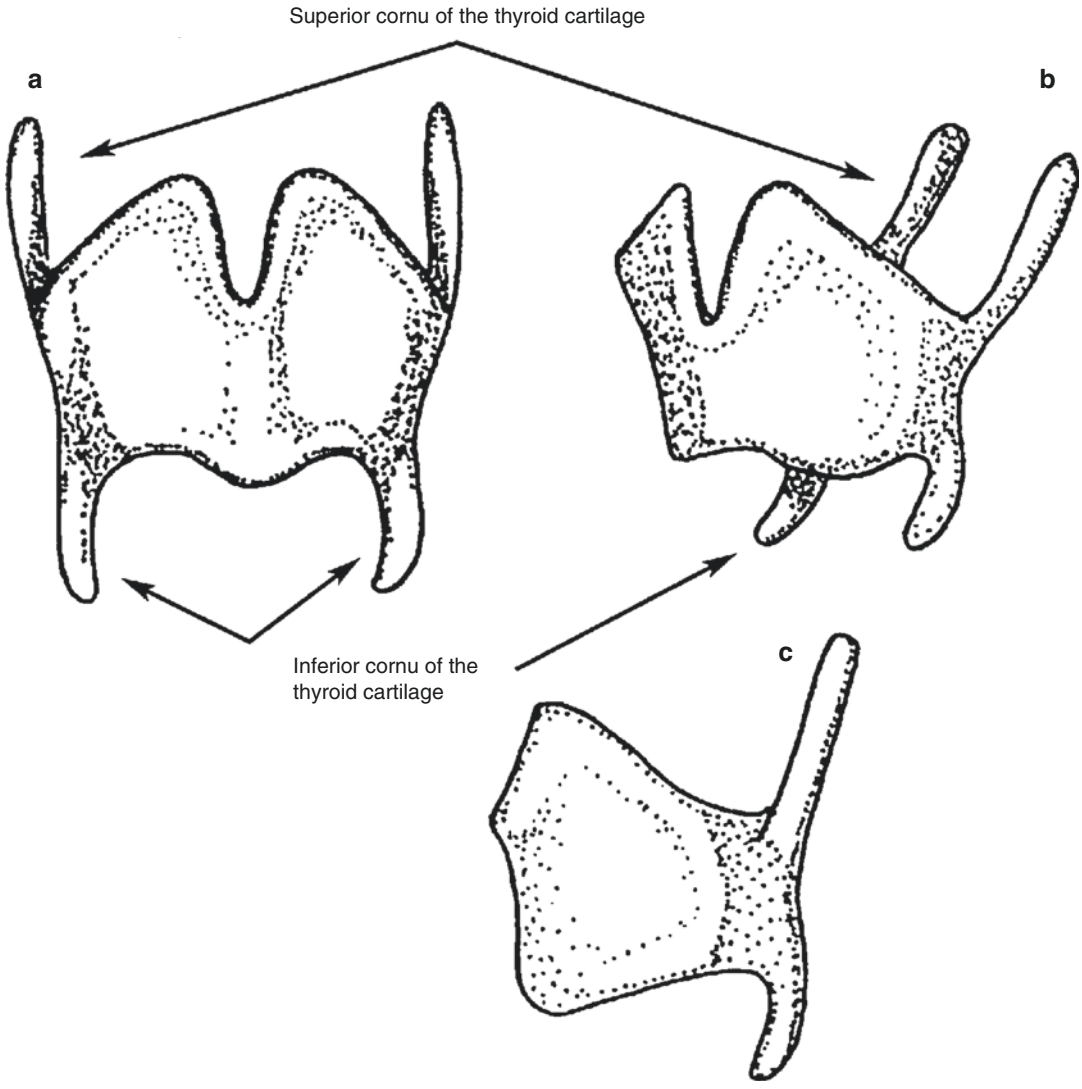

Fig. 3 The thyroid cartilage seen anteriorly (**a**), anteriorly and from the *left* (**b**), and from the *left* (**c**)

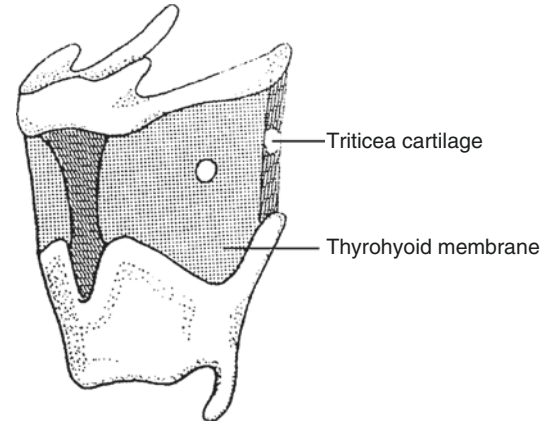

Fig. 4 Hyoid bone and thyroid cartilage seen anteriorly and from the *left*. *Light hatching* the thyrohyoid membrane, *dark hatching* the lateral and median thyrohyoid ligaments. There is a hole in the membrane for the passage of vessels and nerves

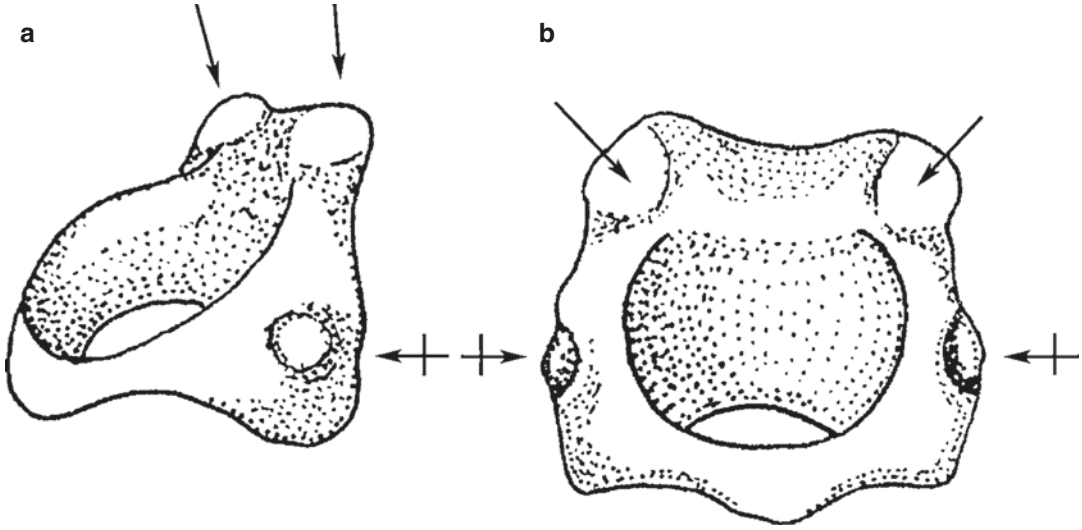

Fig. 5 The cricoid cartilage seen from the *left* (**a**) and anteriorly (**b**). There are two articulate surfaces for the arytenoid cartilages (*plain arrows*). There are also articulate surfaces for the cricoid cornu of the thyroid cartilage (*crossed arrows*)

cornu of the thyroid cartilages. The lamina continues superiorly and dorsally in an eminence that ends with an articulate facet. Against this surface the arytenoid cartilages articulate. Two inferior horns of the thyroid cartilage articulate as described above against the cricoid cartilage. The thyroid and cricoid cartilages are also connected via the cricothyroid ligament (Fig. 6). Inferiorly to the cricoid cartilage is the trachea.

The core of the epiglottis is made up of cartilage. This thin foliate lamella has the form of a racket with a plate and a shaft. The shaft (petiolus) has a ligament (thyroepiglottic ligament) that connects it to the posterior surface of the thyroid cartilage (Fink and Demarest 1978; Fig. 7a).

The anterior surface of the epiglottis has a fan-shaped ligament connecting it to the hyoid bone (Fig. 7b). This ligament is an extension of the median glossoepiglottic ligament.

The arytenoid cartilages are shaped like small pyramids and are located at the posterior and superior corners of the cricoid cartilage. On top of this pyramid is another small cartilage, namely, the corniculate cartilage (Fig. 8).

Thereby there is a wall of cartilages, ligaments, and membranes extending from the hyoid bone and inferiorly. It reaches all the way to the anterior surface of the trachea. In the following the relation of the musculature and mucous membrane to these stabilizing structures will be described.

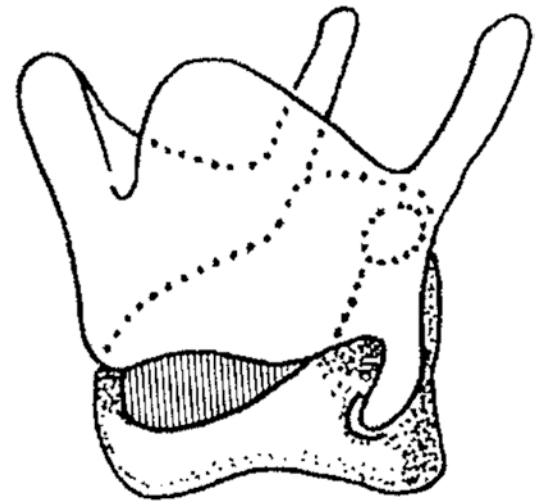

Fig. 6 The thyroid cartilage and cricoid cartilage with the cricothyroid ligament (*shaded*)

2.2 Muscles

The floor of the mouth is made up of several muscles, the positions of which are given in Figs. 9 and 10. The caudal extreme of the floor of the mouth is made up of the geniohyoid muscle and

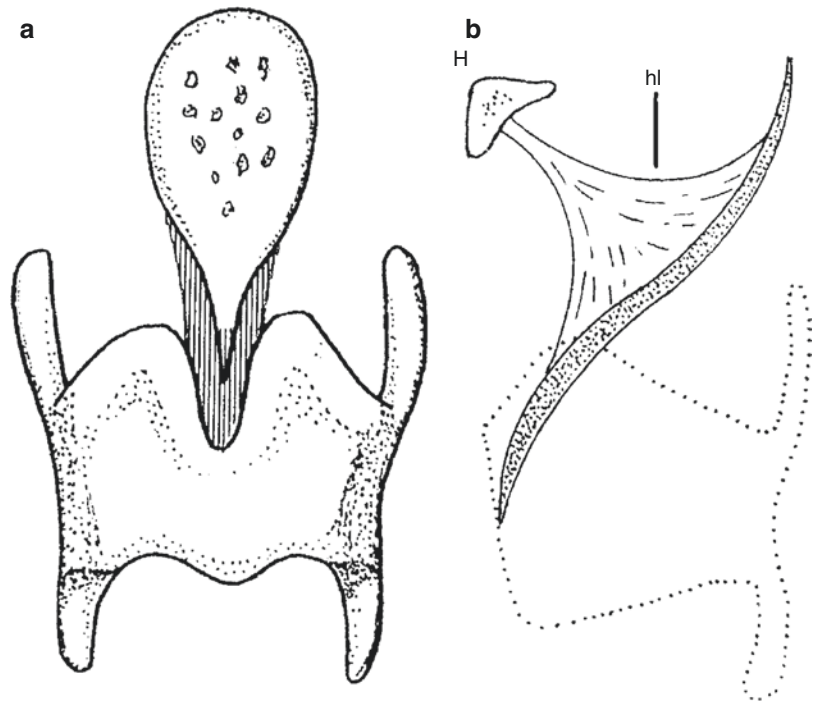

Fig. 7 (**a**) The thyroid cartilage and epiglottis (seen anteriorly) are connected with the thyroepiglottic ligament. (**b**) The hyoid bone (*H*) (seen from the *left*) is connected to the epiglottis via the hyoepiglottic ligament (*hl*)

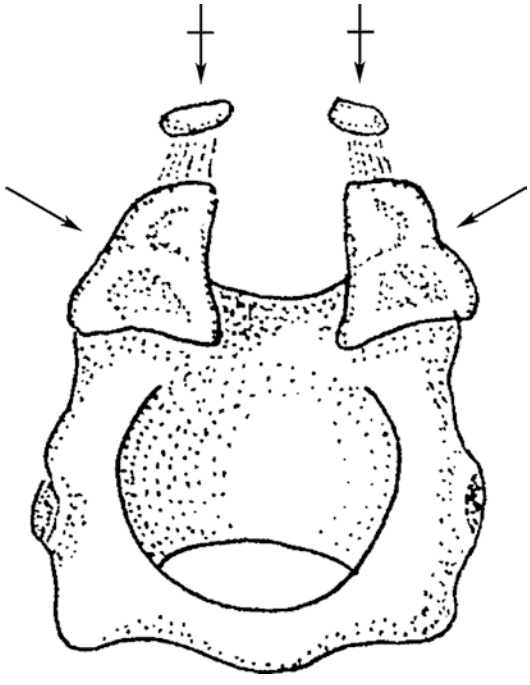

Fig. 8 Cricoid cartilage (seen anteriorly). The arytenoid cartilages (*plain arrows*) and corniculate cartilages (*crossed arrows*) are located on *top*

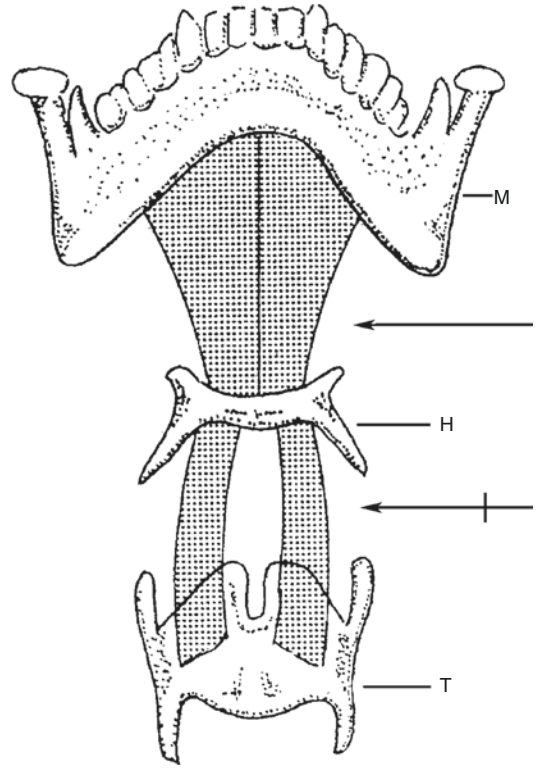

Fig. 9 The mandible (*M*), hyoid bone (*H*), and thyroid cartilage (*T*) seen anteriorly. The mylohyoid (*plain arrow*) and thyrohyoid (*crossed arrow*) muscles are indicated

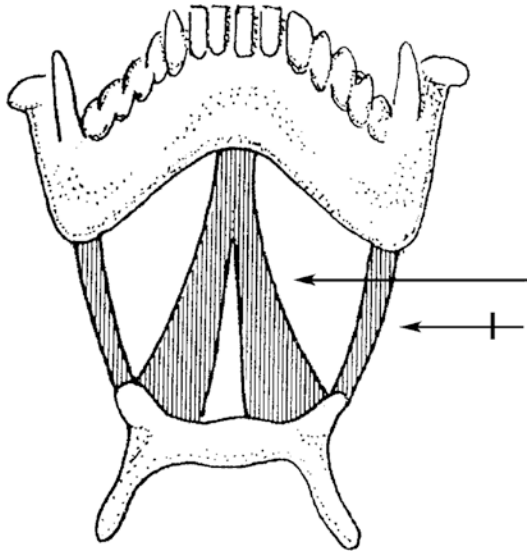

Fig. 10 The mandible and hyoid bone seen from below and anteriorly. The geniohyoid (*plain arrow*) and stylohyoid (*crossed arrow*) muscles are indicated

the mylohyoid muscle. The latter inserts on the mylohyoid line on the mandible. It extends to the hyoid bone, where it inserts (Fig. 9). It is made up of a broad muscular diaphragm that covers most of the floor of the mouth. Covering this muscle is the geniohyoid muscle extending from the mental spines in the midline of the mandible to the body of the hyoid bone. The stylohyoid muscles extend from the styloid process to the lesser cornu on both sides (Fig. 10). Inferiorly are the thyrohyoid muscle, the hyoid bone, and the thyroid cartilage (Fig. 9). Inferior to the hyoid bone are the sternohyoid muscles and the omohyoid muscles.

2.2.1 Muscles of the Tongue

The genioglossus muscle is the largest muscle of the tongue and it extends from the mental spines on the mandible. This fan-shaped muscle widens as it extends backwards into the tongue. The superior fibers run to the tip of the tongue, and the middle fibers run to the dorsum of the tongue and a few of the inferior fibers extend to the hyoid bone, where the muscle inserts on the body of the hyoid bone (Fig. 11a). The hyoglossus muscle extends from the body and greater cornu of the hyoid bone and extends from there superiorly into the lateral portions of the tongue (Fig. 11b). The styloglossus muscle extends from the styloid processes of the skull base and the stylomandibular ligaments. It then extends into the lateral part of the tongue all the way to the tip of the tongue (Fig. 11c).

These three muscles join within the tongue and the muscle bundles fuse (Fig. 11d).

There are also a couple of external tongue muscles that connect the tongue with the skull base, the mandible, and the hyoid bone. Other tongue muscles are separated from these structures and are located solely within the tongue. They can be divided into four muscles: (1) the longitudinal superficial muscle, (2) the longitudinal deep muscle, (3) the transverse lingual muscles, and (4) the vertical lingual muscles. A small portion of the transverse lingual muscles runs up into the soft palate, where it is called the glossopalatine muscle (Fig. 12). Another small portion of this muscle is called the glossopharyngeal muscle and extends into the pharyngeal wall musculature (Fig. 12). In this way the musculature of the tongue inserts on the skull base, mandible, hyoid bone, soft palate, and lateral pharyngeal wall.

2.2.2 Muscles of the Soft Palate

The soft palate has an important function during swallowing. It is made up of a fibrous aponeurosis on which a couple of swallowing muscles insert. The levator veli palatini muscle extends from the inferior and lateral surface of the temporal bone close to the foramen of the internal carotid artery as well as from the inferior aspect of the tubal cartilage (of the auditory tube). The muscle then extends inferiorly, medially, and anteriorly and inserts on the midportion of the aponeurosis of the soft palate (Fig. 13). The tensor veli palatini muscle extends from the skull base and from the pterygoid processes of the sphenoid bone and extends first inferiorly and then turns at a right angle medially over the hamulus of the pterygoid process to spread horizontally in the aponeurosis of the soft palate (Fig. 14).

The palatopharyngeal muscle is the most prominent muscle in the soft palate and constitutes the arch. It extends from the inferior body of the tubal cartilage, pterygoid processes, and aponeurosis of the soft palate. This is the posterior extreme of the soft palate. The muscle then extends further inferiorly and posteriorly and

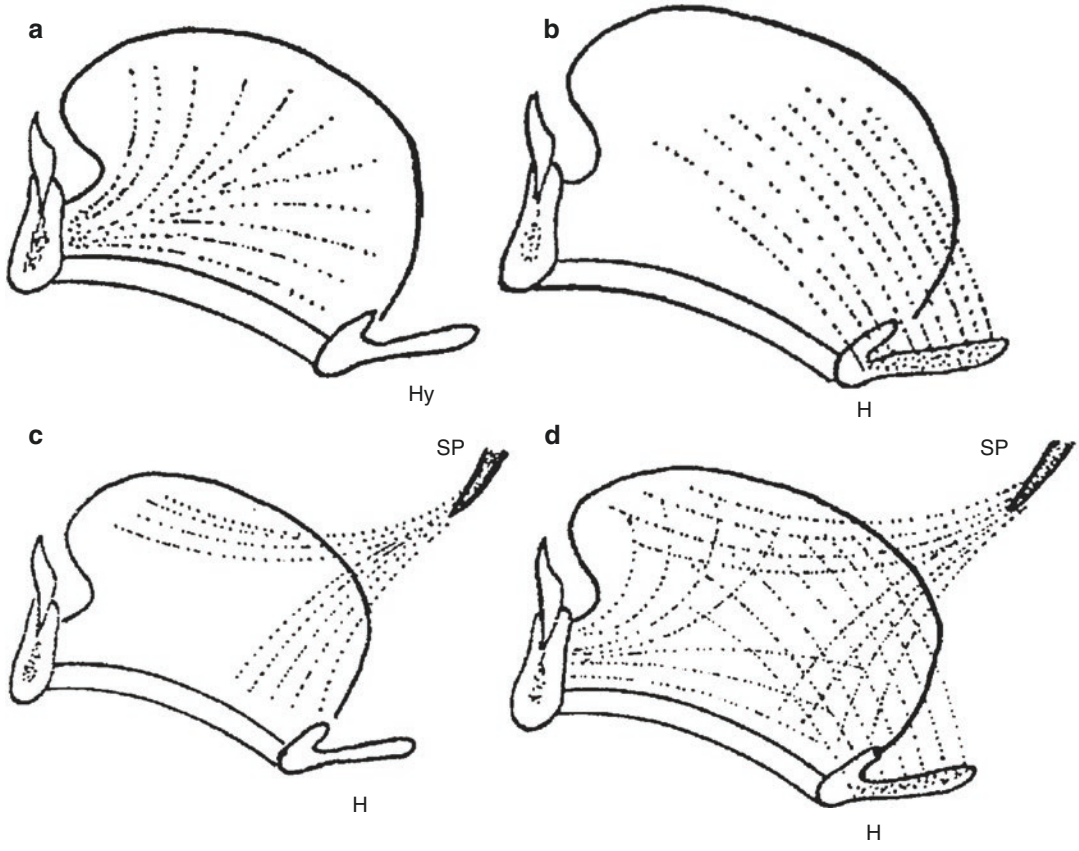

Fig. 11 The tongue musculature, hyoid bone (*H*), and styloid process (*SP*). (**a**) Genioglossus muscle, (**b**) hyoglossus muscle, (**c**) styloglossus muscle, (**d**) composite drawing of the three muscles shown in (**a**–**c**)

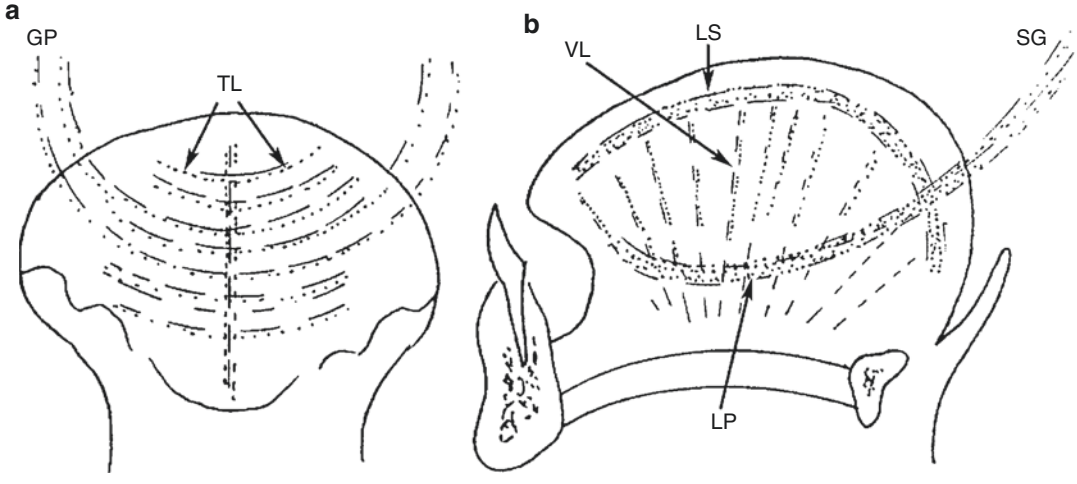

Fig. 12 Internal tongue musculature. The tongue seen (**a**) anteriorly and (**b**) from the *left*. *TL* transverse lingual muscles, *VL* vertical lingual muscles, *LS* longitudinal superficial muscle, *LP* longitudinal deep muscle, *GP* glossopharyngeal muscle, *SG* styloglossus muscle

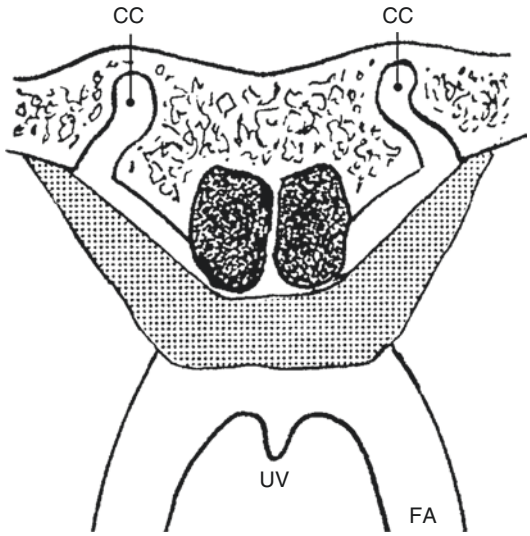

Fig. 13 Levator veli palatini muscle (*shaded*). The picture shows the skull base with choanae (*dark*) as well as the carotid canal (*CC*). The uvula (*UV*) and the faucial arcs (*FA*) are indicated

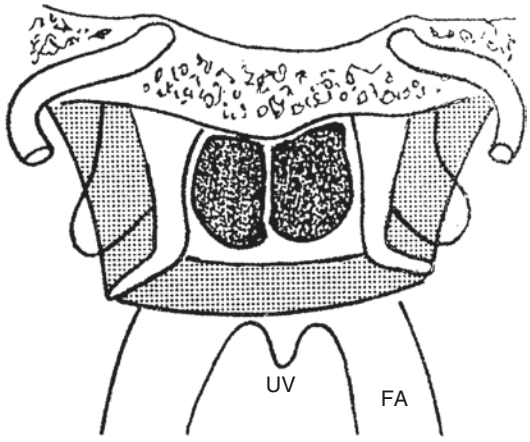

Fig. 14 Tensor veli palatini muscle (*shaded*). The picture shows the skull base with choanae (*dark*) as well as the carotid canal. The pterygoid process (*P*) and the hamulus of the pterygoid process (*H*) are indicated, as are the uvula (*UV*) and the faucial arcs (*FA*)

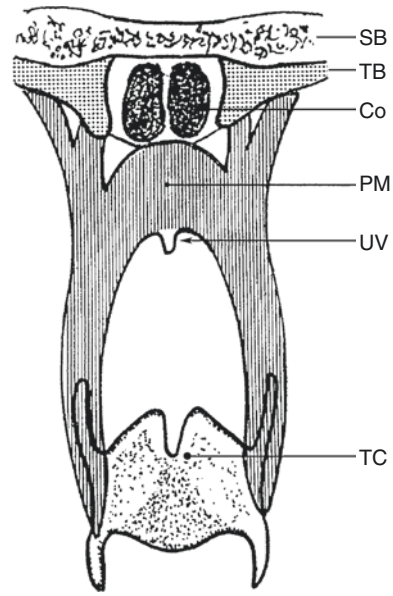

Fig. 15 The palatopharyngeal muscle seen posteriorly. *SB* skull base, *TB* tubal cartilage, *CO* choanae, *SP* soft palate, *UV* uvula, *TC* thyroid cartilage

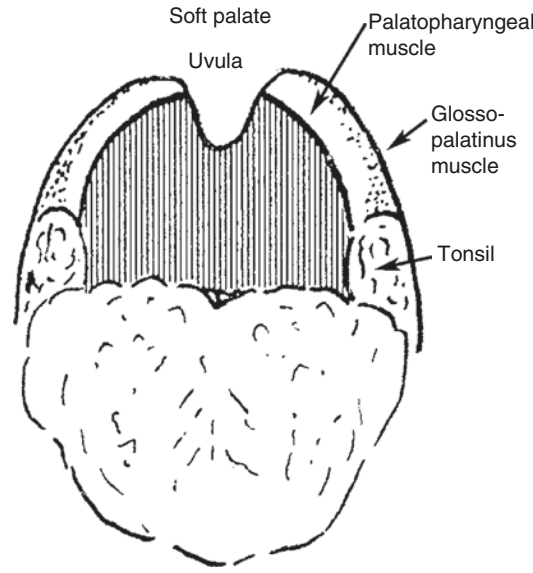

Fig. 16 The pharyngeal arches seen anteriorly. The locations of the palatopharyngeal and glossopharyngeal muscles are indicated

forms part of the posterior wall of the pharynx. It also reaches the posterior surface of the thyroid cartilage (Fig. 15).

2.2.3 Muscles of the Pharynx

All muscles in the oral cavity, larynx, and pharynx are striated. Of the two arches that surround the tonsils, the medial arch is made up of the previously described palatopharyngeal muscle and the lateral arch is made up of the glossopalatine muscle (Fig. 16).

The walls of the pharynx are made up of a fibrous fascia connected to the mucosa on the

inside and to the musculature on the outside of the wall. Superiorly towards the skull base there is no proper muscular layer. The only layers here are the mucosa and fascia, called the fibrous layer of the pharynx. This has a width of about 2 cm. Further inferiorly are the constrictor musculatures (Fig. 17). The main part of the wall of the pharynx is made up of constrictor muscles and elevators. The elevators are located on the inside, which is unique in the gastrointestinal tract. The muscles surrounding the oropharyngeal junction area are schematically shown in Fig. 18.

The pharyngeal constrictors are made up of three portions. The superior pharyngeal constrictor extends from above with four portions, namely, from the pterygoid process of the sphenoid bone, from the pterygomandibular raphe, from the mylohyoid line on the mandible, and also from the transverse musculature of the tongue. These muscle bundles join and extend posteriorly. They make up the wall of the pharynx and meet in the midline dorsally in the pharyngeal raphe (Figs. 17 and 18).

The middle pharyngeal constrictor extends from the hyoid processes and from the stylohyoid ligament. This ligament runs from the styloid process in the skull base to the minor processes of the hyoid bone. It then extends as a plate posteriorly and superiorly, joining the muscles from the other side in the posterior midline in the pharyngeal raphe (Figs. 18 and 19).

The inferior pharyngeal constrictor extends from the cricoid cartilage, from the thyroid cartilage, and also from the lateral thyrohyoid ligament (Figs. 17, 18, 19, and 20). This muscle extends somewhat superiorly and posteriorly surrounding the pharynx and joining the muscle from the other side in a pharyngeal raphe in the posterior midline. Inferiorly the pharyngeal constrictors form a superiorly convex arch.

There are several muscles that elevate the pharynx. The stylopharyngeal muscle extends from the styloid process and its surroundings at the skull base and extends inferiorly and anteriorly in a gap between the superior and middle pharyngeal constrictors. It partly joins with the

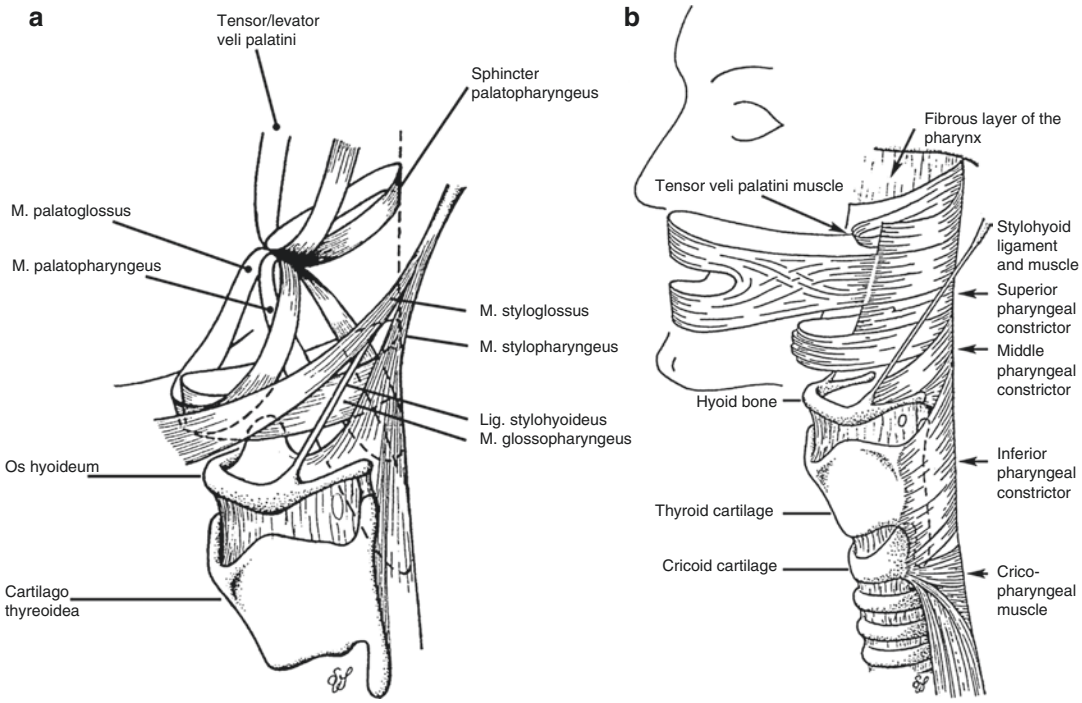

Fig. 17 The pharyngeal musculature seen posteriorly. (**a**) Palatopharyngeal muscles and elevator of the pharynx. (**b**) Constrictor muscles. (Drawing by Sigurdur V. Sigurjonsson)

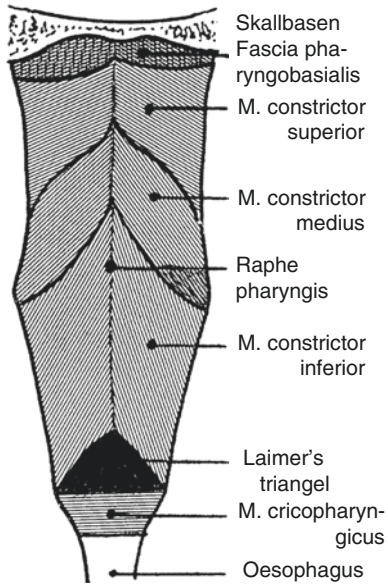

Fig. 18 The pharynx seen from the *left*. (Drawing by Sigurdur V. Sigurjonsson)

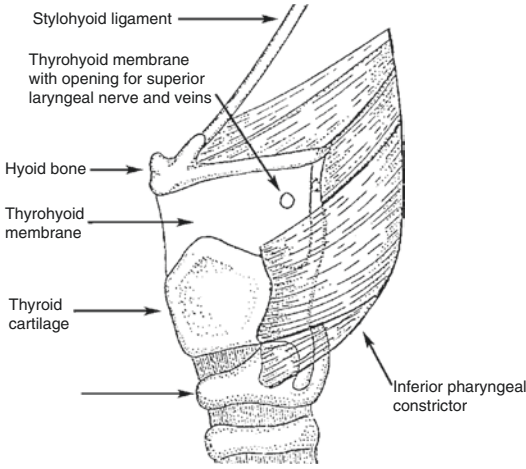

Fig. 19 The hyoid bone, thyroid cartilage, and cricoid cartilage with muscles and membranes seen from the *left*

contralateral muscles and extends inferiorly to insert on the edges of the epiglottis and also on the posterior margin of the thyroid cartilage (Figs. 21 and 22).

The palatopharyngeal muscle is the biggest of the elevators. It inserts on the posterior border of the hard palate and the palatine aponeurosis and on the pterygoid process. It extends inferiorly and inserts on the back of the thyroid cartilage and also within the constrictor musculature (Fig. 15).

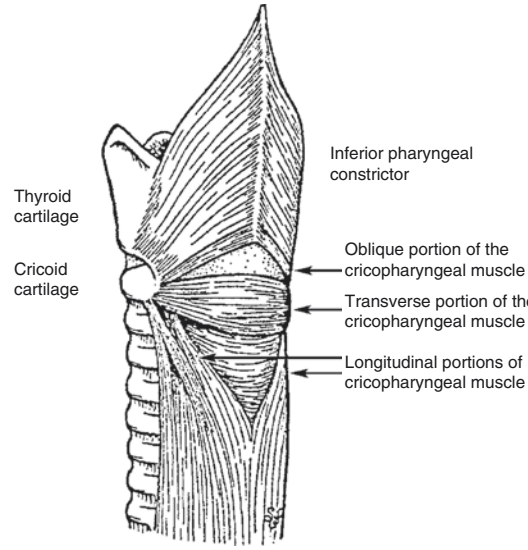

Fig. 20 The cricopharyngeal muscle seen from posteriorly and from *left*. (Drawing by Sigurdur V. Sigurjonsson. From Ekberg and Nylander 1982)

2.2.4 The Pharyngoesophageal Segment

The pharyngeal constrictors make up the muscle wall of the pharynx almost from the skull base and down into the esophagus. Inferiorly to the constrictors there is one more muscle, namely, the cricopharyngeal muscle (Zaino et al. 1970; Fig. 20). This muscle is made up of an oblique portion, a transverse portion (which makes up the bulk of the muscle), and a longitudinal portion of muscle bundles inferiorly. The oblique part extends obliquely, superiorly, and posteriorly from the lateral part of the cricoid cartilage. It is close to the inferior constrictor. Like the latter muscle, it is usually considered that the oblique muscles connect in the pharyngeal raphe. This portion of the cricopharyngeal muscle is anatomically and functionally the inferior (small) portion of the pharyngeal constrictors. The transverse or semicircular portion extends posteriorly from the posterior and lateral part of the cricoid cartilage. Where the two muscles merge in the posterior midline there is *no* fibrous raphe. The two longitudinal muscles, also called esophageal elevators, extend from the inferior portion of the cricoid cartilage and extend on each side of the esophagus, where they join the longitudinal musculature

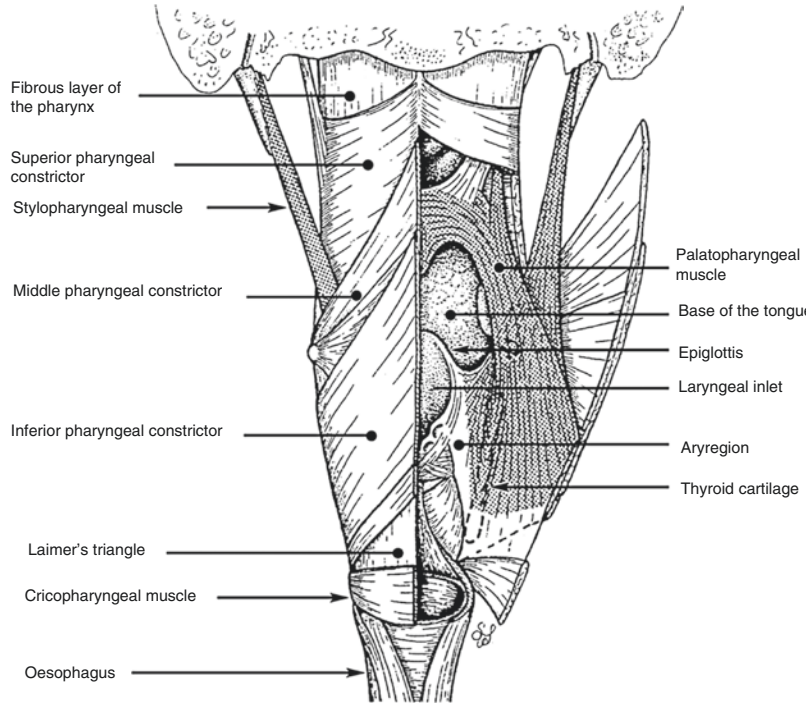

Fig. 21 The pharyngeal musculature seen posteriorly and with the *right side* of the pharynx cut open so that it can be seen from inside. The three constrictor muscles are overlapping. The stylopharyngeal muscle runs from the styloid process inferiorly to insert on the epiglottis, thyroid cartilage, and pharyngeal wall through a gap between the superior and *middle* constrictors. (Drawing by Sigurdur V. Sigurjonsson)

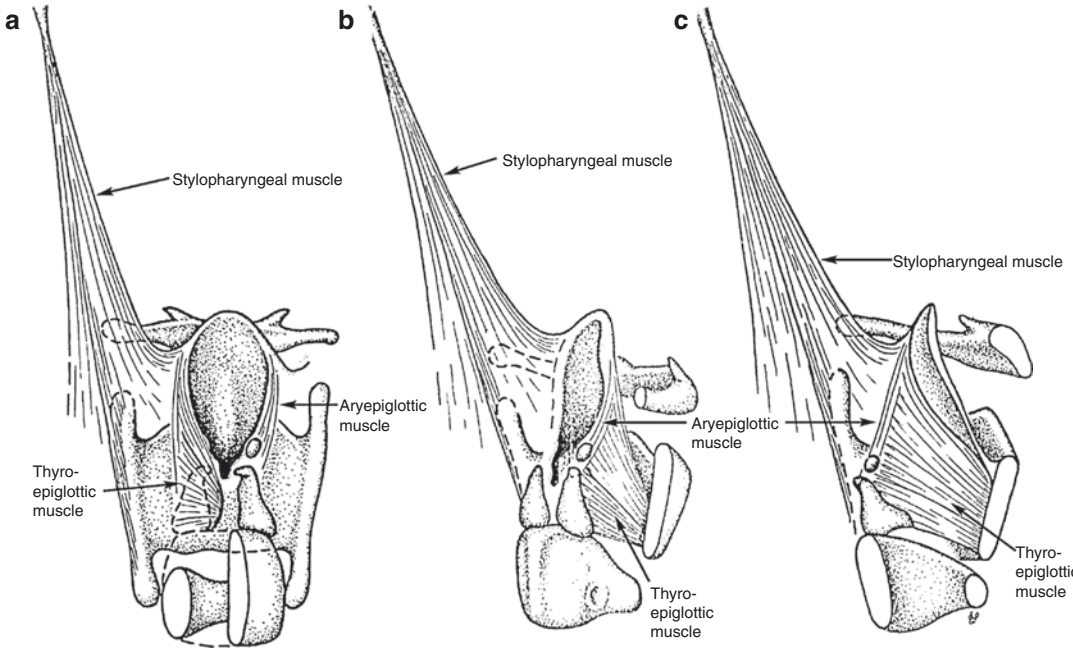

Fig. 22 The stylopharyngeal muscle and epiglottic musculature seen posteriorly (**a**), posteriorly and from the *right* (**b**), and from the *right* (**c**). (Drawing by Sigurdur V. Sigurjonsson. From Ekberg and Sigurjonsson 1982)

of the esophagus, which in turn comes from the median part of the lamina of the cricoid cartilage. Normally the inferior constrictor muscle overlaps the cricopharyngeal muscle, which in turn overlaps the circular muscle of the esophagus (Ekberg and Lindström 1987). However, between the oblique and transverse part of the cricopharyngeal muscles there is a small triangular gap which is a weak point called Killian's opening or Laimer's triangle. It is through this weak area that the Zenker diverticulum extends. Laterally, there is a similar weak point inferior to the transverse portion and above the insertion of the longitudinal portion of the cricoid muscles. Through this gap the Killian–Jamieson diverticula extend (Jamieson 1934).

2.3 The Larynx

During swallowing, the larynx acts like a valve that closes off the airways from the foodway. The closure of the larynx is achieved by the following mechanisms. The tilting down of the epiglottis is achieved in a clear-cut two-step fashion. The first movement is from the upright resting position of the epiglottis to a transverse position. This movement can be explained as consequential to the elevation of the hyoid bone and the approximation between the thyroid cartilage and the hyoid bone. This movement of the epiglottis is thereby the result of contraction of the muscles that elevate the hyoid bone, namely, the stylohyoid, digastric, mylohyoid, and geniohyoid muscles. In addition, the thyrohyoid muscle approximates the hyoid bone and the thyroid cartilage. The epiglottis is laterally fixed by the pharyngoepiglottic plicae and, during laryngeal elevation and thyroid approximation to the hyoid bone, is tilted to the transverse position with these plicae as turning points. The second movement of the epiglottis has been attributed either to the passing bolus which should push the movable lip of the epiglottis further down into the esophageal inlet or to the peristaltic contraction in the pharyngeal constrictor musculature. It is more probable that the second movement of the epiglottis is accomplished by one of the muscles that inserts on the epiglottis. These muscles are the stylopharyngeal, thyroepiglottic, and aryepiglottic muscles. None of these muscles have such a direction that they are able to tilt the epiglottis down from its upright resting position. However, when the epiglottis has attained a transverse position, the conditions may have changed. Still, the stylopharyngeal muscle cannot possibly bring about the second movement, and it is more likely that a contraction in this muscle results in a tilting back of the epiglottis to the upright position. It is possible that the aryepiglottic muscle may be able to pull the epiglottis downwards against the "ary" region, but never as far down as into the esophageal inlet. When these two muscles have been excluded, the thyroepiglottic muscle remains as an able candidate to accomplish the tilting down of the epiglottis. With the epiglottis in the transverse position this muscle has a favorable direction in relation to the epiglottis. A contraction of the thyroepiglottic muscle is therefore very likely to pull the epiglottis down over the ary region. Furthermore, it will change the form of the epiglottis from a downward convex form to an upward convex form. A contraction of the aryepiglottic muscle in this new position of the epiglottis with its tip in the esophageal inlet will tighten the laryngeal inlet in the same manner as the string in a tobacco pouch. It is possible to distinguish two different steps in the closure of the vestibule, both of which are clearly separated from the closure of the rima glottidis. In the first step the supraglottic space of the vestibule is closed by the apposition of the lateral walls. This closure of the supraglottic space is caused by contraction and thickening of the superior portion of the thyroarytenoid muscle. The compressed supraglottic space has an orientation in the sagittal plane.

In the second step the closure of the vestibule is effected by a compression of the subepiglottic space from below. This is caused by the posterior aspect of the epiglottis with its superimposed fat cushion that is gradually pressed against the prominence of the ary region. The compressed subepiglottic space has an orientation nearly in the horizontal plane, with its anterior part more caudally than the posterior part. The tilting down

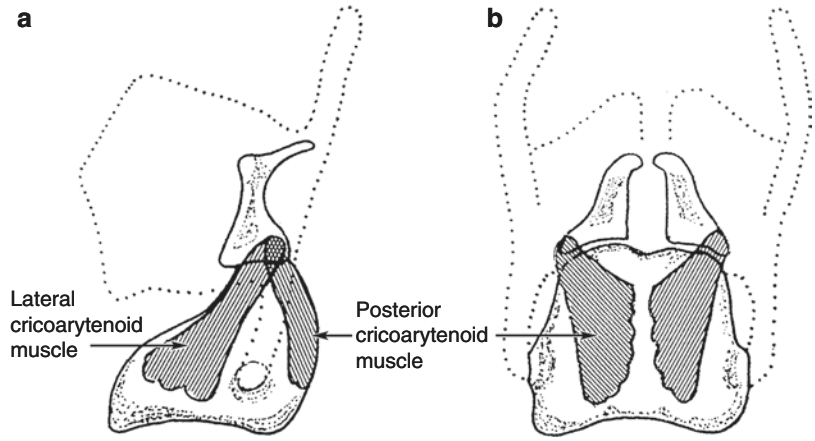

Fig. 23 The cricoid cartilage, arytenoid cartilage, and muscles seen from the *left* (**a**) and posteriorly (**b**)

of the epiglottis is probably due to a contraction of the thyroepiglottic muscles. A backward bulging of the superior–anterior wall of the vestibule is achieved by a folding of the median soft tissue linking the thyroid cartilage to the hyoid bone. This tissue comprises the epiglottic cartilage, the preepiglottic fat cushion, and its bounding ligaments, namely, the thyroepiglottic, the median thyrohyoid, and the hyoepiglottic ligaments. In analogy with other folds in this region the above structures have been designated "the median thyrohyoid fold" (Fink 1976).

The described sequence of events in the closure of the vestibule by a compression from below—the supraglottic followed by the subepiglottic space—is important as it implies a peristaltic-like mechanism that can clear the vestibule of bolus material. After a swallowing act, the vestibule is free from foreign particles when it opens again.

The thyroepiglottic muscle and the aryepiglottic muscles pull the epiglottis downwards over the laryngeal inlet (Fig. 22). The aryepiglottic muscle runs within the aryepiglottic folds from the ary cartilage in a superior and anterior direction and inserts on the lateral border of the epiglottis (Fig. 22). Within the larynx there are several muscles, namely, the dorsal cricoarytenoid muscles, the lateral cricoarytenoid muscles, and the arytenoid muscle (Figs. 23 and 24). The dorsal cricoarytenoid muscle runs from the posterior surface of the cricoid cartilage superiorly and laterally to insert on the lateral and inferior corner of the arytenoid cartilage. The lateral arytenoid muscle runs from the lateral part on the cricoid cartilage superiorly and posteriorly to insert in the same area as the prior described muscle. The arytenoid muscle runs between the two arytenoid cartilages and has a pars recta and also a pars obliqua (Fig. 24). The thyroarytenoid muscle runs from the inside of the lamina of the thyroid cartilage and runs dorsally and laterally to insert on the arytenoid cartilage (Fig. 25a). It creates a muscle plate that laterally covers the larynx and the inlet to the larynx. The inferior portion is more bulky and it is made up of a lateral part and a vocal part. This latter is often called the vocalis muscle within the vocal folds. The somewhat weaker and superior portion of the

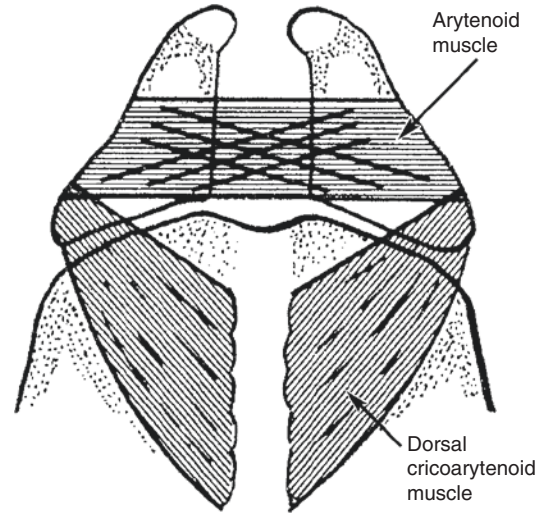

Fig. 24 The cranial portion of the cricoid cartilage, the arytenoid cartilage, and muscles seen posteriorly

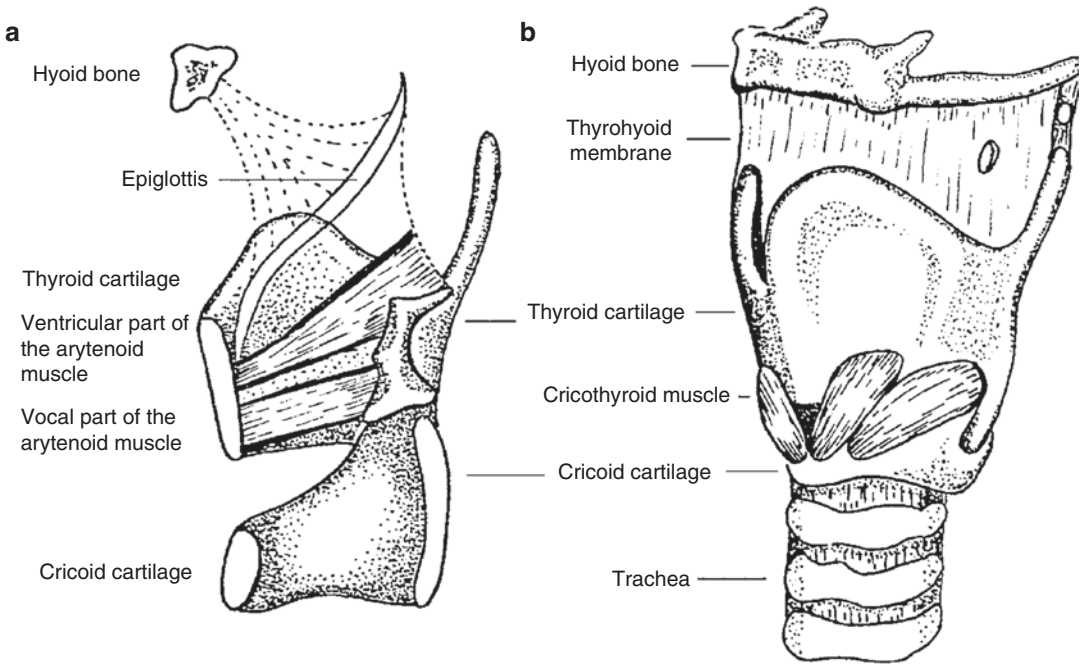

Fig. 25 (**a**) The larynx cut open in the midline and seen from the *left*. (**b**) The larynx seen anteriorly and from the *left*

thyroarytenoid muscle is sometimes called the ventricularis muscle because it forms the ventricular fold. The thyroarytenoid muscle closes the rima glottidis and at the same time compresses the inferior portion of the laryngeal vestibule which we call the supraglottic space.

The cricothyroid muscle is a strong muscle that runs between the cricoid and thyroid cartilages. The pars recta of this muscle runs superiorly and posteriorly from the cricoid cartilage and inserts on the thyroid cartilage. The pars obliqua of the muscle runs from the cricoid cartilage superiorly and posteriorly to insert on the inferior cornu of the thyroid cartilage (Fig. 25b).

2.4 The Mucosal Surface

The previous sections have described a framework of bones, cartilages, ligaments, and muscles, constituting the oral cavity, larynx, and pharynx. Inside this framework is the mucous membrane (Figs. 26 and 27).

The posterior part of the tongue reaches all the way to the vallecula. This corresponds to the level of the hyoid bone. There is a pocket on each side of the midline, the vallecula. Posteriorly and

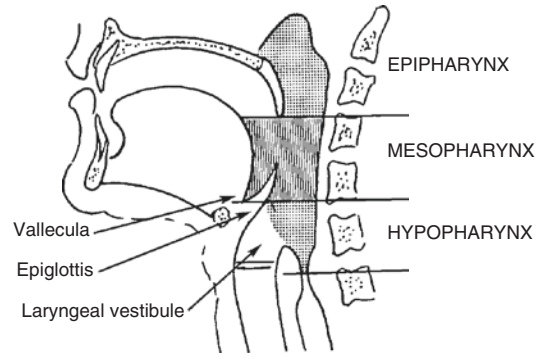

Fig. 26 The pharynx seen from the *left*

laterally the valleculae are bordered by a mucosal fold above the stylopharyngeal muscle. This fold is called the pharyngoepiglottic fold. The two valleculae are separated in the midline by a mucosal fold, the median glossoepiglottic fold (Figs. 26 and 27). The tongue base and valleculae contain a rich network of lymphatic tissue. The vallecula may also contain vessels in the submucosa, which causes a weblike appearance (Ekberg et al. 1986). Further inferiorly (Fig. 27) there is a fold reaching from the lateral border of the epiglottis to the ary region. The folds surround the inlet of the laryngeal vestibule. This is the

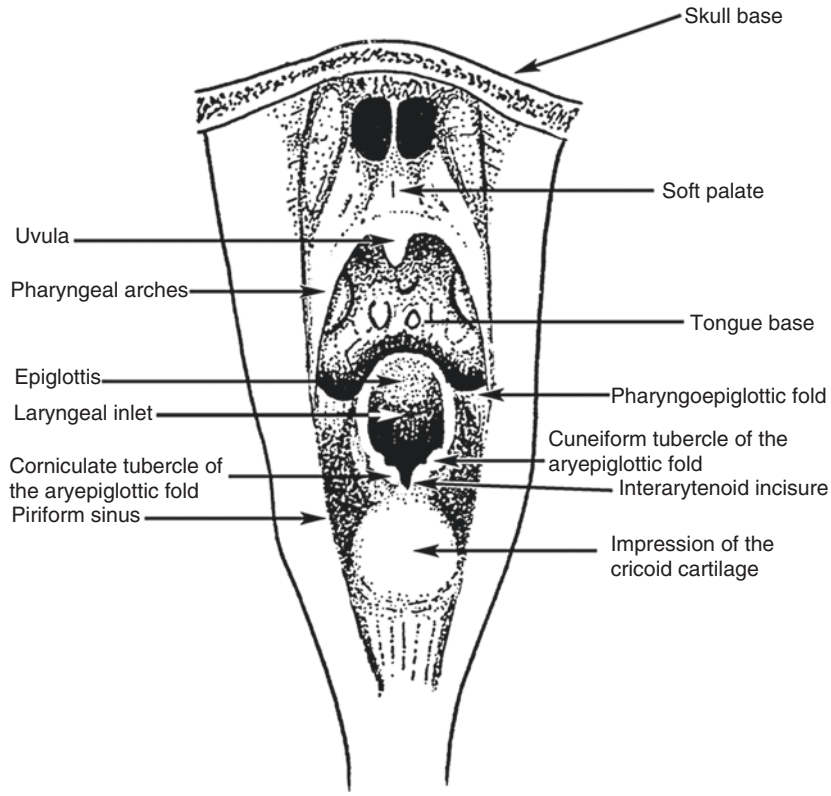

Fig. 27 The pharynx cut open in the posterior midline and seen from behind

aryepiglottic fold which harbors the aryepiglottic muscle. There are two small protuberances caudally/inferiorly due to the cuneiform tubercle superiorly and the corniculate tubercle inferiorly. Between the two corniculate tubercles there is a cleft called the interarytenoid incisure. The aryepiglottic fold is made up of the aryepiglottic muscle posteriorly and the thyroepiglottic muscle anteriorly. The lamina of the cricoid cartilage causes an impression of the pharyngeal lumen. On both sides of these impressions there are two recesses called the piriform sinuses.

3 Anatomy of the Esophagus

The esophagus can be divided into different parts according to the surrounding anatomical structures (Fig. 28). The superior part, the pharyngoesophageal segment (functional term), also called the upper esophageal segment (anatomical term), corresponds to the cricopharyngeal muscle and surrounding pharynx and

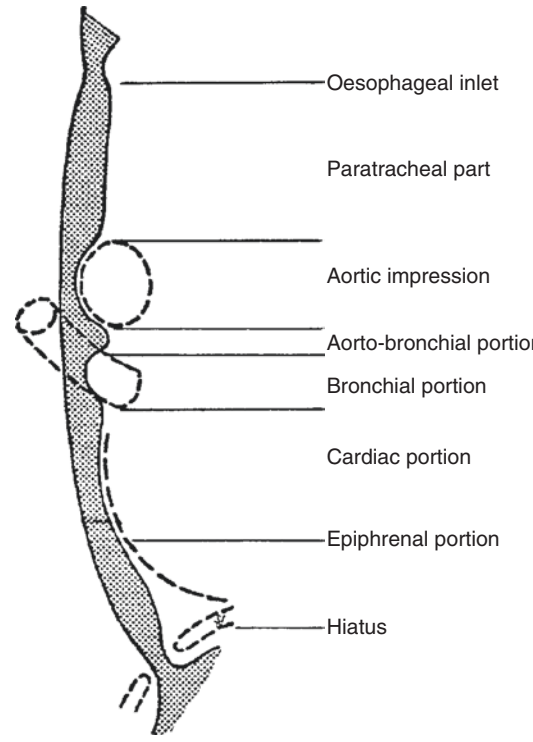

Fig. 28 The different parts of the esophagus

cervical esophagus. This is also called introitus esophagi or Killian's mouth. From here to the impression of the aorta is the paratracheal esophagus (Fig. 28). This is located close to the membranous part of the trachea. The aorta makes a short impression from the left into the aortic lumen. Inferiorly to this and above the left main bronchus is the aortobronchial portion, which is a short, relatively wide segment. The left main bronchus makes a short impression in the esophagus from the left. The cardial portion is that segment of the esophagus which is located close to the left atrium of the heart. A schematic drawing of the gastroesophageal region is given in Fig. 29.

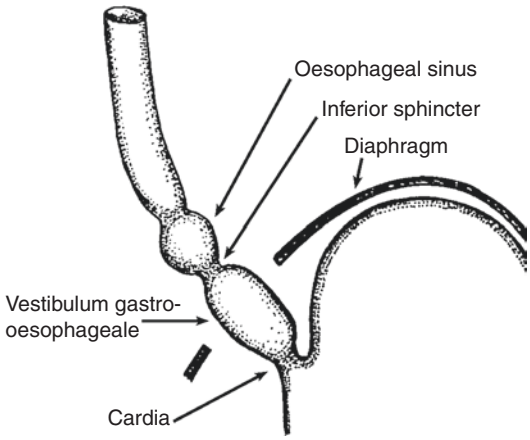

Fig. 29 The gastroesophageal region

The esophagus is made up of three layers, the mucosa, the submucosa, and the muscularis (Fig. 30). The mucosa is made of squamous cell epithelium. Under the epithelium there is a submucosal layer of musculature as everywhere else in the alimentary canal. The mucosa also contains glands and vessels. The mucosa has a tendency to create longitudinal mucosal folds.

The esophagus has two layers of muscles, an inner circular and an outer longitudinal muscle layer. The longitudinal muscles insert on the posterior aspect of the lamina of the cricoid cartilage. The upper third of the esophagus is made up of striated musculature, whereas the lower two thirds is smooth muscles. The transitional zone, however, has a varying position. The circular muscle layer is thinner cranially and increases in thickness distally. Between the two muscle layers there are a multitude of neurons in a plexus formation (Auerbach's plexus). In this there are both sympathetic and parasympathetic nerves. There is a close proximity between the vagus nerve and the esophagus, especially inferiorly.

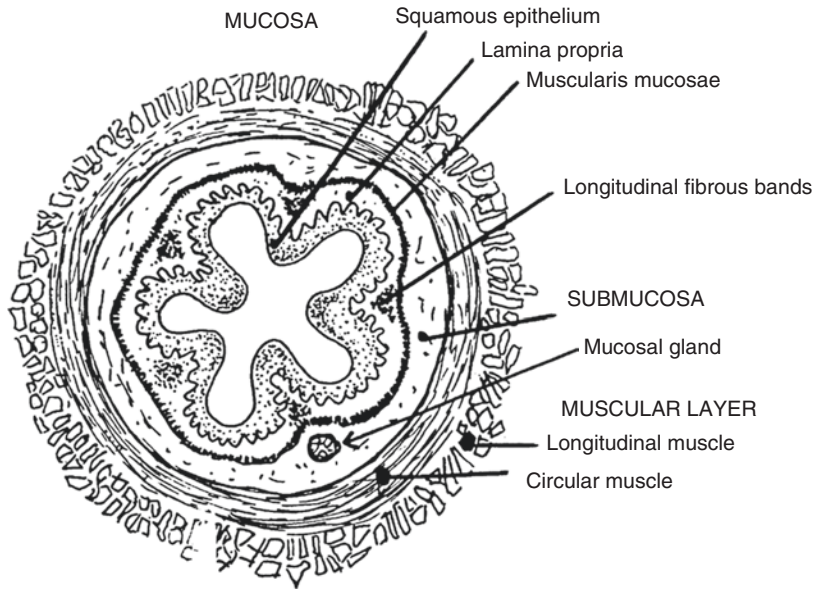

Fig. 30 Cross section of the esophagus

4 Neuroanatomy and Physiology of Swallowing

There are several reviews on the neuroanatomy and neurophysiology of swallowing, the most contemporary by Miller (1999). Several of the cranial nerves are involved in the control of swallowing (Perlman and Christensen 1997). Oral sensation is transmitted in the trigeminal nerve. Efferent information in the trigeminal nerve goes to the mylohyoid muscle, the anterior belly of the digastric muscle, and the four muscles of mastication: the masseter, temporalis, and pterygoid muscles.

Taste sensation is mediated in the facial nerve. Efferent control from the facial nerve goes to the salivary glands and to muscles of facial expression, the stylohyoid and platysma muscles, as well as the posterior belly of the digastric muscle.

The glossopharyngeal nerve conveys taste information from the posterior part of the tongue. It also conveys sensation from the pharynx. It innervates only the stylopharyngeal muscle efferently.

The vagus nerve is the most important nerve for swallowing. It innervates the pharyngeal and laryngeal mucosa. The recurrent laryngeal nerve conveys sensation from below the vocal folds and also the esophagus. Efferent control in the vagus nerve comes from the ambiguus nucleus (striated muscle) and the posterior nucleus of the vagus nerve (smooth muscles and glands).

The hypoglossal nerve provides efferent control of all the intrinsic and some of the extrinsic muscles of the tongue.

The locations of the central swallowing pathways include several cortical and subcortical regions. One such area is located immediately in front of the precentral sulcus cortex. Stimulation in this area evokes mastication followed by swallowing. It is likely that the cortical and subcortical areas merely modify swallowing as pharyngeal and esophageal swallowing can be evoked also in the absence of these areas. This indicates that the brain stem is the primary swallowing area.

Afferent information from the oral cavity and pharynx is mediated via the vagus nerve and other nerves to the nucleus of the solitary tract in the brain stem. Close to the nucleus of the solitary tract is an afferent swallowing center that interprets the information. If it is found appropriate for swallowing, information goes to a swallowing center close to the ambiguus nucleus. Control of the pharynx is managed from that swallowing center. Information also goes to a dorsal swallowing center close to the posterior nucleus of the vagus nerve. The oral stage of swallowing is completely voluntary, whereas the pharyngeal stage of swallowing is automatic. This automatism means that there is a none-or-all situation. Once the pharyngeal swallow has been elicited, it is always completed. It is not modified during the pharyngeal swallowing process and it cannot be interrupted. Swallowing has priority over other activities controlled from the ambiguus nucleus such as breathing, speech, and positioning. The esophageal stage of swallowing is autonomic, which means that it may occur also without control from the brain stem. It is also self-regulatory, i.e., a second swallow interrupts the first, and a secondary peristaltic wave can be elicited. This is achieved by the enteric nervous system.

The oral stage of swallowing includes ingestion, which is a complex act. It also involves blending, mixing, and mincing of ingested material. When the ingested material is found to be appropriate for swallowing (by analyzing information from the nucleus of the solitary tract), the tongue usually scoops up a suitable amount of ingested material, which is from now on called a "bolus," onto the top of the tongue. From there it is propelled by a sweeping movement of the tongue into the pharynx. The pharyngeal stage of swallowing includes sealing off the nasopharynx with the soft palate opposing the posterior pharyngeal wall and also the closing of the airways by elevation and closure of the larynx and tilting down of the epiglottis. Opening of the pharyngoesophageal segment is also mandatory.

The pharyngeal constrictors achieve the final rinsing of the pharynx. An important item is the elevation of the pharynx and larynx. When the bolus reaches the upper part of the esophagus, peristaltic activity occurs. This means that esophageal tonicity is abolished and the bolus is

propelled downwards by a combination of gravity and contraction in the circular musculature. When this occurs in connection with pharyngeal swallowing, it is called primary peristalsis. If it occurs by local distension, for instance, by retained material or regurgitated/reflux material, it is called secondary peristalsis. If contraction is nonpropulsive, it is called simultaneous contraction. In the elderly patient this has also been called tertiary contraction.

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Saliva and the Control of Its Secretion

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Abstract

The various functions of saliva—among them digestive, protective, and trophic ones—not just limited to the mouth and the relative contribution of the different types of gland to the total volume secreted as well as to various secretory rhythms over time are discussed. Salivary reflexes, afferent and efferent pathways, as well as the action of classical and non-classical transmission mechanisms regulating the activity of the secretory elements and blood vessels are in focus. Sensory nerves of glandular origin and an involvement in gland inflammation are discussed. Although the glandular activities are principally regulated by nerves, recent findings of an "acute" influence of gastrointestinal hormones on saliva composition and metabolism are paid attention to, suggesting, in addition to the cephalic nervous phase both a regulatory gastric and intestinal phase. The influence of nerves and hormones in the long-term perspective as well as old age, diseases and consumption of pharmaceutical drugs on the glands and their secretion are discussed with focus on xerostomia and salivary gland hypofunction. Treatment options of dry mouth are presented as well as an explanation to the troublesome clozapine-induced sialorrhea. Final sections of this chapter describe the families of secretory salivary proteins and highlight the most recent results obtained in the study of the human salivary proteome. Particular emphasis is given to the post-translational modifications occurring to salivary proteins before and after secretion, to the polymorphisms observed in the different protein families and to the physiological variations, with a major concern to those detected in the paediatric age. Functions exerted by the different families of salivary proteins and the potential use of human saliva for prognostic and diagnostic purposes are finally discussed.

1 Functions of Saliva: An Overview

Saliva exerts digestive and protective functions and a number of other functions, depending on species, and usually grouped under the heading additional functions. *Digestive functions* include the mechanical handling of the food such as chewing, bolus formation and swallowing. The chemical degradation of the food is by amylase and lipase—these enzymes continue to exert their activities in the stomach, amylase, until the acid penetrates the bolus. The group of digestive functions does also include the process of dissolving the tastants and thus allowing them to interact with the taste buds. If pleasant, taste sets up a secretory reflex of gastric acid, as a part of the cephalic regulation of gastric secretion. To the *protective functions* belong the lubrication of the oral structures by mucins, the dilution of hot or cold food and spicy food, the buffer ability (by bicarbonate, phosphates and protein) maintaining salivary pH around 7.0—note that in many laboratory animals pH is higher, 8.5–9.0—the remineralization of the enamel by calcium, the antimicrobial defence action by immunoglobulin A and α- and β-defensins and the wound healing by growth-stimulating factors such as epidermal growth hormones, statherins and histatins. Since the superficial epithelial cell layer of the oral mucosa is replaced every 3 h, the time is too short for thick layers of biofilm to accumulate and to cover the mucosal surface; the whole 40-cell-thick layer of oral epithelium shows a turnover of 4.5 days (Dawes 2003). *Additionally*,

saliva is necessary for articulate speech, for excretion (as discussed below) and for social interactions. Moreover, saliva exerts trophic effects. It maintains the number of taste buds. Further, it has recently become apparent that salivary constituents secreted during foetal life may be of importance for the development of oral structures (Castagnola et al. 2011a; Dawes et al. 2015; Inzitari et al. 2009; Jenkins 1978; Tenouvo 1998; Mese and Matsuo 2007). It has already been mentioned that the salivary enzymes accompanying the bolus are still active in the stomach. There are further examples of the fact that the action of saliva is not restricted to the mouth. Swallowed saliva protects the oesophageal wall from being damaged by regurgitating gastric acid as is the case at a lowered tone of the lower oesophageal sphincter (Shafik et al. 2005). The defence mechanisms of saliva protect the upper as well as the lower respiratory tract from infectious agents (Fig. 1).

Although the exocrine function of the salivary glands is in focus it may be worth noting that salivary glands have, in addition, excretory and possibly endocrine functions. Circulating non-protein-bound fractions of hormones, such as of melatonin, cortisol and sex steroids, passively move into the saliva as does a number of pharmaceutical drugs (Gröschl 2009). With respect to melatonin, recent studies indicate that the hormone, in addition to passive diffusion, is actively transported intracellularly by an adaptive melatonin (MT1) receptor-linked carrier system, stored attached to the secretory granules, and eventually delivered to the lumen by exocytosis upon gland stimulation (Isola et al. 2013, 2016; Isola and Lilliu 2016). Interestingly, melatonin, when in the oral cavity, exerts antioxidative, immunomodulatory and anti-cancerogenic effects (Cutando et al. 2007). Iodide is actively taken up by the glands by the same transport system as in the thyroid gland. A situation that may be deleterious for the salivary glands is if iodide happens to be radiolabelled and used in the treatment of thyroideal tumours (Mandel and Mandel 2003). Salivary substances may appear in the blood as indicated by amylase and the epidermal growth factor, which suggests endocrine functions of the glands (Isenman et al. 1999).

In animals, saliva may be secreted in order to lower the body temperature by evaporating cooling (dog's panting and rat's spreading of saliva on the scrotum and the fur), to groom (rats and cats) and, by salivary pheromones, to mark territory or to attract mates (mice and pigs); particularly, sex steroids of the saliva serve as olfactory signals (Gregersen 1931; Gröschl 2009; Hainsworth 1967).

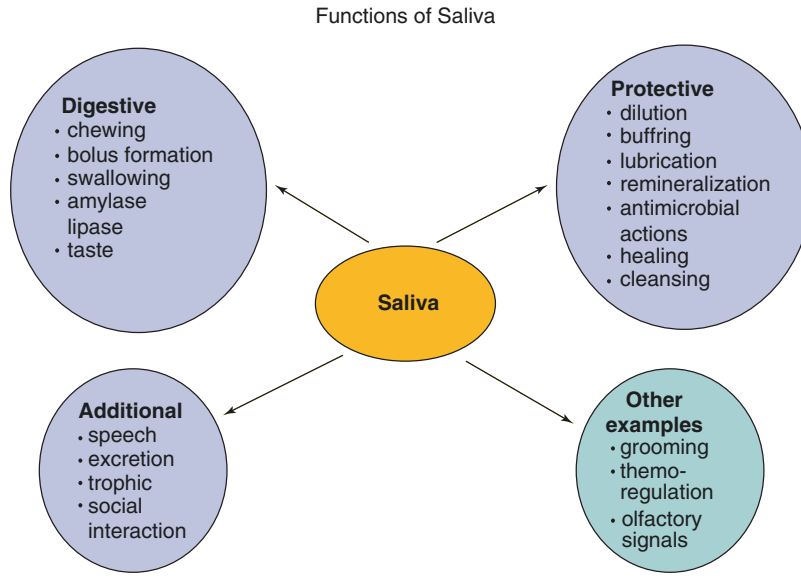

Fig. 1 Functions of saliva

2 Major and Minor Salivary Glands and Mixed Saliva

Saliva is produced by three pairs of major glands, the parotids, the submandibulars and the sublinguals, located outside the mouth, and hundreds of minor glands—each of the size of a pinhead and located just below the oral epithelium (Figs. 2 and 3). As judged by magnetic resonance image, the volume of the parotid gland is about 2 1/2 times that of the submandibular gland and 8 times that of the sublingual gland (Ono et al. 2006). Similar relationships are obtained when the comparisons are based on gland weights, the parotid gland weighing 15–30 g (Gray 1988). The saliva from the parotid and submandibular glands reaches the oral cavity via long excretory ducts (7 cm and 5 cm, respectively), the parotid duct (also called Stensen's duct) opening at the level of the second upper molar and the submandibular duct (Wharton's duct) opening on the sublingual papilla. In about 20% of the population, the parotid duct is surrounded by a small accessory gland. Sublingual saliva empties into the submandibular duct via the major sublingual duct (Bartholin's duct) or directly into the mouth via a number of small excretory ducts opening on the sublingual folder. Likewise, the saliva of minor glands, such as of the buccal, palatinal (located in the soft palate), labial, lingual and molar glands, empties into the mouth directly via small, separate ducts just traversing the epithelium (Tandler and Riva 1986). Unless saliva is collected directly from the cannulated duct, the saliva in the mouth will be contaminated by the gingival crevicular fluid, blood cells, microbes, antimicrobes, cell and food debris, and nasal-pharyngeo-secretion. Consequently, mixed saliva ("whole saliva") collected by spitting or drooling is not pure saliva, although the term "saliva" is usually used.

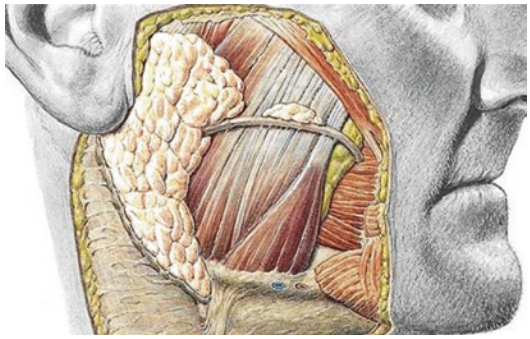

Fig. 2 Parotid gland and accessory gland (with permission from Elsevier)

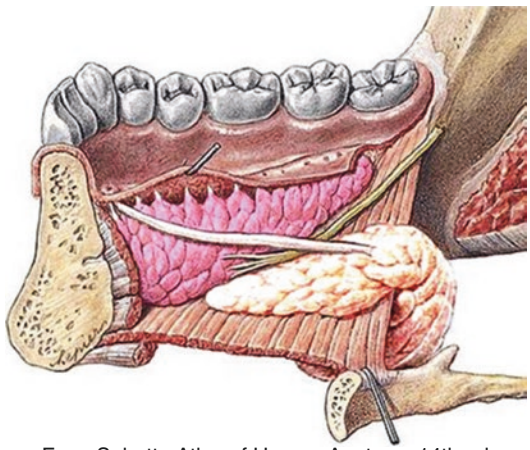

Fig. 3 Submandibular and sublingual glands. Note the many small ducts from the sublingual gland (with permission from Elsevier)

3 Spontaneous, Resting and Stimulated Secretion

Some salivary glands have an inherent capability to secrete (Emmelin 1967). The type of gland varies among the different species. In humans, only the minor glands secrete spontaneously. Though these glands are innervated and may increase their secretory rate in response to nervous activity, they secrete at a low rate, without exogenous influence during the night. In daytime and at rest, a nervous reflex drive—set up by low-graded mechanical stimuli due to movements of the tongue and lips, and mucosal dryness—acts on the secretory cells, particularly engaging the submandibular gland (Fig. 4). In the clinic, the saliva secreted at rest is often called "unstimulated secretion", despite the involvement of nervous activity. With respect to stimulated secretion, the parotid contribution becomes more dominant: in response to strong stimuli, such as citric acid, the flow rate is about

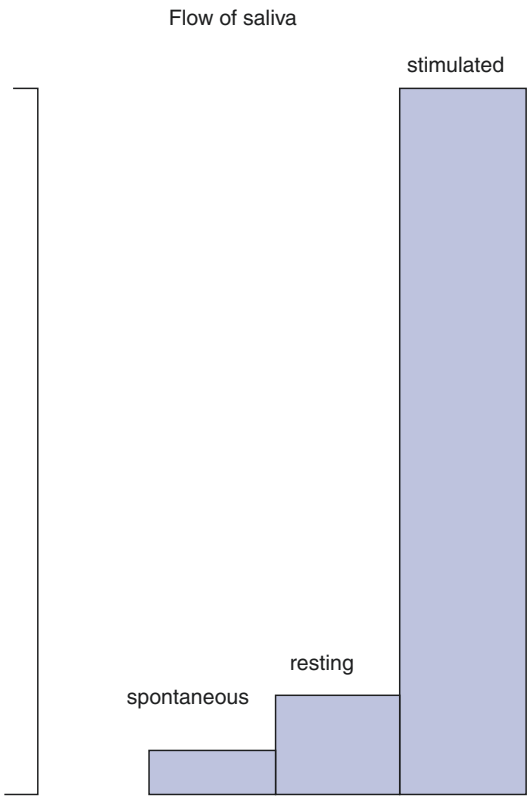

Fig. 4 Different rates of salivary flow

equal to that from the submandibular gland, while to chewing, the flow rate is twice as high as that from the submandibular gland. The total volume of saliva secreted amounts to 0.75–1 L per 24 h. The flow rate correlates with gland size, and is higher in males than in females (Heintze et al. 1983). When considering the relative contribution of each type of gland to the total volume secreted, the percentage figures are roughly 30% for the parotid glands, 60% for the submandibular glands, 5% for the major sublingual glands and 5% for the minor glands (Dawes and Wood 1973). Different types of glands produce different types of secretion. Depending on the reaction to the histochemical staining of the acinar cells for light microscopy examination, the cells are classified as (basophilic) serous or (eosinophilic) mucous cells. The serous cells are filled with protein-storing granules and associated with the secretion of water and enzymes, while the mucous cells are associated with the secretion of the viscous mucins stored in vacuoles. The parotid gland is characterized as a serous gland, the submandibular gland is characterized as sero-mucous (90% serous cells and 10% mucous cells) and the major sublingual gland and most of the minor glands are characterized as mucous glands. The deep posterior lingual glands (von Ebner's glands), found in circumvallate and foliate papillae close to most of the taste buds, are, however, of the serous type. Though the contribution of the minor glands is small, they continuously, during day and night, provide the surface of the oral structures with a protective layer of mucin-rich saliva that prevents the feeling of mouth dryness from occurring. Together with the major sublingual glands, they are responsible for 80% of the total mucin secretion per 24 h.

4 The Salivary Response Displays Circadian and Circannual Rhythms

On the whole, the flow rate of resting/unstimulated as well as of stimulated saliva is higher in the afternoon than in the morning (Dawes 1975; Ferguson and Botchway 1980), the peak occurring in the middle of the afternoon. Also the salivary protein concentration follows this diurnal pattern. In addition, the flow of the resting/unstimulated saliva is higher during winter than during summer indicating a circannual rhythm (Elishoov et al. 2008). Just a small change in the ambient temperature (by 2°C) in a warm climate is enough to inversely affect the flow rate (Kariyawasam and Dawes 2005).

5 The Diversity of the Salivary Response

Pavlov drew attention to the fact that the volume of saliva secreted and its composition vary in a seemingly purposeful way in response to the physical and chemical nature of the stimulus (see Babkin 1950). Not only does the secretion adapt "acutely" to the stimulus but long-term demands may induce changes in gland size and secretory capacity. The variety in the salivary

response is attained by the involvement of different types of glands, different types of cells within a gland, different types of reflexes displaying variations in intensity, duration and engagement of the two divisions of the autonomic innervation, different types of transmitter and varying transmitter ratios, different types of receptors and various intracellular pathways mobilized either running in parallel or interacting synergistically (Fig. 5).

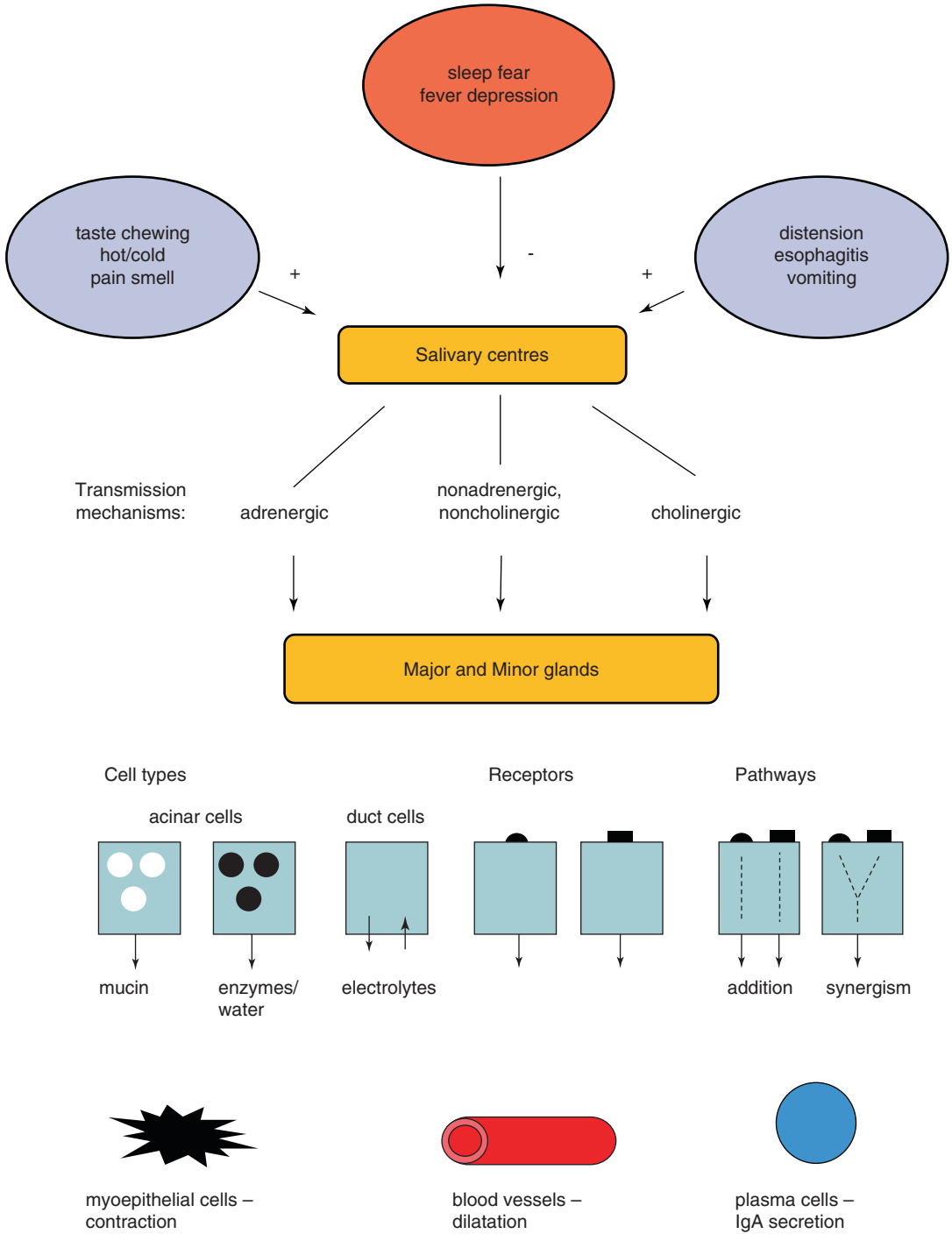

Fig. 5 Afferent and efferent nerves, and various elements of salivary glands

6 Afferent Stimuli for Secretion

Eating is a strong stimulus for the secretion of saliva (Hector and Linden 1999). A number of sensory receptors are activated in response to the food intake: gustatory receptors, mechanoreceptors, nociceptors and olfactory receptors (Fig. 5). All four modes of taste (sour, salt, sweet and bitter) elicit secretion ("gustatory-salivary reflex") but sour, followed by salt, is the most effective stimulus. Taste buds reside in the papillae of the tongue. The sensation of salt is particularly experienced at the tip of the tongue and of bitter at the dorsum of the tongue, while the sensations of sweet and sour are experienced in between. Other regions than the tongue, in particular the soft palate but also the epiglottis, the esophagus, nasopharynx and the buccal wall, do also contain areas of taste buds. Chewing causes the teeth to move sideways, thereby stimulating mechanoreceptors of the periodontal ligaments ("masticatory-salivary reflex"). In addition, gingival mucosal tissue mechanoreceptors are activated during chewing. Olfactory receptors are located at the cribriform plate, i.e., at the roof of the nasal cavity, and they respond to volatile molecules of the nasal and the retronasal airflow (the latter arising from the oral cavity or the pharynx). Sniffing increases the airflow and thereby the access of stimuli to the receptor area. The epithelium containing the olfactory receptors has a rich blood supply. Interestingly, blood-borne odorants may pass the vessel walls and stimulate these receptors. The submandibular glands, but not the parotid glands, are regulated by an "olfactory-salivary reflex". Irritating odours, do, however, mobilize the parotid gland, in addition to the submandibular gland, in this case, in response to the stimulation of epithelial trigeminal "irritant receptors". The nociceptors may also be activated in response to spicy food (e.g. chilli pepper). Thermal stimuli do also influence the rate of secretion. Ice-cold drinks produce greater volume of saliva than hot drinks (Dawes et al. 2000). Dryness of the mucosa acts as yet another stimulus for secretion ("dry mouth reflex", Cannon 1937). Salivary secretion as a consequence of pain is a well-known phenomenon, and both pain- and mechanoreceptors may cause secretion elicited by oesophageal distension due to swallowing dysfunctions (Sarosiek et al. 1994). When applied unilaterally, the stimulus may evoke secretion from the glands of both sides. However, the secretory response is more pronounced on the stimulated side. Afferent signals arising from the anterior part of the tongue preferentially engage the submandibular gland, while signals arising from the lateral and posterior parts preferentially engage the parotid gland (Emmelin 1967). Patients suffering from chronic gastro-oesophageal reflux of acid may experience salivation in response to acid directly hitting the muscle layers of a damaged oesophageal wall ("oesophageal-salivary reflex", Helm et al. 1987). This reflex is elicited also in healthy subjects (Shafik et al. 2005). Salivation is part of the vomiting reflex set up by a number of stimuli, including distension of the stomach and duodenum as well as of chemical stimuli acting locally or centrally. The phenomenon of conditioned reflexes is tightly associated with salivary secretion, since the pioneering work by Pavlov on dogs. In humans, however, it is difficult to establish conditioned salivary reflexes to sight, sound or anticipation of food. The feeling of "mouth watering" at the sight of an appetizing meal is attributed to anticipatory tongue and lip movements as well as to an awareness of pre-existing saliva in the mouth (Hector and Linden 1999).

7 Efferent Stimuli for Secretion

Since the days of the ninetieth-century pioneers of experimental medicine, who were exploring the action of nerves, the secretion of saliva has been thought to be solely under nervous control (Garrett 1998). Recent studies do, however, imply an "acute" role for hormones in the regulation of saliva composition (see below). The secretory elements (acinar-, duct- and myoepithelial cells) of the gland are invariable richly supplied with parasympathetic nerves. The sympathetic innervation varies in intensity between the glands, however. In humans, the secretory elements of the parotid glands are reported to be less supplied with sympathetic nerves than the submandibular glands, and the labial glands are thought to lack a sympathetic secretory innervation (Rossini et al. 1979). The parasympathetic innervation is responsible for the secretion of large volumes of saliva, while, in the event of a sympathetic secretory innervation, the sympathetically nerve-evoked

flow of saliva is usually sparse. Both the parasympathetic and sympathetic innervations cause the secretion of proteins. While gustatory reflexes activate both types of autonomic nerves, masticatory reflexes preferentially involve the activity of the parasympathetic innervation (Jensen Kjeilen et al. 1987). Since the accompanying flow of saliva is much greater in response to parasympathetic stimulation than to sympathetic stimulation, the salivary protein concentration is lower in parasympathetic saliva than in sympathetic saliva. In case of a double innervation of the secretory cells, parasympathetic and sympathetic nerves interact synergistically with respect to the response (Emmelin 1987). The secretion of saliva requires a large water supply from the circulation. Parasympathetic activity causes vasodilation, and the glandular blood flow may increase 20-fold, Fig. 6.

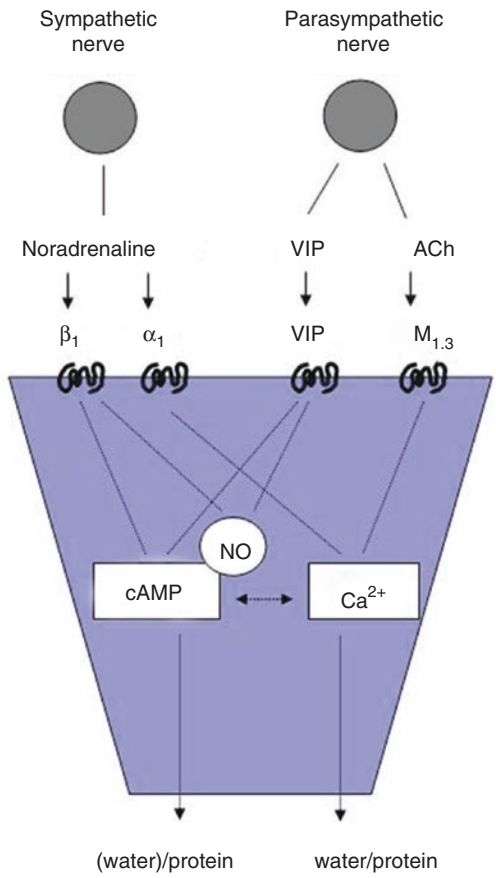

Fig. 6 Acinar cells: transmitters, receptors and intracellular pathways

8 Autonomic Transmitters and Receptors

Traditionally, acetylcholine is the parasympathetic postganglionic transmitter and noradrenaline the sympathetic postganglionic transmitter that act on the secretory elements of the glands (Fig. 6). Noradrenaline acts on α_1- and β_1-adrenoceptors, while acetylcholine acts on muscarinic M1 and M3 receptors. The parasympathetic nerve of the salivary glands has been found to use other transmission mechanisms besides the cholinergic one, i.e. peptidergic (vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide, calcitonin gene-related peptide, substance P, neurokinin A, neuropeptide Y) and nitrergic (nitric monoxide) mechanisms (Ekström 1999a). The neuronal peptide set-up as well as the gland response to the various neuropeptides may vary between species. In some species, such as the rat, substance P evokes a profuse secretion. This is, however, not the case in humans. Human salivary acinar cells lack a substance P-innervation and the glands do not respond with fluid or protein secretion to exogenous administration of the peptide (Del Fiacco et al. 2015). The co-transmitters to acetylcholine may, on their own, evoke secretory effects and potentiate the acetylcholine-evoked responses (Ekström 1987). For instance, vasoactive intestinal peptide causes the secretion of proteins with no (or little) fluid. However, in concert with acetylcholine, both the protein and the fluid secretion are enhanced by vasoactive intestinal peptide. Though the parasympathetic innervation of the salivary glands contains the nitric oxide (NO)-synthesizing enzyme, NO-synthase, NO of parasympathetic origin does not seem to take part in the regulation of the secretory activity. Instead, NO of intracellular origin is mobilized, and particularly upon sympathetic nerve activity (Ekström et al. 2007). With respect to the parasympathetic evoked vasodilator response, both vasoactive intestinal peptide and nitric oxide are, besides acetylcholine, involved.

9 Secretory Units

The glands are divided into lobules, each lobule consisting of a number of secretory units composed of acini and ducts. The acini, the lumen of which is surrounded by the secretory cells, form a blind end and the saliva produced passes through intercalated, intralobular and excretory ducts to finally empty into a main excretory duct; on its way through the duct system the primary saliva is modified.

10 Fluid and Protein Secretion

Fluid and protein secretion is an active, energy-dependent process. The acinar cells are responsible for the secretion of fluid. They are also responsible for the majority of the protein secretion, while the ductal cells contribute to a minor proportion of the total protein output. Large volumes of water are transported from the interstitium to the lumen by paracellular and transcellular passages in response to the osmotic force exercised by intraluminal NaCl. An intracellular rise in calcium opens basolateral channels for potassium and apical channels for chloride. Potassium leaves the cell for the interstitium and chloride leaves the cell for the lumen. Next, the luminal increase in chloride drags sodium, via paracellular transport, from the interstitium to the lumen and, as a result, water will move along the osmotic gradient produced by sodium chloride (Melvin et al. 2005; Poulsen 1998) (Fig. 7a and b).

The primary isotonic saliva formed in the acini undergoes changes along its passage through the duct system. The water permeability of the ducts is extremely small. Sodium and chloride are reabsorbed without accompanying water. A certain secretion of potassium and bicarbonate occurs at a lower rate than the rate of reabsorption of sodium and chloride. Consequently, the so-called secondary saliva that enters the mouth is hypotonic. The low salivary sodium concentration, one-fifth of that of the primary saliva, makes it possible for the taste buds to detect salt at low concentrations.

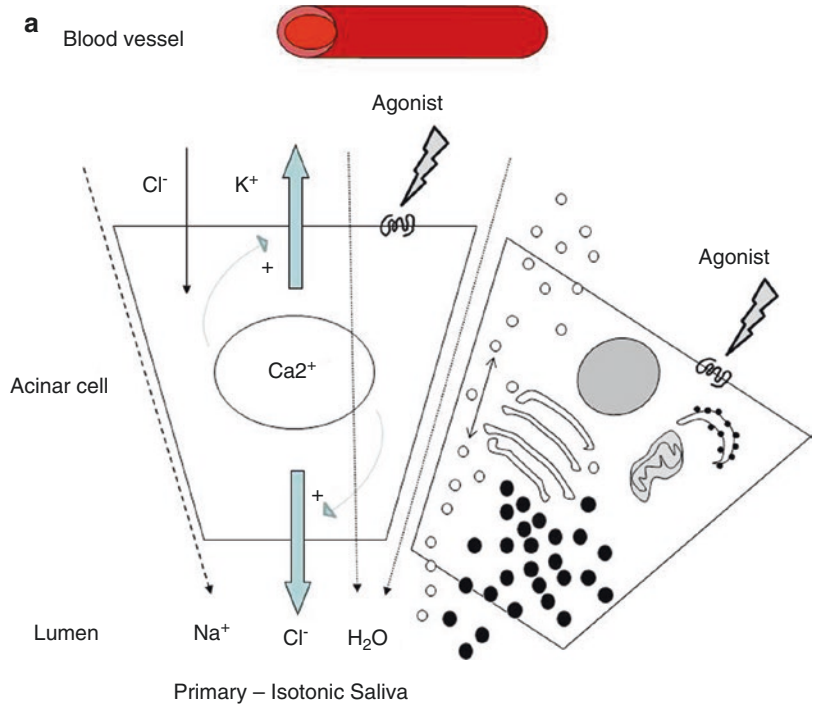

Fig. 7 (**a**) Acinar cells: water and protein secretion via vesicular and granular pathways—primary secretion. (**b**) Duct cells: modifications of saliva—secondary secretion

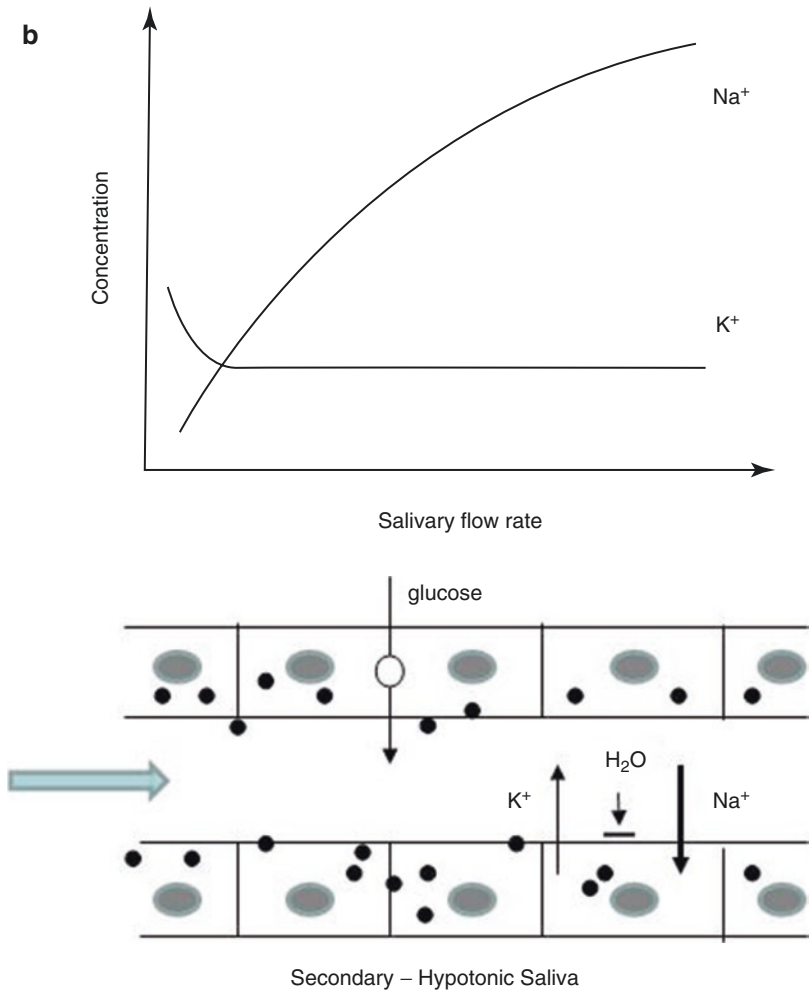

Fig. 7 (continued)

The permeability of the duct system may increase under conditions that elevate the blood level of circulating catecholamines, released from the adrenal medulla, as illustrated by the appearance of glucose in the saliva in response to cold stress, mental stress and physical exercise (Borg-Andersson et al. 1992; Teesalu and Roosalu 1993).

Immunoglobulins, in particular secretory-immunoglobulin A (s-IgA), are transported across the epithelial cells of acini and ducts. They are formed by B-lymphocytes within the gland. After release to the interstitium, they form a complex with polymeric immunoglobulin receptor which serves as transporter (Brandtzaeg 2009), a complex that splits in the saliva. The salivary concentrations of s-IgA1, one of the two subclasses of secretory immunoglobulin A (Engeland et al. 2016; Phillips et al. 2006), increase in response to acute stress and exercise, and decrease in response to chronic stress. The decrease in salivary concentration is attributed to reduced synthesis of the immunoglobulin rather than to reduced transport activity. Low salivary IgA1 concentrations are associated with recurrent respiratory tract diseases in humans exposed to chronic stress (and high plasma levels of cortisol).

The secretion of proteins is of two types (Gorr et al. 2005). The constitutive (vesicular) secretion is a direct release of proteins as soon as they are synthesized by the Golgi. The constitutive

secretion is responsible for a continuous secretion of several proteins without any ongoing external stimuli. The constitutive secretion is, however, also influenced by the nervous activity and, upon intense and prolonged stimulation, the importance of this pathway will increase concomitantly with the depletion of granules as demonstrated experimentally (Garrett and Thulin 1975). Granular secretion is the regulated type of secretion. After synthesis, the proteins are stored in granules (Fig. 8). Upon stimulation, the granules empty their content of proteins into the lumen; that is, the secretion occurs by exocytosis. The various routes for secretion may allow variations in the composition of the constituencies (Ekström et al. 2009). Mobilization of the intracellular messenger adenosine 3′, 5′-cyclic monophosphate (cAMP) by stimulation of β_1-adrenergic receptors and vasoactive intestinal peptide receptors is associated with protein secretion by exocytosis and a small volume response. Mobilization of the intracellular messenger Ca^{2+} by stimulation of muscarinic receptors (M1, M3) and α_1-adrenergic receptors is associated with fluid secretion—and particularly large volumes in response to muscarinic agonists—and protein secretion via vesicular secretion and, at intense stimulation, via exocytosis also (Ekström 2002). In acinar cells, agonists using cAMP may activate nitric oxide synthase of neuronal type but of non-neuronal origin to generate NO, which catalyzes the formation of guanosine 3′, 5′-cyclic monophosphate (cGMP) (Sayardoust and Ekström 2003). The NO/cGMP pathway may contribute to the protein secretion partly by prolonging the action of cAMP (Imai et al. 1995), partly by catalyzing the generation of cyclic adenosine diphosphate (cADP) ribose, which triggers the release of Ca^{2+} by its action on ryanodine-sensitive receptors of intracellular Ca^{2+} stores (Gallacher and Smith 1999) (Fig. 7).

It should be pointed out that the combined mobilization of Ca^{2+} and cAMP results in synergistic interactions with respect to both fluid and

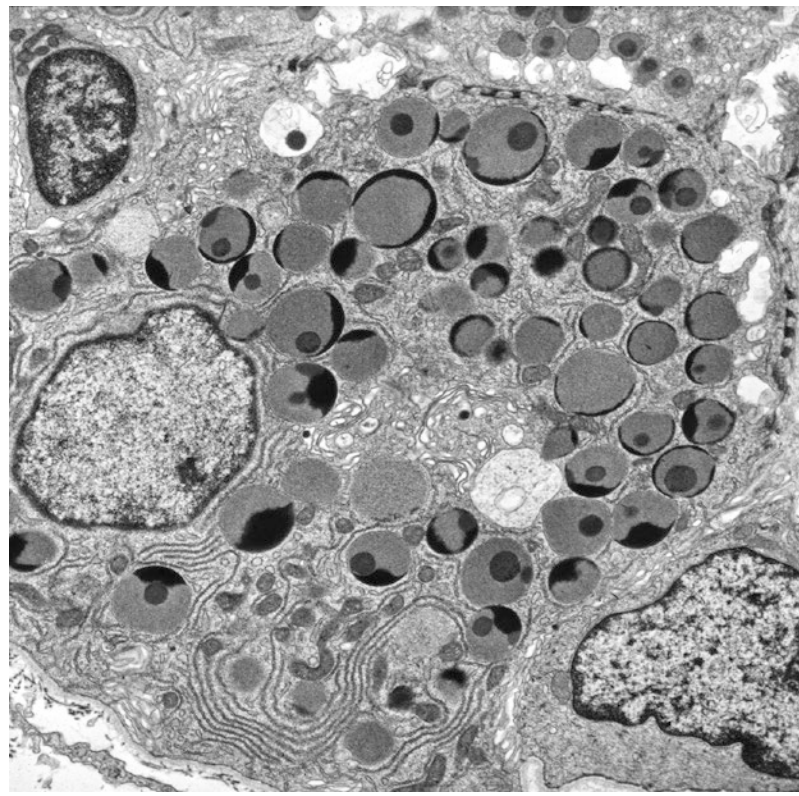

Fig. 8 Serous acinus of a human submandibular gland filled with secretory granules. Transmission electron microscopy, magnification ×2500 (courtesy of Alessandro Riva, Cagliari University)

protein secretion (Ekström 1999a). Moreover, the two sets of autonomic innervations are also involved in the protein synthesis. The non-adrenergic, non-cholinergic mechanisms play a major role in the parasympathetically nerve-induced protein synthesis (Ekström et al. 2000). The sympathetically nerve-induced protein synthesis is exerted via the two types of adrenergic receptors with a predominance for β-adrenergic receptors (Sayardoust and Ekström 2004). Importantly, the parasympathetic non-adrenergic, non-cholinergic mechanisms have been shown to take part in the regulation of salivary gland activities under reflex activation due to taste and chewing (Ekström 1998, 2001).

11 Myoepithelial Cell Contraction

Myoepithelial cells display characteristics in common with both smooth muscle cells and epithelial cells. They embrace acini and ducts (Fig. 9). They receive a dual innervation, and both muscarinic receptors and α_1-adrenergic receptors, upon stimulation, cause the cells to contract; in some species tachykinins do also cause contraction (Garrett and Emmelin 1979). Myoepithelial cell contraction increases the ductal pressure, which may be of importance for the flow of high-viscosity mucin-rich saliva and for overcoming various obstacles to the flow. Moreover, the contraction of the myoepithelial cells may play a supportive role for the underlying parenchyma, particularly at a high rate of secretion.

12 Blood Flow

Salivary glands are supplied with a dense capillary network comparable with that of the heart (Edwards 1988; Smaje 1998). The capillaries are extremely permeable to water and solutes but not to macromolecules like albumin. Parasympathetic induced vasodilatation may generate a 20-fold increase in gland blood flow which ensures the secretory cells to produce large volumes of saliva over a long period of time. The parasympathetic transmitter vasoactive intestinal peptide, besides acetylcholine, plays a major role in the vasodilator response, which also involves the action of NO. Stimulation of the sympathetic innervation causes vasoconstriction by α_1-adrenergic receptors and neuropeptide Y-receptors. However, the sympathetic innervation of the blood vessels of the gland is not activated in response to a meal but to a profound fall in systemic blood pressure in order to restore the blood pressure. The sympathetic vasoconstrictor nerve fibres originate from the vasomotor centre and are separated from the sympathetic secretomotor nerve fibres

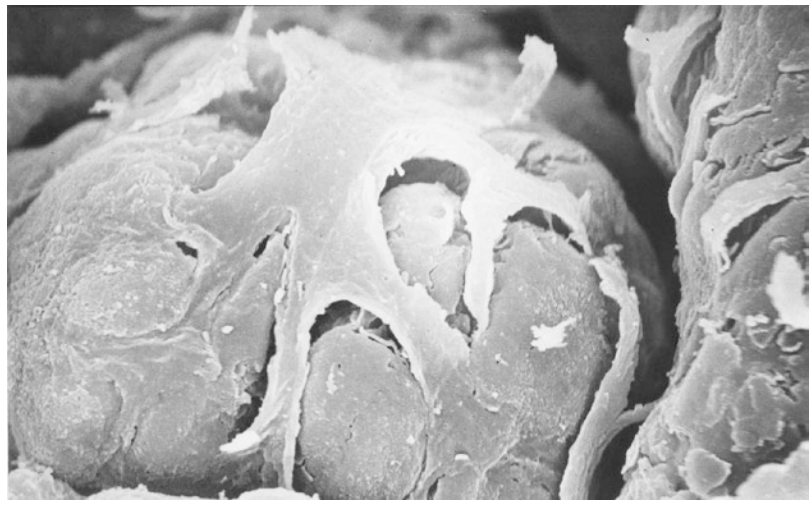

Fig. 9 Myoepithelial cells on the surface of, and embracing, a human parotid acinus. NaOH maceration method. Scanning electron microscope image, magnification ×2000 (courtesy of Alessandro Riva, Cagliari University)

taking part in alimentary reflexes (Emmelin and Engström 1960). Interestingly, the sympathetic nerve fibres to the blood vessels contain the potent constrictor transmitter neuropeptide Y (NPY), while the sympathetic secretomotor fibres lack this peptide (Ekström 1999a, b; Ekström et al. 1996).

13 Salivary Centres

The parasympathetic salivary centre is located in the medulla oblongata and divided into a superior and an inferior salivatory nucleus, and, in addition, an intermediate zone. The superior nucleus connects (the facial nerve) with the submandibular and the sublingual glands, while the inferior nucleus connects (the glossopharyngeal nerve) with the parotid gland (Emmelin 1967; Matsuo 1999). The intermediate zone makes connections with both the submandibular and parotid glands. The sympathetic salivary centre resides in the upper thoracic segments of the spinal cord. Higher centres of the brain exert both excitatory (glutamate) and inhibitory (γ-aminobutyric acid and glycine) influences on the salivary centres. The inhibitory influence is illustrated by the reduced flow of saliva associated with depression, fever, sleep and emotional stress. Note that oral dryness in response to emotional stress is a consequence of the withdrawal of the outflow of parasympathetic impulses and *not* a consequence of sympathetic inhibition of the secretion at the gland level: there do not exist any inhibitory sympathetic fibres to the secretory cells (Garrett 1988).

14 Efferent Nerves

The parasympathetic preganglionic nerve fibres of the submandibular and sublingual glands leave the facial nerve and join, via the chorda tympani nerve, the lingual nerve to form the chorda-lingual nerve to reach the submandibular ganglion. The postganglionic nerve fibres of the submandibular ganglion innervate the submandibular and sublingual parenchyma (Rho and Deschler 2005). In humans this ganglion is located outside the parenchyma of the two glands, which is in contrast to the intraglandular localization in many laboratory animals. The parasympathetic preganglionic nerve fibres of the parotid gland travel via the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve), the tympanic plexus and the lesser superficial petrosal nerve and, after relaying in the otic ganglion, the postganglionic nerve fibres are usually thought to reach the gland via the auriculo-temporal nerve. With respect to the preganglionic innervation of the parotid gland, reflex studies do suggest that not only fibres of the glossopharyngeal nerve but also fibres of the facial nerve (chorda tympani nerve) contribute, since cutting the chorda tympani nerve in the tympanic membrane reduces the response (Reichert and Poth 1933; Diamant and Wiberg 1965). The routes of the postganglionic cholinergic nerve fibres may vary as judged by extensive animal studies. Cholinergic nerve fibres may detach at an early stage from the auriculo-temporal nerve, to reach the gland via the internal maxillary artery. Moreover, and in contrast to the general textbook view, the facial nerve passing through the parotid gland parenchyma, with its twigs, does supply the secretory cells with a cholinergic innervation that takes part in the reflex secretion (Ekström and Holmberg 1972; Khosravani et al. 2006; Khosravani and Ekström 2006). The facial nerve is therefore a potential contributor to the development of Frey syndrome (Dunbar et al. 2002). Frey syndrome is characterized by sweating, redness, flushing and warming over the parotid region when eating. It develops over a period of months following parotid gland surgery, neck dissection, blunt trauma to the cheek and chronic infection of the parotid area. It is considered to be due to aberrant regeneration of postganglionic parasympathetic cholinergic nerve fibres of the auriculo-temporal nerve that innervate sweat glands and skin vessels following loss of the sympathetic postganglionic *cholinergic* innervation but may, in the light of a secretory role for the facial nerve, also involve regenerating parasympathetic postganglionic cholinergic nerve fibres of the facial nerve. Since botulinum toxin, preventing transmitter exocytosis, is more effective than

the muscarinic receptor antagonist atropine, in the treatment of the syndrome, a co-transmitter or co-transmitters to acetylcholine is/are likely to contribute to the symptomatology; vasoactive intestinal peptide is such a co-transmitter (Drummond 2002).

The routes of the parasympathetic nerves of the minor glands (Tandler and Riva 1986) are via the buccal branch of the mandibular nerve with respect to the molar, buccal and labial glands (postganglionic nerves originate from the otic ganglion), via the lingual nerve with respect to the lingual glands (Remak's ganglia, intralingually located) and via the palatine nerve with respect to palatinal glands (sphenopalatine ganglion).

The sympathetic preganglionic nerve fibres ascend in the paravertebral sympathetic trunk to synapse with their postganglionic nerve fibres in the superior cervical ganglion, which then reach the glands via the arteries. However, their actual anatomical pathways are not completely defined; for example the parotid gland may be reached both via the external carotid artery and via intracranial routes (Garrett 1988).

15 Sensory Nerves of Glandular Origin

Pain in the salivary gland region is a well-known phenomenon in response to gland swelling upon inflammation or sialolithiasis. Although the pain is usually attributed to an increase in the intercapsular tension and activation of afferent nerves of the glandular fascia (Leipzig and Obert 1979; Shapiro 1973), sensory nerves occur in the glands and are therefore likely to be involved in the response. Nerve fibres showing co-localization of substance P and calcitonin gene-related peptide are of sensory origin, and in the glands, these fibres are present in close connection with ducts and blood vessels (Ekström et al. 1988). The facial nerve and the great auricular nerve are pathways for this type of nerves of the parotid gland, originating from the trigeminal ganglion and dorsal root ganglia, respectively (Khosravani et al. 2006, 2008); in addition, the great auricular nerve innervates the parotid fascia (Zohar et al. 2002). The lingual nerve is thought to supply the submandibular and sublingual glands with sensory fibres of trigeminal origin. The periductal sensory nerves may serve protective functions. They may release defence substances from the duct cells (such as β-defensins) and by causing the myoepithelal cells to contract noxious substances may be expelled and ductal distension may be overcome. Substance P in combination with calcitonin gene-related peptide evokes protein extravasation and periglandular oedema (Asztély et al. 1998). Therefore, the perivascular sensory nerve fibres may be involved in gland swelling and gland inflammation. A role for sensory nerves in chronic inflammation has been pointed out, for instance, in asthma. In analogy, there might be a role for these nerves in chronic salivary gland inflammation. The levels of both substance P and calcitonin gene-related peptide increase following extirpation of the superior cervical ganglion (Ekström and Ekman 2005), a phenomenon that may be associated with the clinical condition of parotid post-sympathectomy pain upon eating (Schon 1985).

16 Hormones

Animal experiments demonstrate a long-term influence of sex steroids, growth hormone and thyroid hormones on salivary gland metabolism, morphology and secretory capacity (Johnson 1988). In humans, the development of postmenopausal hyposalivation illustrates the consequence of the loss of the continuous influence of oestrogen and progesterone (Meurman et al. 2009). The opposite, i.e. excessive salivation, has been reported during pregnancy (Jenkins 1978). Apart from the effect of circulating catecholamines from the adrenal medulla in response to sympathetic activity, little attention has been paid to a short-term hormonal influence on the glands and their secretion. Aldosterone-induced ductal uptake of sodium (without water), lowering the sodium concentration of the saliva, is a well-known phenomenon in the parotid gland of the sheep but in man the effect of aldosterone is small (Blair-West et al. 1967).

Recent investigations on the effects of some gastrointestinal hormones—gastrin, cholecystokinin and melatonin, the latter found in large amounts in the intestines—do, however, imply that the secretory activity of both animal and human salivary glands is, like other exocrine glands of the digestive tract, under the control of both nerves and hormones, and that the secretion from the salivary glands can be divided into three separate phases depending on the location from where the stimulus for secretion arises during a meal (Çevik-Aras and Ekström 2006, 2008; Ekström and Çevik Aras 2008; Çevik Aras et al. 2011; Loy et al. 2012, 2015). Thus, in addition to the well-known cephalic phase (nerves), a gastric phase (gastrin) and an intestinal phase (cholecystokinin and melatonin) may regulate salivary gland secretion. The hormones cause the secretion of proteins and stimulate the synthesis of secretory proteins but have little effect on the volume response.

It should be pointed out that gastrointestinal hormones such as cholecystokinin, gastrin and melatonin exert anti-inflammatory actions on salivary glands (Çevik-Aras and Ekström 2010).

17 Trophic Effects of Nerves: Gland Sensitivity to Chemical Stimuli and Gland Size

When the amount of a drug required to elicit a certain submaximal biological response diminishes the tissue is referred to as being supersensitive (Ekström 1999b; Emmelin 1965). Salivary glands, in particular, have been used as model organs to explore the phenomenon of supersensitivity. Depriving the glands of their receptor stimulation by trauma, surgery or pharmacology results in the gradual development of denervation supersensitivity. The sensitization is most pronounced in response to the loss of the influence of the postganglionic parasympathetic nerve. Restoration of a functional innervation normalizes the sensitivity. Experimentally, variations in the gland sensitivity can be brought about in animals supplied with functionally intact reflex arcs by varying the intensity of the reflex stimulation, the gland subjected to disuse (liquid diet) being more sensitive to stimuli than the gland subjected to overuse (chewing-demanding pelleted diet)—thus illustrating that the state of "normal sensitivity" is indeed a relative phenomenon (Ekström and Templeton 1977). Supersensitivity is attributed to intracellular events rather than to a change in the number of receptors on the cell membrane. The phenomenon is usually regarded as nonspecific but it seems, in fact, possible to demonstrate agonist-specific patterns associated with the degree of disuse of the various intracellular pathways (Ekström 1999b).

As might be expected, under physiological conditions the gland size is of primary importance for the volume response of the gland. Preclinical studies show that when the chewing-demanding diet is changed to a liquid diet in rats, the parotid gland loses about 50% of its dry weight, the amount of saliva secreted to *submaximal* muscarinic stimulus is reduced by 40% and the *maximally* evoked muscarinic volume response is reduced by 25% (Ekström and Templeton 1977). Parasympathetic postganglionic denervation causes a profound fall in gland weight (by 30–40%). However, loss of the action of acetylcholine on the gland is probably not the cause: prolonged treatment with the muscarinic antagonist atropine results in no fall in weight. Instead parasympathetic non-adrenergic, non-cholinergic transmission mechanisms maintain the gland weight, and induce mitotic activity in the glands (Ekström et al. 2007). The nature of the transmitter or transmitters involved is presently unknown.

As previously pointed out, salivary glands are supplied with β_1-adrenergic receptors (Ekström 1969). However, the sympathetic system seems to play a minor role in the regulation of gland size under physiological conditions. Although the β-adrenergic agonist isoprenaline is known to cause gland swelling after prolonged treatment of asthma in the past and isoprenaline in preclinical studies is known to increase gland weights severalfold (Barka 1965), sympathetic denervation only slightly, if at all, reduces gland weight. In agreement, treatment with the β_1-

adrenergic receptor antagonist metoprolol causes only a small fall in gland weight (Ekström and Malmberg 1984). It should be noted that the severalfold gain in weight to isoprenaline does not correspond to a similar increase in secretory capacity (Ohlin 1966).

18 Ageing

The secretory capacity is usually thought to decline with age. However, functional data do not support such an assumption (Österberg et al. 1992; Nagler 2004; Vissink et al. 1996). No doubt, the proportion of fat and fibrovascular tissue is gradually increasing with time and consequently the proportion of functional parenchyma decreases. However, despite these morphological changes, the secretory volumes of resting/unstimulated and stimulated saliva are only slightly affected, if at all. With respect to the salivary composition of saliva, the individuality of the glands comes to light since the parotid saliva composition is considered unchanged whereas the mucin secretion of the mucous/sero-mucous glands as well as the immunoglobulin A secretion of the labial glands is thought to decrease (Fig. 10).

A number of events, associated with ageing, will make salivary gland functions particularly vulnerable, and in concert, these events may eventually have implications for the production of the saliva. For instance, the intensity of the reflex activity diminishes due to loss in the number of olfactory and taste receptors as well as loss of teeth; the neuro-glandular junction widens, diminishing the amount of transmitters acting on the receptors; the blood levels of the sex steroids decrease; and the blood perfusion of the glands is reduced. To this list of changes, diseases and pharmaceutical drugs are added. In 70-year-olds, 64% of the women and 55% of the men were found to be on medication in a recent Swedish study; the average number of drugs was 4.0 in women and 3.3 in men (Johanson et al. 2015).

19 Xerostomia, Salivary Gland Hypofunction and Dry Mouth

Usually, the salivary secretion is estimated after an overnight fast or 2 h after a meal (Birkhed and Heintze 1989; Navazesh and Kumar 2008). To collect whole resting/unstimulated saliva, the subject, sitting in a chair, is instructed to swallow and then to lean the body forward, allowing the saliva to drip passively through a funnel into an (ice-chilled) graduated (or pre-weighed) cylinder for 15 min. The stimulated whole saliva is usually collected over 5 min: by paraffin-wax chewing, usually at a fixed frequency (for instance, 40

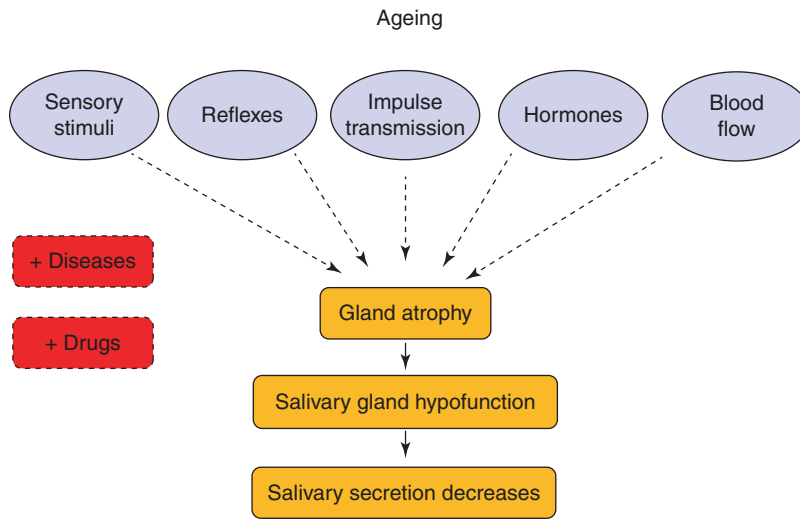

Fig. 10 Physiological changes at old age contributing to hyposalivation

or 70 strokes per min); by citric acid either applied on the dorsum of the tongue for 30 s or as a solution (2.5%) held in the mouth for 1 min; or by sucking a lemon-flavoured candy. The saliva pouring into the mouth is spat into a cylinder, preferentially at fixed intervals. The secretion is expressed per mL/min or per mg/min (the density of saliva is assumed to be 1.0 g/mL).

In humans, salivary ducts are not usually cannulated to measure the flow of saliva from individual glands. However, by applying the Lashley-Crittenden "cup" over the orifice of the parotid duct, the flow of parotid saliva can be recorded. Devices of various models have been constructed for the collection of submandibular/sublingual secretion—but here, saliva from the two types of gland is mixed. By the so-called Periotron method, saliva from the minor glands can be estimated (Eliasson and Carlén 2010). A filter paper is placed over a small area of the oral epithelium, and the fluid collected on the filter paper is measured using the change in conductance to indicate fluid.

A resting/unstimulated flow rate of whole saliva less than 0.1 mL/min and a stimulated flow rate of whole saliva less than 0.7 mL/min are considered to indicate *salivary gland hypofunction* (Ericsson and Hardwick 1978). *Xerostomia* is the subjective sensation of dryness of the oral mucosa. Importantly, xerostomia and salivary gland hypofunction may or may not be related phenomena—only about 55% of those complaining of xerostomia show, by objective measurement, a decrease in saliva volume (Field et al. 1997; Longman et al. 1995). The term *dry mouth* refers to the oral sensation of dryness with or without the demonstration of salivary gland hypofunction.

The thickness of the fluid layer covering the oral mucosa varies markedly, being 70 μm at the posterior dorsum of the tongue and 10 μm at the hard palate (DiSabato-Mordaski and Kleinberg 1996; Wolff and Kleinberg 1998). The volume of saliva in the mouth is dependent not only on the secretion of saliva but also on evaporation, absorption of fluid through the oral mucosa and swallowing. Mouth breathing and speaking are the main causes of the fluid loss by evaporation; the hard palate with its thin fluid layer is directly exposed to the flow of inspired air (Thelin et al. 2008). Excess of saliva in the mouth elicits a swallowing reflex. Usually, the volume of saliva that enters the mouth at rest exceeds the volume loss by evaporation and swallowing. Despite wide differences in the rate of resting/unstimulated secretion, a decrease by about 50% of this secretion in an individual will give rise to the sensation of oral dryness (Dawes 1987; Wolff and Kleinberg 1999). In this case, the thickness of the saliva film of the anterior dorsum of the tongue and the hard palate is less than 10 μm. It is also from these locations that the subject experiences the most pronounced symptoms of xerostomia (Wolff and Kleinberg 1999). A decrease in the labial secretion by only 20% is correlated to the feeling of oral dryness (Eliasson et al. 1996).

20 Causes of Dry Mouth

The prevalence of dry mouth is 15–40%. The condition is more common among women and increases with age (Österberg et al. 1984; Nederfors et al. 1997). Dry mouth dramatically impairs the quality of life (Ship et al. 2002; Wärnberg et al. 2005), and is both a physical and a social handicap. It is associated with difficulties in chewing, swallowing and speaking. The lips are cracked and dry. Taste acuity weakens and oral mucosal infections, dental caries and halitosis develop. Among known causes of dry mouth are chronic gland inflammation as Sjögren's syndrome, diabetes, depression, head and neck radiotherapy, radioiodide therapy, HIV/AIDS, orofacial trauma, surgery and use of medications (Grisius and Fox 1988). Drugs presently in use may interfere with the reflexly elicited secretion at the level of the central nervous system and/or at the level of the neuro-glandular junction (Villa et al. 2016). In this connection it should be remembered that the salivary glands are effectors of the autonomic nervous system and that they are supplied with the same set of receptor types as other effector organs of this system. Consequently, when treating a dysfunction of an effector within this system by interfering with the

transmission mechanisms, e.g. overactive urinary bladder (by muscarinic receptor antagonists) or hypertension (see below), the functions of the salivary glands are invariably influenced. Drugs with antimuscarinic actions cause a marked reduction in the volume of saliva produced. It should be noted that although the volume is not always changed to any great extent, the composition of the saliva may have undergone changes resulting in the subjective feeling of oral dryness. The use of drugs belonging to the cardiovascular category or the psychotropic category is particularly correlated with a decreased rate of secretion as side effect. Antihypertensive drugs may block α_1-adrenergic receptors and β_1-adrenergic receptors, and stimulate pre-junctional (neuronal) α_2-adrenergic receptors (that inhibits the transmitter release). Though diuretics in in vitro experiments influence various electrolyte exchange processes in the glands (Poulsen 1998) and dry mouth is a common complaint in response to the treatment with diuretics, the salivary flow rate in humans is only slightly affected, if at all (Atkinson et al. 1989; Nederfors et al. 1989). Oral mucosal tissue dehydration has been suggested as cause of the dry mouth feeling. Anti-arrhythmics block β_1-adrenergic receptors and exert anticholinergic effects. Apart from the central action of antidepressants, this group of drugs blocks peripherally the muscarinic receptors. Antipsychotics, particularly those of the first generation, are notorious for jeopardizing the oral health; besides being dopamine antagonists, they have affinity for a number of receptors and exert both antimuscarinic and anti-α_1-adrenergic actions. Importantly, when one set of receptor type is blocked not only is the response itself mediated by this particular receptor abolished but the synergistic interaction provided by the receptor is also abolished.

Several hundred drugs are said to be xerogenic, and dry mouth is the third most common side effect of drug treatment. It is important to realize that reference guides to drugs causing dry mouth are usually put together based on the sensation of oral dryness rather than on the actual measurement of the saliva output. However, an evidence-based list of the medications causing salivary gland hypofunction and/or xerostomia, sponsored by the World Workshop on Oral Medicine VI, was recently published (Wolff et al. 2017). There is a correlation between the total intake of the number of drugs and dry mouth (with or without hyposalivation). The use of four drugs or more increases the probability for the phenomenon of dry mouth to appear. By increasing the number of drugs the chance of consuming a drug producing dry mouth by itself or by its interaction with other drugs is likely to increase.

21 Treatment of Dry Mouth

The options to treat dry mouth are, unfortunately, limited and focused on maintaining the salivary reflexes by flavoured gums or lozenges, or by the use of salivary substitutes such as artificial saliva, oral rinses and oral gels. These treatments are of short duration. In addition, a scrutiny of the medication list may make it possible to achieve a reduction in the number of drugs taken by the patients or in the dosage of individual drugs and, in addition, a replacement with drugs of less xerogenic effects may take place. A number of drugs for systemic use have been introduced such as parasympathomimetics, cholinesterase inhibitors, bile-stimulating agent anethole trithione, the mycolytic agents bromhexine and guaifenesin, the immune-enhancing substance alpha interferon, the cytoprotective amifostine and the antimalarial drug hydroxychloroquine. In many cases, the clinical effects are questionable and moreover some of these drugs are associated with serious side effects. The parasympathomimetics pilocarpine (Salagen®) and cevimeline (Evoxac®) stimulate the flow of saliva but may also cause nausea, sweating, gastrointestinal discomfort, respiratory distress, urges to bladder emptying and hypotension. Recent clinical trials, using topical application of the cholinesterase physostigmine on the oral mucosa, have demonstrated local treatment of dry mouth as an alternative approach to the systemic treatment (Khosravani et al. 2009). After diffusion of the drug through the mucosal barrier, the underlying mucin-producing minor glands are stimulated to secrete, while at the same time the systemic effects are minimized.

Electrostimulation of the lingual nerve, by an intraoral device, may be a promising approach to cause relief of xerostomia and increase in salivary flow rate, while at the same time avoiding side effects, as judged by the outcome of clinical trials including patients suffering from Sjögren's syndrome (Alajbeg et al. 2012). Since the lingual nerve carries efferent (parasympathetic) nerves for the submandibular and sublingual glands, and afferent nerves of the salivary reflex arch, such an approach is likely to elicit the secretory activity of additional salivary glands, including the parotid glands. Besides its acute secretory effect, the electrostimulation is likely to release non-adrenergic, non-cholinergic trophic mediators (of unknown nature) that increase the mitotic activity of the salivary glands (Ekström et al. 2000; Ekström and Reinhold 2001), and thus promoting gland regeneration. Emerging approaches to repair salivary glands involve gene therapy by the use of viral vectors, transplantation of stem/progenitor cells and bioengineered tissue for salivary gland replacement (Lombaert et al. 2017).

The patient suffering from dry mouth should maintain a meticulous oral hygiene including the use of a fluoride-rich gel, frequent visits to the dental hygienist and, in addition, avoiding food and beverages that are sweet, acidic or carbonated.

22 Sialorrhoea

Neuromuscular dysfunctions associated with cerebral palsy, Parkinson's disease, amyotrophic lateral sclerosis and stroke are examples of conditions that cause drooling. Under these conditions, saliva pools in the mouth due to lack of swallowing rather than to an increased rate of secretion of saliva (Young et al. 2011). Systemic use of antimuscarinics, local injections of botulinum toxin in the major glands, salivary duct ligations or surgical repositioning of salivary ducts are examples of measures that may be undertaken (Khadivi et al. 2013; Martin and Conley 2007; Petracca et al. 2015). An increase in the rate of secretion may occur in the treatment of Alzheimer's disease and myasthenia gravis due to the medication with reversible cholinesterases (Freudenreich 2005; Ecobichon 1995). Mixed secretory actions, dry mouth and sialorrhoea occur in response to clozapine, the flagship of atypical antipsychotics (i.e. the second generation of antipsychotics), used when traditional antipsychotics fail to treat schizophrenia. Clozapine is a dopamine receptor antagonist but, in addition, has affinity for a number of various receptor types. Sialorrhoea is reported as side effect of clozapine in about one-third of the patients (Praharaj et al. 2010). During the night, the patients are troubled with choking sensations and the aspiration of saliva. During daytime, drooling occurs. The situation may be so bothersome that the drug regimen is discontinued. The phenomenon has been largely unexplained, and some authors have referred it to a weakened swallowing reflex. A number of various categories of drugs have been suggested for the treatment of clozapine-induced hypersalivation, usually with limited success and with side effects of their own (Sockalingam et al. 2007). Preclinical studies do show that both clozapine and its main metabolite *N*-desmethylclozapine exert mixed actions on the salivation and further the studies offer an explanation to the dual actions, and may serve as a rationale for treatment options (Ekström et al. 2010a, b; Godoy et al. 2011). The drugs are *antagonists* to muscarinic M3 receptors and α_1-adrenergic receptors and *partial agonists* to muscarinic M1 receptors of the acinar cells. Upon high demands on the reflex secretion, such as during a meal, the flow rate of saliva will be lower than expected due to the antagonistic actions of clozapine/N-desmethylclozapine. During sleep (when the secretion is spontaneous) and at rest during daytime (when a low-graded reflexly elicited secretion adds to the spontaneous secretion), the flow rate of saliva will be higher than expected due to the agonistic action by clozapine/N-desmethylclozapine. In addition, the parasympathetic co-transmitter vasoactive intestinal peptide (by VIP-receptors) and the sympathetic transmitter noradrenaline (by β_1-receptors) are likely to interact synergistically with clozapine/N-desmethylclozapine (by

muscarinic M1 receptors), a synergism that probably will contribute to the increased volume response at rest (Ekström et al. 2014). Although amisulpride—another atypical antipsychotic but with high selectivity for dopamine receptors—is among suggested drugs to treat clozapine-induced sialorrhoea, preclinical studies reveal unexpected secretory effects of amisulpride (Godoy et al. 2011, 2012). While amisulpride does not inhibit ongoing clozapine-induced secretion, it enhances, by a direct action at the gland level, secretory responses evoked by reflex secretion and autonomic drugs without causing secretion on its own. Ultrastructural investigations of both animal and human glands show amisulpride to put the acinar cells in a state of readiness for secretion (Loy et al. 2013).

It may be worth keeping in mind that with respect to the oral health, salivary secretion in patients under treatment with antipsychotics should, in most cases, be regarded as a beneficial side effect that should be preserved rather than abolished.

23 Protein Components of Human Saliva and Post-translational Modifications

The recent availability of mass spectrometry (MS)-based techniques applicable to the study of complex protein mixtures has stimulated the effort to obtain a qualitative and quantitative comprehensive understanding of the protein composition of saliva.

Indeed, mass spectrometry techniques are capable of identifying and quantifying thousands of protein components in complex samples. The mass spectrometer makes it possible to obtain precise mass values through the measure of the mass-to-charge (m/z) ratio of the ions generated from peptides and proteins at the source. Selected ions may also be submitted to a fragmentation process (this technique is called MS/MS), and the determination of the m/z ratio of the fragments allows the peptide structure to be investigated. Thus, the power of MS relies on the possibility to obtain information not only on the exact mass value of a given peptide/protein, but also on its sequence. Two main strategies may be used to investigate protein mixtures: the top-down and the bottom-up approach. In the bottom-up approach the non-fractionated sample is submitted to digestion, typically by trypsin, and the resulting digestion mixture fractionated and analyzed by MS. Thus, presence and quantification of the proteins in the sample are inferred from the ensemble of identified digestion peptides, supposing that any peptide identified derives from a unique protein. Even though this approach is of high throughput, the digestion step introduces a limitation, since relevant naturally occurring cleavages may obviously not be disclosed. The top-down approach overcomes this problem, since peptide and protein separation followed by MS analysis is performed on undigested samples. However, top-down platforms often cannot cover the entire proteome, because some proteins could escape from the analysis (e.g. proteins insoluble in acidic milieu).

High-performance liquid chromatography (HPLC) is more suitable than gel electrophoresis as separation step technique for the analysis of the salivary proteome, since it is mainly represented by peptides and small/medium-size proteins. Moreover, with respect to gel electrophoresis, HPLC offers the advantage that MS analysis can be performed online; that is, peptides and proteins are submitted directly to the ion source of the MS apparatus.

24 The Salivary Proteome

Most of the about 3400 different proteins of whole saliva characterized in recent years by proteomic studies are not of glandular origin but probably originate from exfoliating epithelial cells and oral microflora. Proteins of gland secretion origin should be not more than 200–300 and they represent more than 85% by weight of the salivary proteome (Fig. 11). They belong to the following major families: α-amylases, carbonic

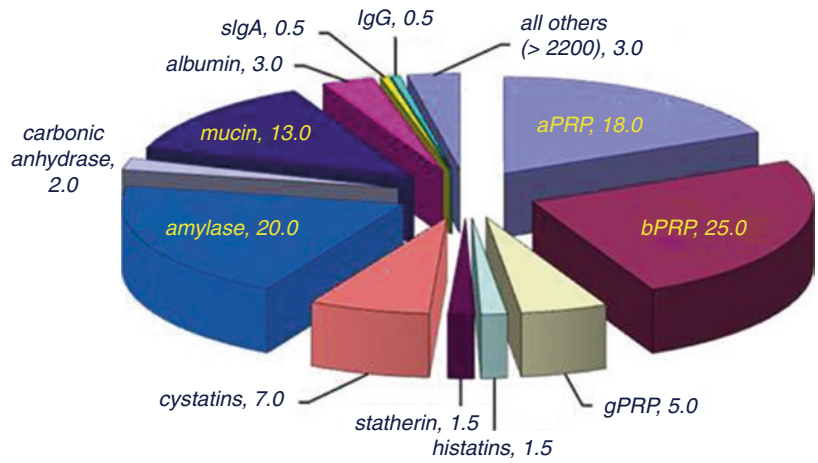

Fig. 11 Approximate percentages (w/w) of the different protein families present in human adult whole saliva, assuming a comparable contribution of parotid and submandibular/sublingual glands (modified from Messana et al. 2008b)

anhydrase, histatins, mucins, proline-rich proteins (PRPs), further divided in acidic (aPRPs), basic (bPRPs) and basic glycosylated (gPRPs), statherin, P-B peptide and S (salivary)-type cystatins (Fig. 11).

The function, origin and encoding genes of the major salivary proteins are reported in Table 1, together with the name of mature proteins and the main post-translational modifications occurring before, during and after secretion.

Histatins are a family of small peptides, the name referring to the high number of histidine residues in their structure. All the members of this family arise from histatin 1 and histatin 3, sharing very similar sequences and encoded by two genes (HTN1 and HTN3) located on chromosome 4q13 (Sabatini and Azen 1989). Statherin is an unusual tyrosine-rich 43-residue phosphorylated peptide involved in oral cavity calcium ion homeostasis and teeth mineralization (Schwartz et al. 1992). Its gene (STATH) is localized on chromosome 4q13.3 (Sabatini et al. 1987), near to the histatin genes. Usually P-B peptide is included in the basic proline-rich protein family. However, it is the product of PROL3 gene localized on chromosome 4q13.3, very close to the statherin gene, and several characteristics of P-B peptide suggest a functional relationship with statherin (Inzitari et al. 2006). Salivary cystatins comprise cystatin S, SN and SA; they are inhibitors of cysteine proteinases and this property suggests its role in the protection of the oral cavity from pathogens and in the control of lysosomal cathepsins (Bobek and Levine 1992). Cystatin S1 and cystatin S2 correspond to mono- and di-phosphorylated cystatin S, respectively. The loci expressing all the S cystatins (CST1–5) are clustered on chromosome 20p11.21 together with the loci of cystatins C and D. While cystatin SA seems to be specifically expressed in the oral cavity, cystatin S and SN have also been detected in other body fluids and organs, such as tears, urine and seminal fluid (Dickinson 2002; Ryan et al. 2010). Human salivary acidic proline-rich proteins consist of five principal isoforms codified by two distinct loci called PRH1 and PRH2 localized on chromosome 12p13.2. They show an acidic character in the first 30 amino acid residues of the amino-terminal region; the remaining part is basic and, similarly to basic proline-rich proteins, shows repeated sequences rich in proline and glutamine. Basic and glycosylated (basic) proline-rich proteins are the most complex group of salivary peptides, encoded by four different genes named PRB1–PRB4 clustered on chromosome 12p13.2. Numerous homologous and unequal crossing over are present within the tandem repeats of the third exon, producing frequent length polymorphisms.

Salivary amylases consist of two families of isoenzymes, called A and B, each family comprising three isoforms whose differences are

Table 1 Families of major salivary proteins: function, origin, genes, name of mature proteins and main post-translational modifications (*PTMs*)

Family	Function	Origin	Gene	Mature proteins	Other PTMs
α-Amylases	Antibacterial, digestion, tissue coating	Pr Sm/Sl	*AMY1A*	α-Amylase 1	Disulfide bond, N-glycosylation, phosphorylation, proteolytic cleavages
Acidic PRPs	Lubrication, mineralization, tissue coating	Pr Sm/Sl	*PRH1, PRH2*	Db-s, pa, PIF-s, pa 2-mer, Db-f, PIF-f, PRP-1, PRP-2, PRP-3, PRP-4, P-C peptide	Disulfide bond, further proteolytic cleavages, phosphorylation, protein network
Basic PRPs Glycosylated PRPs	Binding of tannins, tissue coating Antiviral, lubrication	Pr	*PRB1, PRB2 PRB3, PRB4*	II-1, II-2, CD-IIg, IB-1, IB-6, IB-7, IB-8a (Con1−/+), P-D, P-E, P-F, P-J, P-H, proline-rich protein Gl 1–8, protein N1, salivary proline-rich protein Po	Disulfide bond (Gl 8), further proteolytic cleavages N- and O-glycosylation, phosphorylation, protein network
Carbonic anhydrase VI	Buffering, taste	Pr Sm	*CA6*	Carbonic anhydrase 6	Disulfide bond, glycosylation
Cystatins	Antibacterial, antiviral, mineralization, tissue coating	Pr Sm/Sl	*CST1,CST2 CST3, CST4 CST5*	Cystatin SN, cystatin SA, cystatin C, cystatin S and cystatin D	Disulfide bond, O-glycosylation, phosphorylation, sulfoxide, truncated forms
Histatins	Antifungal, antibacterial, mineralization, wound healing	Pr Sm/Sl	*HTN1, HTN3*	Histatin 1, histatin 2, histatin 3, histatin 5, histatin 6	Further proteolytic cleavages, phosphorylation, sulfation
Lactoferrin	Antibacterial, antifungal, antiviral, innate immune response	All salivary glands	*LTF*	Lactoferrin	Disulfide bond, glycosylation, phosphorylation
Lysozyme	Antibacterial	Pr Sm	*LYZ*	Lysozyme C	Disulfide bond
Mucins	Antibacterial, antiviral, digestion, lubrication, tissue coating	All salivary glands	*MUC5B, MUC19 MUC7*	Mucin-5B, mucin-19 Mucin-7	Disulfide bond, N- and O-glycosylation, phosphorylation
Peptide P-B	Not defined	Pr Sm/Sl	*SMR3B (PROL3)*	Proline-rich peptide P-B	Proteolytic cleavages
Statherins	Inhibits crystal formation, lubrication, mineralization, tissue coating	Pr Sm/Sl	*STATH*	Statherin, statherin SV2	Phosphorylation, proteolytic cleavages, protein network

Pr Parotid, *Sm/Sl* Submandibular/sublingual, *GCF* Gingival crevicular fluid
Modified from Castagnola et al. (2011b)

connected to different post-translational modifications (Scannapieco et al. 1993).

Salivary mucins are divided into two distinct classes: the large gel-forming mucins (MG1), and the small soluble mucins (MG2). MG1 represents a heterogeneous family of 20–40 m Da glycoproteins expressed by MUC5B, MUC4 and MUC19 genes (Offner and Troxler 2000; Thomsson et al. 2002). MG2, a much smaller mucin of 130–180 kDa, is the product of the MUC7 gene mapped to chromosome 4q13-q21 (Bobek et al. 1996). Mucins are comprised of approximately 15–20% protein and up to 80% carbohydrate, present largely in the form of serine and threonine O-linked glycans (Strous and Dekker 1992; Gendler and Spicer 1995). The polypeptide backbone can be divided into three regions: the central region contains tandemly repeated sequences of 8 to 169 amino acids. This domain serves as the attachment site for the O-glycans, and each mucin has a unique, specific tandem-repeat sequence. Many mucins with monomeric molecular weights greater than 2 m Daltons form multimers more than ten times bigger than that size.

25 Proteome of Human Minor Salivary Gland Secretion

Labial minor salivary gland secretion from healthy volunteers analyzed by liquid chromatography-electrospray ionization-tandem mass spectrometry led to the identification of 56 proteins, 12 of which had never been identified in any salivary secretion. Among the known salivary proteins, typical members of immunoglobulins, proline-rich proteins, cystatins (A, B, D, SN), mucins, histatins, calgranulins and amylase were identified, in relative proportions similar to those found in major gland secretions, with the exception of immunoglobulins which were found more represented. Among the new salivary proteins (21% of all proteins identified) fatty acid synthase was recognized (Siqueira et al. 2008).

26 Polymorphism of the Salivary Proteome

The human salivary proteome shows a high interindividual variability. The different isoforms of salivary proteins may be genetic in origin (different alleles codifying acidic proline-rich proteins, basic proline-rich proteins, mucins, cystatins; differential splicing), but may also derive from several post-translational modifications which occur during the trafficking of the proteins through the secretory pathway and after secretion.

One of the better known examples of polymorphism and modifications occurring *before, during and after* secretion concerns acidic proline-rich proteins. The two loci which encode acidic proline-rich proteins show different alleles. PRH2 locus is bi-allelic, and the expression products are PRP-1 and PRP-2 proteins. The alleles of PRH1 locus are three and they express Pif-s (parotid isoelectric-focusing variant, slow), Db-s (double band, slow) and Pa (parotid acidic protein) proteins (Inzitari et al. 2005). All the isoforms are N-terminally modified (pyro-glutamic moiety) and submitted to phosphorylation before granule storage. The major derivatives are di-phosphorylated, but low levels of mono-phosphorylated and tri-phosphorylated forms are also detected in saliva. Another important modification is the cleavage. Before granule storage PRP-1, PRP-2, Pif-s and Db-s are in part cleaved at the Arg_{106} residue by a specific enzyme of the convertase family. Cleavage generates four truncated derivatives, called PRP-3, PRP-4, Pif-f and Db-f, and a common C-terminal peptide of 44 amino acids, called P-C peptide (Messana et al. 2008a). Pa isoform is not cleaved, since the substitution $Arg_{106} \rightarrow Cys$ eliminates the consensus sequence recognized by the proteinase. However, the cysteine residue generates a disulfide bridge and only the Pa dimeric form may be detected in whole saliva.

Also histatins, statherin, P-B peptide and principally basic proline-rich proteins undergo proteolytic cleavage before granule storage and

during secretion, but the entire forms of basic proline-rich proteins, differently from the other salivary proteins, are not detected in saliva (Messana et al. 2008a). Following proteolytic cleavage many salivary peptides are also submitted to the removal of C-terminal residues by the action of specific carboxypeptidases, and this modification is considered an event common to all the secretory processes (Steiner 1998). An important example concerns the formation of histatin 5 from histatin 6. The two histatins derive from the parent peptide of 32 amino acid residues called histatin 3. Histatin 3, from the presence of the RGYR↓ convertase consensus sequence recognized by an unknown, but specific, proteinase acting before granule storage, generates histatin 6 (histatin 3 fr 1/25). Subsequently, an unknown carboxypeptidase removes the C-terminal Arg residue generating histatin 5 (histatin 3 fr 1/24). Sequentially, histatins 5 and 6 are submitted to further proteolytic cleavages after granule secretion as shown in Fig. 12 (Castagnola et al. 2004; Messana et al. 2008a).

Before granule storage salivary proteins are also submitted to phosphorylation, glycosylation and sulfation. Salivary glycosylated proteins are MG1, MG2, gPRPs and amylase (Ramachandran et al. 2006). The glycomoiety may be N- and/or O-linked and the sugars show the same architectures demonstrated for other glycoproteins (Guile et al. 1998). In the same way, the tyrosylprotein sulfotransferase (TPST) involved in the polysulfation of histatin 1 seems the same enzyme acting in other tissues (Cabras et al. 2007).

The salivary proteome changes dynamically also after secretion under the action of endogenous and exogenous enzymes, the latter derived from microorganisms resident in the oral cavity. For instance, it has been demonstrated that a glutamine endoproteinase localized in the dental plaque—likely of microbial origin—generates in the oral cavity a lot of small fragments (from 7- to 20-amino acid residues) from different basic proline-rich proteins (Helmerhorst et al. 2008). Another important modification occurring in the oral cavity is the formation of cross-linked derivatives of salivary proteins, generating a protective proteinaceous network on tooth surfaces (enamel pellicle) and oral mucosa. This protein film is important for the integrity of tooth enamel, because it acts as a boundary lubricant on the enamel surface (Douglas et al. 1991). Moreover, interactions between pellicle proteins and bacterial surfaces are responsible for specificity of the bacterial colonization during

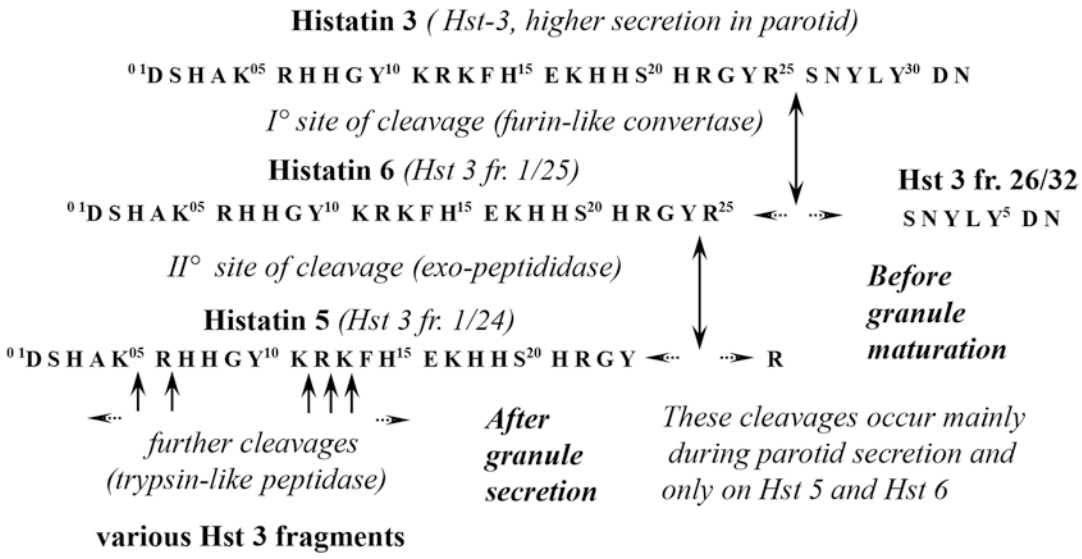

Fig. 12 The sequential proteolytic cleavage of histatin 3, which generates histatin 6 and histatin 5, before granule maturation, and a multitude of other fragments after granule secretion (from data reported in Castagnola et al. 2004; Messana et al. 2008a)

the earliest stage of plaque formation (Gibbons and Hay 1988). This protein network could also interact with the oral epithelial-cell plasma membrane and its associate cytoskeleton and might contribute to the mucosal epithelial flexibility and turnover. Histatins, statherin and aPRPs are among the proteins involved. It has been indeed demonstrated that acidic proline-rich proteins, statherin and major histatins are substrates of oral transglutaminase 2 and they participate in cross-linking reactions (Yao et al. 1999).

After the outstanding review on the genetic polymorphisms of human salivary proteome published in 2007 by Oppenheim and co-workers (Oppenheim et al. 2007), other polymorphisms of salivary proteins have been characterized. Halgand et al. (2010) demonstrated the existence of two new variants of peptide P-C differing by the nominal mass of ±1 Da and probably deriving from DNA slippage or differential mRNA splicing and by the occurrence of a single-nucleotide polymorphism (Halgand et al. 2010). Recently, during a screening of the acidic soluble fraction of about 200 human adult whole-saliva samples, a new isoform called PRP-1 Roma-Boston $pSer_{22} \rightarrow Phe$ (PRP-1 RB) has been characterized in three subjects. The top-down high-resolution MS/MS spectra allowed discriminating the variant from PRP-1 and PRP-2 proteoforms (the last differing only for 1 Da) and defining the three phenotypes (Iavarone et al. 2014). A bPRP with an average mass of 10433.5 Da, detected in whole saliva and in parotid secretory granules (Messana et al. 2004, 2008a), was characterized and named P-Ko by Halgand and colleagues (Halgand et al. 2012), who also found a variant of II-2 peptide, lacking the proline residue at position 39. A contribution to bPRP heterogeneity derives from *N*- and *O*-glycosylations that give rise to the family of glycosylated PRPs. Six glycosylated protein species of IB-8a Con1$^+$, *N*-glycosylated at Asn_{98}, have been characterized together with the nonglycosylated protein, in adult human saliva by HPLC-ESI-MS (Cabras et al. 2012a, b). A biantennary N-linked glycan fucosylated in the innermost N-acetylglucosamine of the core and showing from zero to four additional fucoses in the antennal region was present in five of the glycoforms, a monoantennary monofucosylated oligosaccharide in the sixth one. The glycoforms were detected on 28 of 71 adult saliva specimens. A heterogeneous mixture of glycosylated derivatives of the human basic salivary proline-rich protein 3 M (bPRP 3 M) was detected as one of the major components of the acidic soluble fraction of human whole saliva in the first years of life. The mixture of proteoforms derives from the combination of eight different neutral and sialylated glycans O-linked to threonine 50, and 33 different glycans N-linked to asparagine residues at positions 66, 87, 108, 129, 150, 171, 192 and 213 of bPRP 3 M (Manconi et al. 2016). Several polymorphisms of MUC5B have been recently associated to the susceptibility to idiopathic-pulmonary fibrosis (Lee and Lee 2015) while genetic polymorphisms of MUC7 were associated to periodontitis (Gomes et al. 2011).

27 Physiological Variability

Composition of oral fluid varies depending on various factors. It has already been reported that the contribution of the different salivary glands to whole saliva in resting/unstimulated and stimulated conditions is different, and parotid saliva is the prevalent contributor to stimulated saliva. It has also been demonstrated that protein composition of mixed submandibular/sublingual saliva is different from that of parotid saliva (Table 2). For instance, the levels of acidic proline-rich proteins, histatin 1 and α-amylases are higher in parotid than in submandibular/sublingual saliva. Conversely, S-cystatins are more concentrated in submandibular/sublingual saliva. Furthermore, the secretion of some peptides is gland specific, and basic proline-rich proteins are secreted only by the parotid glands. Finally, it may be noted that among the other proteins detected in whole saliva, α-defensins 1–4 and β-thymosins 4 and 10 originate mainly from gingival crevicular fluid (Pisano et al. 2005).

As a consequence, the salivary output is characterized by variations not only of the flow rate but also of the protein concentration and composition.

Table 2 Different contributions to salivary peptides and proteins

Peptide or family	Parotid glands	Sm/Sl glands	Plasma exudate	GCF
Acidic PRP (all the isoforms)	••••	•••		
Basic PRP	••••			
Basic glycosylated PRP	•••			
Histatin 3	••••	•••		
Histatin 1	•••	•••		
Statherin	••••	••••		•
P-B peptide	••	••••		•
"S-type" cystatins	•	••••		
Amylase	••••	•		
MG1		••••		
MG2		•••		
Albumin			••	••
Thymosins β_4 and β_{10}			?	••
α-Defensins 1–4			•	••

GCF gingival crevicular fluid, *Four circles* high contribution, *three circles* medium contribution, *two circles* low contribution, *one circle* very low contribution, *question mark* unknown
Modified from Messana et al. (2008b)

Age is another important factor affecting protein saliva composition. A recent study performed on human preterm newborns demonstrated the profound difference in the protein composition of their saliva with respect to that of adults (Castagnola et al. 2011a). Indeed, in saliva from preterm human newborns more than 40 protein masses usually undetected in adult saliva were revealed. Among them, stefin A and stefin B (three isoforms), S100A7 (two isoforms), S100A8, S100A9 (eight isoforms), S100A11, S100A12, small proline-rich protein 3 (two isoforms), lysozyme C, thymosins β4 and β10, antileukoproteinase, histone H1c and α- and β-globins were identified. Salivary concentration of these proteins decreased as a function of post-conceptional age, reaching the values observed in full-term newborns at about 270 days of post-conceptional age, and the values observed in adult whole saliva later in development. Interestingly, the shape of decrease for many proteins was different, suggesting that the variations were connected to coordinate and hierarchical actions of these proteins. Many of the identified proteins are candidates as tumour markers in the adult. This observation led to the suggestion that during foetal development the interplay between these proteins contributes to the molecular events that regulate cell growth and death. A preliminary study showed that salivary glands are responsible for the high levels of oral thymosin β_4 detected in preterm newborn saliva, while in adult saliva this peptide is primarily derived from crevicular fluid (Inzitari et al. 2009; Nemolato et al. 2009). These studies suggest that salivary glands switch their secretion to adult salivary proteins only after the normal term of delivery.

Whereas basic proline-rich proteins in whole saliva do not reach their mature concentration levels until the age of adolescence (Cabras et al. 2009), other proteins show mature levels as early as at an age of 3 years or show variable concentrations as a function of the age, i.e. acidic proline-rich proteins, histatin 1, histatin 5, histatin 6 and cystatins S. For instance, acidic proline-rich proteins show a minimum of concentration around 6–9 years of age, probably in connection with events occurring in the mouth during the replacement of the deciduous dentition. A process called "exfoliation" might cause a decrease of specific salivary protein and peptide concentration, due to their recruitment to dental and gingival surfaces. The higher concentration of histatin 1 around 3–5 years of age is of particular interest, since it may be associated with its recently demonstrated wound-closing properties (Oudhoff et al. 2008).

Further investigations on the physiological variability of the human salivary proteome confirmed that age represents a major factor influencing human salivary protein pattern, particularly in the first years of age. Indeed, two studies highlighted that deep variations occur on the salivary proteome during human development and that proteins peculiar of the adults appear in saliva with different time courses. The salivary proteome of human children from birth to 48 months of age showed important quantitative modifications, and, with the exception of

statherin and histatin 5, the concentrations of the major salivary proteins showed a minimum between 0 and 6 months of age when their expression in salivary glands is probably not fully activated. Concentration of histatin 1 showed the highest value between 7 and 12 months of age, followed by a decrease, suggesting a possible role in the phenomenon of eruption of primary dentition (Manconi et al. 2013). A longitudinal study performed on saliva of preterm newborns from birth up to 1 year of age, and subjects ranging in age from 0 to 17 years and from 27 to 57 years, allowed to complete the picture of the variations of the salivary proteome during human development. Among the proteins typically detected in the adult human saliva, acidic proline-rich proteins and glycosylated bPRP3M were the first to be detectable, followed by histatin 1, statherin and P-B peptide. S-type cystatins appeared only at 1 year, and basic proline-rich proteins at 4 years of age. Moreover, on the basis of the phosphorylation level of acidic proline-rich proteins, statherin and histatin 1 it was evidenced that the activity of Fam20C kinase reached levels comparable to adults at about 2 years of age (Messana et al. 2015). To increase knowledge on variations of the salivary proteome during development, the acid-insoluble fraction of whole saliva from adults, preterm and at-term newborns has also been investigated by 2-DE coupled to HPLC–high-resolution ESI–MS/MS (Arba et al. 2016). Three over-expressed proteins in at-term newborns with respect to preterm newborns and adults bactericidal permeability-increasing protein (BPI) fold-containing family A member 1, annexin A1 and keratin type 1 cytoskeletal 13, and several over-expressed proteins in adults (fatty acid-binding protein, S100 A6, S100 A7, S100 A9, prolactin-inducible protein, Ig kappa chain, cystatin SN, cystatin S/SA and α-amylase 1), were characterized.

28 Function of Salivary Proteins

No doubt exists about the fundamental role of saliva and its protein content in the protection of oral mucosa and teeth. It is enough to consider the devastating macroscopic effects detectable in the oral cavity of patients affected by severe Sjögren's syndrome. The mucosal epithelium is subjected to wounds and infections. The dental arc is compromised by recurrent periodontitis and caries. It is, however, very difficult to establish, at the molecular level, not only the specific role played by each salivary protein in the oral safeguard but also the interactions between the different salivary proteins in their protection of the mouth and, since saliva is swallowed, of the entire digestive tract. Some roles seem evident, such as the lubricating and protecting role of mucins, or the buffering properties of carbonic anhydrase, as reported in Table 1. The high concentration of salivary amylase is traditionally associated with starch pre-digestion. However, due to the low enzymatic activity of the enzyme, some researchers are convinced that oral amylase plays a presently not specified role in the protection of the mouth.

The information obtained by the recent proteomic studies are clue and stimulus for the comprehension of the roles of the different families of salivary proteins in the oral cavity. For instance, it is challenging to decipher the significant qualitative and quantitative differences in gland secretions, which suggest specific molecular requirements for different oral districts. Other suggestions could emerge from the variations observed in protein composition during the paediatric age which could offer valuable information on possible functions.

Except for their tannin-binding properties (Lu and Bennick 1998), the function of basic proline-rich proteins is still not completely defined. Several studies demonstrated that an unidentified component of basic proline-rich protein family displayed antiviral activity against HIV (Robinovitch et al. 2001), and a peptide fragment of ten amino acid residues considerably inhibited *Propionibacterium acnes* growth (Huang et al. 2008) revealing interesting antiviral properties for peptide fragments related to basic proline-rich proteins. These studies were in agreement with recent researches showing that a 20-residue proline-rich fragment, named p1932, was internalized within primary gingival fibroblast cell

lines and within the nuclei of squamous cancer cell lines (Radicioni et al. 2015). This basic proline-rich proteins fragment showed a dose-dependent antagonistic effect on the cytosolic Ca^{2+} mobilization induced by progesterone in a tongue squamous carcinoma cell line. The activity of the peptide resides in the C-terminal region characterized by a four-proline stretch flanked by a lysine residue. The progesterone receptor involved in the peptide action was probably PRGMC1 suggesting a modulation role of the peptide mediated by this receptor (Palmerini et al. 2016). A PxxP motif in the primary structure of p1932 is characteristic for intracellular targets of the SH3 domain family. Surface plasmon resonance spectroscopy showed that Fyn, Hck and c-Src SH3 domains interact with the peptide with dissociation constants ranging from nanomolar to micromolar values suggesting its role as a modulator of the signal transduction pathways mediated by the Src kinase family (Righino et al. 2016). Moreover, recent studies showed that bitter taste sensitivity responsiveness to 6-n-propylthiouracil in subjects genotyped for TAS2R38 and gustin gene polymorphisms is associated to the level of two basic proline-rich proteins, namely II-2 and Ps-1 (Cabras et al. 2012a, b), suggesting that specific basic proline-rich proteins are involved in taste perception.

Acidic proline-rich proteins are responsible for the modulation of the salivary calcium ion concentration and are involved in the formation of acquired enamel pellicle and oral mucosal pellicle, networks originated by cross-linking of the proteins due to the action of transglutaminase 2. However, no information is available on the functional differences exerted by the entire and truncated isoforms or on the possible role of the P-C peptide, the C-terminal peptide deriving from the cleavage of all the isoforms of acidic proline-rich proteins.

The majority of salivary peptides and proteins are directly or indirectly involved in innate immunity and in the modulation of the oral microflora (Gorr 2009). In this respect, the antifungal activity shown by histatin 3 and its fragments on *Candida albicans* species are particularly interesting. Recently, it has been demonstrated that histatin 3 binds to heat-shock cognate protein 70 (HSC70) during the G1/S transition in human gingival fibroblasts (Imamura et al. 2009), it prevents ATP-dependent dissociation of HSC70-p27 complex and it induces DNA synthesis. These findings suggest that histatin 3 may also be involved in oral cell proliferation.

Recently, it was shown that histatin 1 displays wound-healing activity (Oudhoff et al. 2008). Interestingly, histatin 1 induced cell spreading and migration in a full-skin human wound model; however, the peptide did not stimulate cell proliferation. N- to C-cyclization potentiated peptide activity 1000-fold, indicating that a specific peptide conformation was responsible for the effect (Oudhoff et al. 2009a). The minimally active domain was found to be the fragment 20–32 of the parent histatin peptide. The wound-healing effect was strongly inhibited by mucin-5B, probably by blocking re-epithelialization. Interestingly, histatin 1 stimulated wound closure of primary cells of both oral and non-oral origin (Oudhoff et al. 2009b), which suggests a therapeutic application of histatin 1-derived peptides in the treatment of skin wounds.

Statherin is a singular salivary phosphopeptide of 43-amino acid residues involved in the inhibition of calcium phosphate precipitation and in the formation of acquired enamel pellicle (Schüpbach et al. 2001). However, statherin may hide other relevant oral functions implicated in the formation of the oral epithelial protein pellicle, and it probably has a functional connection with the P-B peptide whose function is still completely obscure (Messana et al. 2008b).

29 Pathological Modifications

Numerous efforts have been made in the last two decades to establish if saliva may be considered a reliable bodily fluid to evaluate the health status. Indeed, several characteristics of saliva are attractive for its possible use in diagnostics, such as the safe, easy and economical way of collection, that can be performed without pain and without the help of healthcare workers allowing for

home-based sampling, also with patients in the paediatric age range (Tabak 2001).

Salivary proteome presents several unique proteins, and thus saliva-based diagnostics may provide complementary information to blood- and urine-based diagnostics. Since about one-fourth of the salivary proteome overlaps with the plasma proteome (Loo et al. 2010), it will be important to establish if disease-linked plasma modifications are reflected in the saliva secreted in order to rely upon non-invasive tests, for disease screening, detection and monitoring. The studies carried up to now demonstrated that systemic diseases may affect the human salivary proteome, and excellent reviews outlined that saliva may contain real-time information describing overall physiological condition supporting the possible use of this biofluid for diagnostic purposes (Cuevas-Córdoba and Santiago-García 2014; Schafer et al. 2014; Wang et al. 2015). In a recent paper the advancements in the field of salivary biomarkers and proteomics have been largely reviewed (Castagnola et al. 2017).

Among various studies for the discovery of biomarkers of disease, the most relevant for their possible connection with dysphagia are those addressed towards the early detection of different oral tumours such as oral squamous cell carcinoma (Jou et al. 2010; Shintani et al. 2010; Hu et al. 2008) and head and neck squamous cell carcinoma (Dowling et al. 2008; Ohshiro et al. 2007; de Jong et al. 2010; Chen et al. 2002). Jou et al. (2010), using 2D electrophoresis coupled to MALDI-TOF MS, found salivary transferrin to be increased in patients with oral squamous cell carcinoma. Shintani et al. (2010), using SELDI-TOF analyses, showed an increase of a truncated form of cystatin SN. Hu et al. (2008), using both LC-MS/MS and 2D electrophoresis on saliva of oral squamous cell carcinoma patients, found increased amounts of protectin, catalase, profilin and S100A9. A comparative 2D electrophoretic analysis of whole saliva of patients with oral squamous cell carcinoma and healthy controls was able to identify α1-antitrypsin, haptoglobin b chains, complement C3, hemopexin and transthyretin as potential biomarkers oral squamous cell carcinoma, which were also validated by ELISA. In particular, a strong association of α1-antitrypsin and haptoglobin b chains with oral squamous cell carcinoma patients was further supported by immunochemical staining of cancer tissues (Jessie et al. 2013).

Recent proteomic studies added further information, suggesting 17 up-regulated protein biomarkers of oral squamous cell carcinoma (Wang et al. 2015) including the interleukins 6, 8 and 1b, cyclin D1 thioredoxin and profilin 1. Furthermore, a study performed by SDS-PAGE coupled to LC-MS/MS on individuals with potentially malignant disorders or those suffering of oral squamous cell carcinoma evidenced 22 over-expressed proteins in the oral squamous cell carcinoma group with respect to controls and potentially malignant disorders. Resistin levels had significant correlation with late-stage primary tumours, advanced overall stage and lymph node metastasis (Wu et al. 2015) The same group identified 64 protein candidates for oral squamous cell carcinoma by spectral counting-based label-free quantification. Among these, thrombospondin-2 was associated with a higher overall pathological state, positive perineural invasion and poorer prognosis (Hsu et al. 2014). Using nano-LC-MS/MS and validation by Western blot and ELISA, Jou et al. demonstrated that high level of S100A8 characterized 3.4, 13.9, 92.9 and 100% of saliva of oral squamous cell carcinoma patients with T1, T2, T3 and T4 stages, respectively (Jou et al. 2014).

Sivadasan et al. (2015) were able to identify 1256 salivary proteins and to update the salivary proteome to 3449 proteins, 806 of which were differentially expressed in oral cancer. The authors provided a list of 139 proteins along with their proteotypic peptides, which might serve as a reference for targeted investigations as secretory markers for clinical applications in oral malignancies.

Recent research has suggested that potential biomarkers in other cancer types, as well as in oral chronic graft-versus-host disease, Sjögren's syndrome and other autoimmune diseases, psychiatric diseases, such as schizophrenia and bipolar disorders, and other systemic diseases may be detected in human saliva (Castagnola et al. 2017).

For instance, the salivary proteome of patients affected by primary Sjögren's syndrome has been extensively investigated with the aim to evidence pathology-related modifications (Giusti et al. 2007; Ryu et al. 2006; Peluso et al. 2007; Fleissig et al. 2009). The principal platform utilized was based on 2D electrophoresis followed either by MALDI-TOF MS or by ESI-MS/MS analyses of the tryptic protein digests. Some controversial results were, however, obtained. For instance, while Giusti and co-workers (2007) found salivary α-amylase to decrease, Fleissig and co-workers (2009) found it to increase, suggesting that the search of new biomarkers has to be carried out in a large number of patients and validation of the majority of results reported is necessary.

Even if it is a demanding task, for a widespread introduction of saliva-based diagnostics, it is mandatory to define proper reference proteomes and further to standardize analytical procedures. As for blood and urine samples, time and site of specimen collection, as well as the definition of specific treatments for sample stabilization, need to be established. Thus, high-throughput proteomic approaches, applied under standardized conditions, will provide the introduction of simple, sensitive and specific analytical procedures to demonstrate salivary biomarkers in the clinical practice.

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Feeding and Respiration

Olle Ekberg, Anna I. Hårdemark Cedborg, Katarina Bodén, Hanne Witt Hedström, Richard Kuylenstierna, Lars I. Eriksson, and Eva Sundman

Contents

Abstract

Coordination of breathing and swallowing is essential for normal bolus transportation through the pharynx and for protection of the airways. During passage of the bolus through the pharynx, respiration is interrupted. Normal swallowing occurs during the expiratory phase of breathing. Incoordination of the feeding respiratory pattern may lead to penetration of the bolus into the airways. This may cause choking, death, aspiration pneumonia, or chronic laryngitis.

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1 Introduction

Swallowing and breathing are closely controlled by specialized neuronal groups colocalized to the brain stem. Interaction occurs between neuronal groups controlling breathing and those controlling swallowing (Dick et al. 1993; Saito et al. 2002; Ertekin and Aydogdu 2003). Such central neuronal control, together with local anatomic conditions and sensory input from the larynx and pharynx, allows safe and direct passage of air, liquids, and solids. Moreover, factors primarily thought to influence breathing (e.g., arterial partial pressure of CO_2) affect swallowing (Nishino et al. 1998; Sai et al. 2004), and other factors controlling pharyngeal function affect breathing pattern (Nilsson et al. 1997; Hadjikoutis et al. 2000; Butler et al. 2007; Terzi et al. 2007). Posture and positioning are such factors.

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Miller (1999), in his neurophysiological investigations of swallowing, concluded that brain stem neuronal control is involved in the central inhibition of respiration during swallowing. Therefore, swallowing apnea is not an effect of closure of the vocal folds even though, together with laryngeal closure, it often occurs at the same time as apnea.

Swallowing apnea has also been registered in patients after laryngectomy (Hiss et al. 2003). The presence of swallowing apnea also remains 10 years after laryngectomy. Therefore, swallowing apnea is a central phenomenon and not the result of obstructive forces of closed airways during swallowing. On the other hand, closure of the laryngeal vestibule, including vocal folds, is an important part of the protective mechanism that hinders the bolus from reaching the airways. Swallowing apnea may start long before vocal fold closure; however, it ends when the vocal folds begin to reopen.

2 Feeding Respiratory Pattern

In a recent study, Hårdemark Cedborg et al. (2009) explored breathing during spontaneous swallowing using a bidirectional gas flow discriminator. They used a complex experimental setting in volunteers including manometry for registration of pressure at the level of the tongue base, midpharynx, and upper esophageal sphincter and including nasal and oral airflow. A diaphragmatic and abdominal EMG was used as well. Spirometry was used for quantitative registration of airflow in liters per minute. They studied spontaneous swallowing during normocapnia and hypercapnia. The latter was achieved by subjects breathing air with the addition of 5% CO_2. The term "spontaneous swallowing" refers to the fact that the subjects were allowed to swallow saliva spontaneously and were not given any instruction for how to swallow. Hypercapnia was used to evaluate how an increased respiratory drive and higher breathing frequency interfered with spontaneous swallowing (Fig. 1).

Hårdemark Cedborg et al. (2009) found that all swallows occur during expiration. The normal sequence is that expiration is interrupted by a period of apnea, during which time the bolus passes through the pharynx. Then the expiration is resumed. The expiration before swallowing may be as short as 30 ms. Expiration before swallowing lasts about 1.3 s and expiration after swallowing lasts about 1.5 s. The preswallowing expiration time could be very short but could always be discerned. They speculated that swallowing is in fact controlled by the respiratory neurons, in that sense that swallowing was only allowed to occur during an expiratory phase. By studying the EMG pattern, they confirmed the phrenic nerve activity described by Saito et al. (2002). This EMG pattern is distinctly different from that of an inspiration and was not followed by airflow. They called this "active breath holding." This central control of breathing ensures that respiration is stopped before pharyngeal swallowing and that a significant proportion (approximately 200 mL) of the tidal volume is "put on hold" by the activated diaphragm, only to be expired at the end of swallowing apnea. Expiratory airflow after swallowing clears the laryngeal inlet from misdirected bolus material, and thereby aspiration is prevented (Fig. 2).

In an experimental prospective study, Gross et al. (2003) showed that during a standardized pudding-like consistency swallow at three randomized lung volumes (total lung capacity, functional residual capacity, and residual volume), the pharyngeal activity duration of deglutition for swallows produced at residual volume was significantly longer than that for swallows occurring at total lung capacity or at functional residual capacity. No significant differences were found for the bolus transit time or intramuscular electromyography of the superior constrictor. This supports the hypothesis that the respiratory system may have a regulatory function related to swallowing and that positive subglottic air pressure may be important for swallowing integrity.

Hårdemark Cedborg et al. (2009) also studied the length of preswallowing and postswallowing apnea. The duration of swallowing apnea decreased considerably at hypercapnia. Interestingly, they found that the duration of preswallowing apnea shortened, whereas the duration of postswallowing apnea did not change during hypercapnia. Hence, the temporal positioning of pharyngeal swallowing is asymmetrical, occurring in the late part of swallowing apnea at

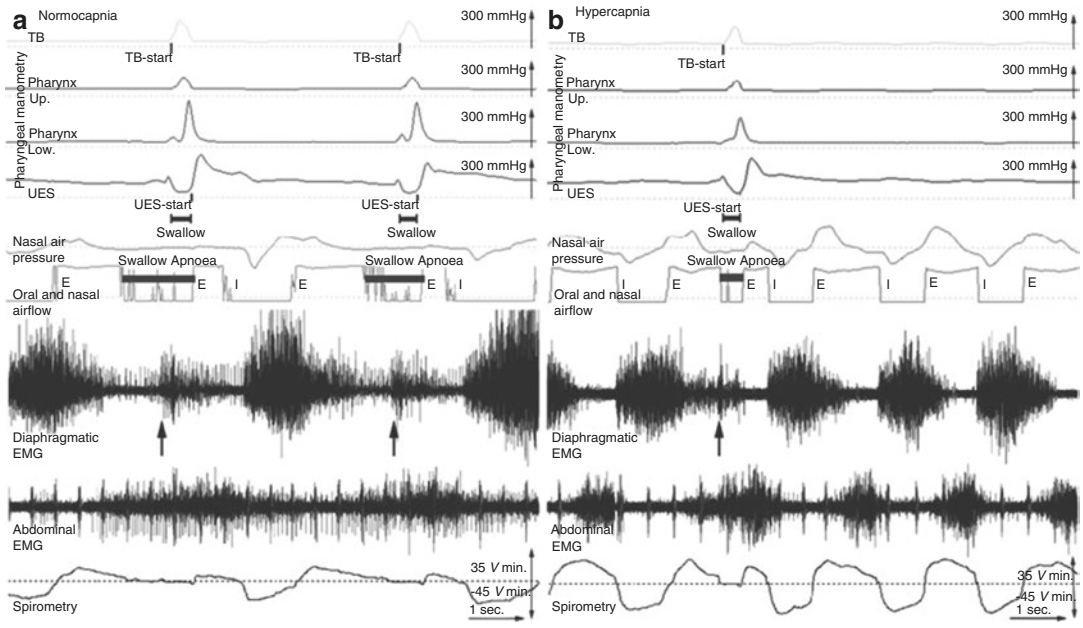

Fig. 1 Registrations of pharyngeal manometry, nasal air pressure, and oral and nasal respiratory airflow by the bidirectional gas flow discriminator, diaphragmatic and abdominal EMG, and spirometry. Recordings of two swallows at normocapnia (**a**) and one swallow at hypercapnia (**b**). The swallows presented show the respiratory phase pattern E–E (inspiration–expiration–swallow–expiration). The start of pharyngeal swallowing was defined as the start of pressure rise at the tongue base (*TB-start*) and the end was defined as the point in time when the upper esophageal sphincter started to contract (*UES-start*). The duration of pharyngeal swallowing is marked with a *horizontal bar* (swallow). Swallowing apnea was detected by the respiratory airflow discriminator as an oscillating signal, representing zero airflow. Diaphragmatic activity during swallowing apnea is marked with *arrows*. Pharyngeal manometry was recorded at the tongue base (*TB*), *upper/lower* level of the pharynx (*Pharynx Up*/*Pharynx Low*) and upper esophageal sphincter (*UES*). *I* inspiration, *E* expiration. (Reprinted from Hårdemark Cedborg et al. 2009)

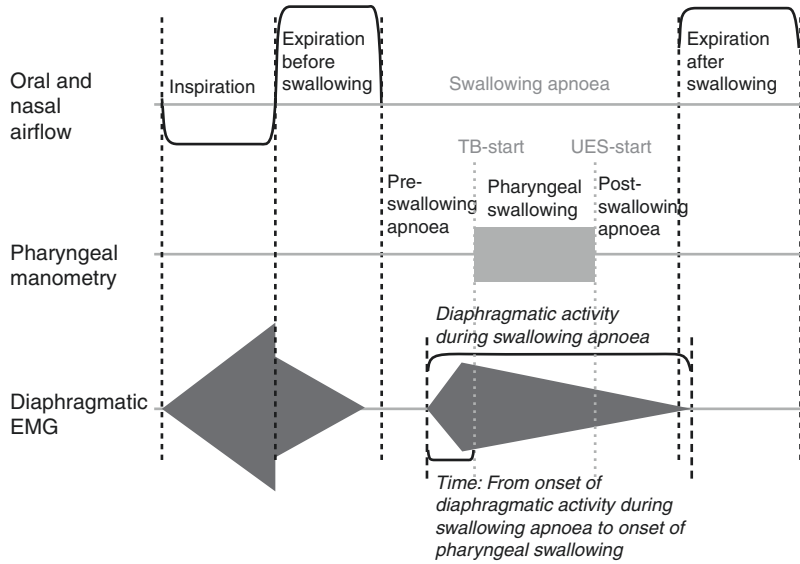

Fig. 2 A swallow preceded and followed by expiration (E–E pattern) and the diaphragmatic activity during swallowing apnea. The time from the onset of diaphragmatic activity during swallowing apnea to the onset of pharyngeal swallowing was measured and is marked in the figure. The start of pharyngeal swallowing is defined as the start of the pressure rise at the tongue base (*TB-start*) and the end of pharyngeal swallowing is defined as the start of the pressure rise at the upper esophageal sphincter (*UES-start*). (Reprinted from Hårdemark Cedborg et al. 2009)

normocapnia but not at hypercapnia. This means that when breathing at a high frequency the preswallowing apnea period shortens considerably and that may put the patient at risk of misdirected swallowing. This may be a considerable problem in patients with chronic obstructive pulmonary disease who have a high respiration frequency (Martin et al. 1994; Martin-Harris et al. 2003, 2005). Chronic aspiration may then aggravate the patient's pulmonary condition, introducing a vicious cycle (Gross et al. 2009).

Respiration and swallowing coordination is not affected by changes in body position, bolus types, and respiratory drive (Hårdemark Cedborg et al. 2010). However, during water swallows, the duration of preswallowing apnea is significantly longer than that of spontaneous saliva swallow (Hårdemark Cedborg et al. 2010). During water swallow, the duration of the postswallowing apnea is also very constant.

Elderly adults have been shown to have a longer swallowing apnea duration than young and middle-aged adults (Hiss et al. 2001). That study also showed that women have a longer swallowing apnea duration than men and that the swallowing apnea duration increases as the bolus volume increases.

Martin-Harris et al. (2005) showed a higher occurrence of inhalation with swallowing apnea, with increased occurrence in individuals older than 65 years. Although it was not shown, the hypothesis is that this predisposes the elderly to aspiration pneumonia. However, they also found that the elderly have a prolonged swallowing apnea duration. Particularly, the onset of apnea could occur rather early compared with the onset in young individuals.

The coordination of respiration and swallow rhythms has also been studied in preterm and term infants (Gewolb and Vice 2006). The initial feeding efforts at 32–34 weeks (postmenstrual age) are characterized by periods of apneic suckle-feeding that alternate with tidal respiration. With further development, respiration is interposed into spaces partitioned by the swallows and the breathing efforts are integrated into an oral suck–swallow–breathing rhythm.

It has also been shown that an increase in respiratory drive by inhalation of 7% CO_2 in preterm infants is accompanied by a decrease in the rate of both sucking and swallowing during nutritive feeding. Increased ventilatory drive may directly inhibit nutritive feeding behavior in premature infants. Also, this speaks in favor of respiratory neurons in the brain stem that have superior control of swallowing and not vice versa (Timms et al. 1993).

Temporal coordination of swallowing and respiratory events has also been studied in a more global perspective (Bodén et al. 2009; Fig. 3). This confirms several of the studies forming the basis for the concept of a fixed pattern generator that controls muscular activity in the swallowing apparatus (Miller 1999).

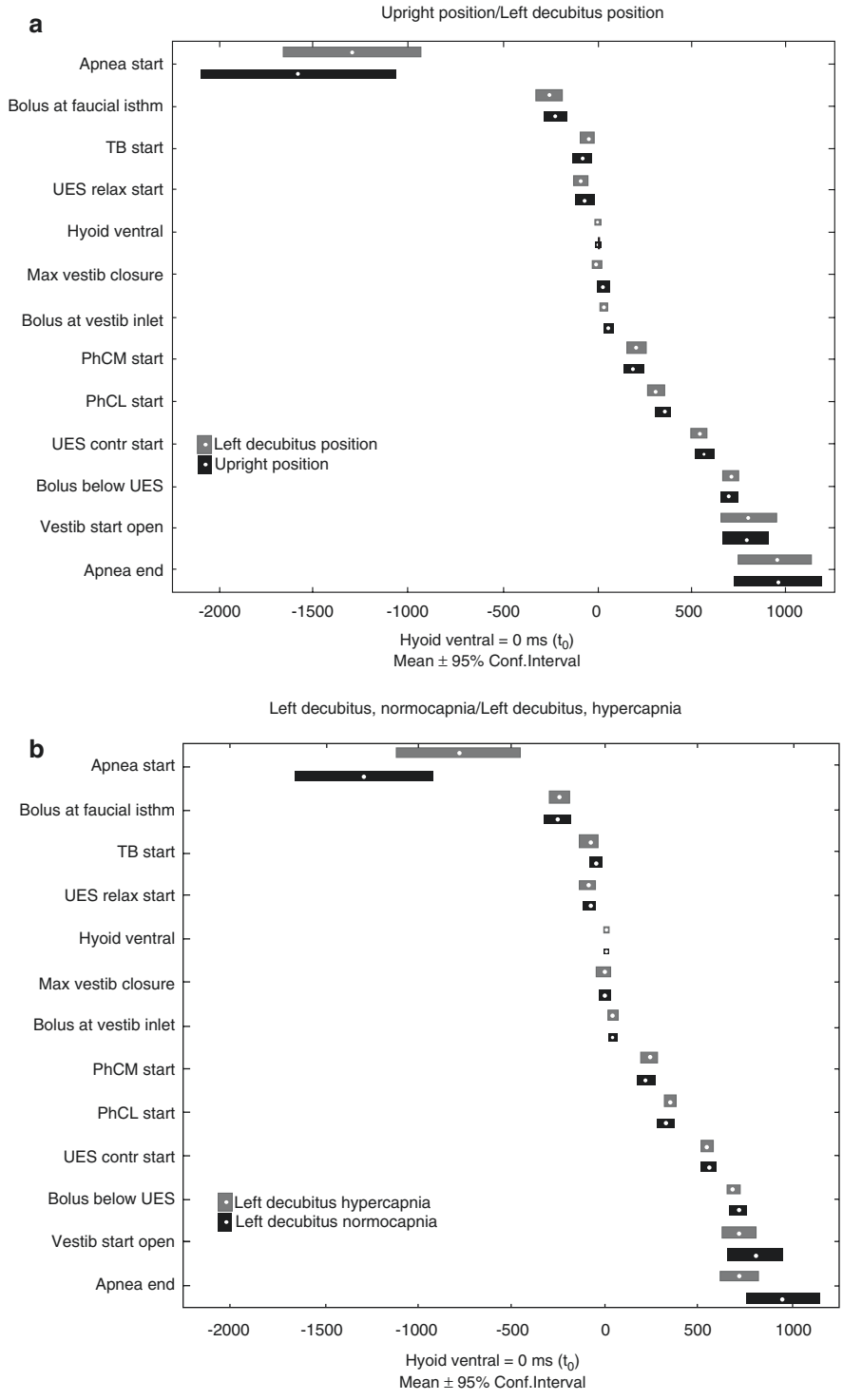

Fig. 3 Temporal coordination of swallowing and respiratory events in (**a**) the *upright* and *left* decubitus positions with normocapnia and (**b**) the *left* decubitus position with normocapnia and with hypercapnia. All values are in milliseconds and are mean values ± the 95% confidence interval. *TB* tongue base, *UES* upper esophageal sphincter, *PhCM* middle pharyngeal constrictor, *PhCL* lower pharyngeal constrictor. (Reprinted from Bodén et al. 2009)

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Oral and Pharyngeal Function and Dysfunction

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Contents

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Abstract

Normal pharyngeal swallow is coordinated in a precise and exact manner. It is controlled from a swallowing center in the brain stem. Normal swallowing is adjusted to bolus volume temperature and viscosity. Abnormal pharyngeal swallow may lead to misdirected swallowing that challenges the airways. Inefficient transportation into the esophagus, stomach, and bowel may lead to dehydration and malnutrition.

1 Introduction

Normal pharyngeal swallow is precisely scheduled and symmetric. It is finely tuned and coordinated in a precise and exact manner to establish a safe swallow (Miller 1986; Dodds 1989). The swallowing process is regulated by a command center in the brain stem, a central program generator which receives input from the cerebral cortex and peripheral muscle and directs the sequence of swallowing. This process is both voluntary and involuntary and incorporates motor activity from the oral cavity, pharynx, and esophagus. It involves both motor and sensory activity. There is an evolving amount of knowledge concerning normal and abnormal swallowing (Jones and Donner 1991; Ekberg and Wahlgren 1985; Hannig and Hannig 1987; Brühlmann 1985; Pokieser et al. 1995; Dodds 1989).

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2 The Normal Swallow

2.1 The Oral Stage

The oral, pharyngeal, pharyngoesophageal segment (PES), and esophageal stages of swallowing are readily appreciated radiographically (Fig. 1). The oral stage of swallowing is bolus-specific, i.e., the patient handles different boluses differently, i.e., a strawberry is handled differently from a cup of tea. Therefore, the oral stage is notoriously more difficult to evaluate radiologically than the rest of the swallowing apparatus. However, the oral stage should be included in the radiologic evaluation. The recording should start with the ingestion. During oral processing there is superior and inferior and some anterior–posterior movement of the hyoid bone. However, liquid barium should not be processed or modified in the oral cavity. Therefore, oral preparation for swallowing is tested with a solid or semisolid bolus. When the ingested material is ready to be swallowed, the material is brought onto the back of the tongue, which obtains the shape of a groove (Hamlet et al. 1988). This is the preparatory position for swallowing.

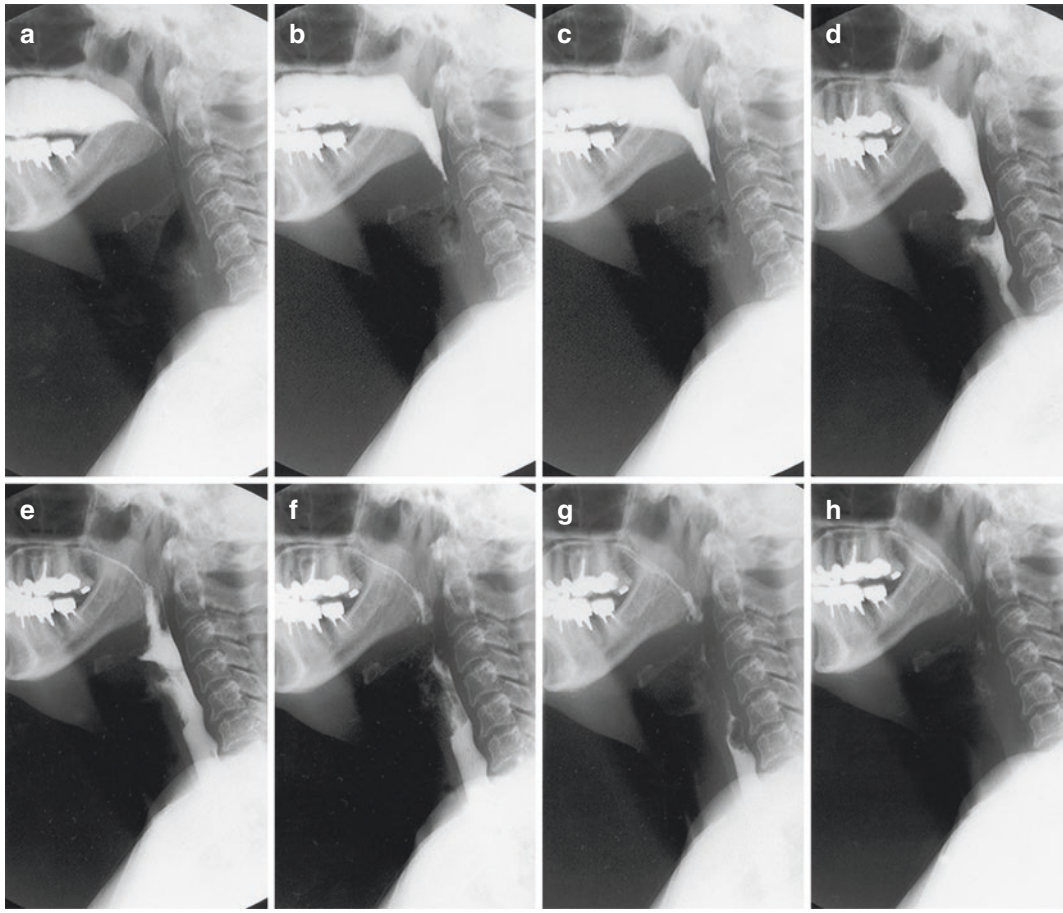

Fig. 1 The oral, pharyngeal, and pharyngoesophageal segment (PES) stages are readily appreciated radiographically. This is a sequence of a barium swallow (**a**–**h**) in lateral projection. The bolus is gathered in the oral cavity (**a**–**c**) and is propelled into the pharynx by an upward and backward movement of the back of the tongue (**d**). The tilting down to a horizontal position of the epiglottis is seen in (**d**). The airways are closed and none of the barium reaches into the laryngeal vestibule or trachea. The PES opens. The upward and forward movements of the larynx including the hyoid superiorly and the PES inferiorly are extremely important for the normal execution of pharyngeal transit. There are no, or only minimal, remnants of barium in the pharynx after swallowing

No part of the bolus is allowed to leak anteriorly from the mouth through the lips. Even more important radiologically is to observe if posterior leak occurs. The patient should be able to control the sealing of the tongue-base to the soft palate and posterior pharyngeal wall.

2.2 The Pharyngeal Stage

The pharyngeal swallow is initiated voluntarily and the material to be swallowed is usually called a bolus from this point. Initiation of the pharyngeal swallow coincides with the beginning of the anterior movement of the hyoid bone from an elevated position. Pharyngeal constriction is probably cued by the bolus interfering with sensory innervation at the faucial isthmus. Radiologically it is convenient to use the beginning of the anterior hyoid movement as the starting point of pharyngeal swallow. The tongue then propels the bolus posteriorly into the pharynx and further down into the PES and cervical esophagus. If the pharyngeal constrictor wall has normal compliance, only minor dilatation of the pharynx occurs (Fig. 2).

The palatopharyngeal isthmus is closed by elevation of the muscular palate and constrictor convergence, which is most medial of the lateral walls. Normally, no regurgitation of barium into the nasopharynx occurs.

In a patient with severe oral impairment, the pharyngeal phase may be elicited by injecting a small barium bolus directly into the pharynx through a soft tube. This may be placed into the pharynx via either the mouth or the nose. Such techniques, however, are used only for examination and not for feeding. Patients with uncoordinated, weak, or jerky tongue movements commonly cannot correctly position the bolus on the tongue. Accordingly, the tongue cannot displace the bolus posteriorly. There is a strong correlation between an abnormal anterior movement of the hyoid bone and overall abnormal oral and pharyngeal function, as well as defective opening of the PES.

Protection of the airways occurs at four separable anatomically and functionally different sites, i.e., the vocal folds, the supraglottic portion of the laryngeal vestibule, the subepiglottic portion of the laryngeal vestibule, and the epiglottis (Curtis and Hudson 1983; Curtis and Sepulveda 1983; Ekberg 1982). The most crucial of these levels is the supraglottic portion of the laryngeal vestibule. Barium in the vestibule commonly extends into the trachea, as the vocal folds offer poor protection of the lower airway (Ekberg and Hilderfors 1985). Radiographic observation of

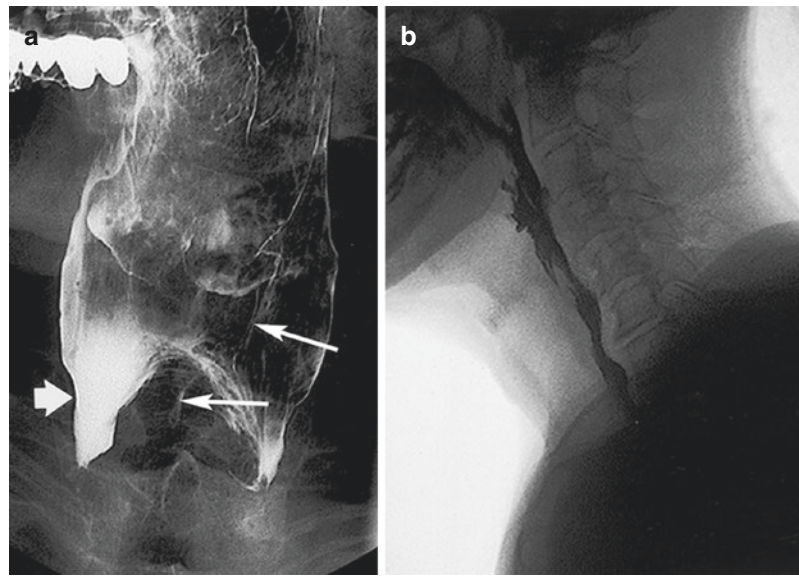

Fig. 2 An 80-year-old man with cerebrovascular disease. There is paresis in the right side of the pharynx. This is not seen in lateral projection (**b**) and is only seen in frontal projection (**a**). There is pooling of contrast medium in the right piriform sinus (*broad arrow*). Small amounts of barium are also seen coating the inside of the laryngeal vestibule down to the false vocal cords

barium penetration into the larynx and trachea is strategic in dysphagia evaluation. Bedside evaluation for aspiration has a low sensitivity. This is partly because many of these patients have sensory impairment in the larynx and/or trachea and fail to cough (Splaingard et al. 1988).

Of even more fundamental importance, and basically a prerequisite for airway closure and constrictor activity, is the elevation of the pharynx and larynx. The airways are also protected by a movement of the thyroid cartilage toward the hyoid and by closure of the laryngeal vestibule. Additional protection is offered by the epiglottis and the vocal folds. Closure of the larynx starts at the vocal folds and progresses in a superior direction in a peristaltic-like manner.

The constrictors have a minor role in the conveyance of a bolus through the pharynx. The tongue-base pressure does not differ significantly between those individuals with and those individuals without retention (Olsson et al. 1997). This finding is important because many research groups advocate normal tongue-base and constrictor activity as a prerequisite for a successful outcome of cricopharyngeal myotomy (Buchholz 1995). Tongue-base pressure has been appreciated as the driving force of the bolus, and the tongue-base has been associated with a compensatory function, namely, overcoming weak pharyngeal constrictors by increasing tongue-base activity. This tongue driving force propels the bolus and the pharyngeal constrictors stabilize the pharyngeal tube; the tongue then closes the lumen behind the bolus to prevent retrograde escape (McConnel et al. 1988; Cerenko et al. 1989; McConnel 1988).

In patients with pharyngeal retention, the PES does not open as much as in patients without such retention. This reduced opening of the PES is not associated with an increased intrabolus pressure, but is seen together with decreased laryngeal elevation. This is in agreement with a study in which traction on the PES was found to be the main force leading to the PES opening (Hsieh et al. 1995). The suprahyoid muscles are therefore much more important than other muscles in the pharynx. Also, tongue-base pressure, which is reflected by the intrabolus pressure, was the same in patients with and in patients without retention. Thus, pharyngeal shortening could be the most important mechanism in pharyngeal bolus transport (Ergun et al. 1993a, b).

Such intrabolus pressure was shown to be the same for the two groups in this study.

The pharyngeal phase of swallowing is complex because of the intricate anatomic relationships and the close temporal activation of the more than two dozen muscles that are required to function together to effectively transport the bolus from the mouth to the esophagus. In a classic electromyographic study by Doty and Bosma (1956), temporal activation of the muscles of deglutition was shown. Activation begins in the mylohyoid muscle, and the muscle action is then propelled inferiorly. Early events during the pharyngeal phase of swallowing include activation and sealing of the nasopharynx and contraction of the mylohyoid, hyoglossus, and geniohyoid muscles (i.e., the suprahyoid pharyngeal shorteners). A number of other muscles also contract early, namely, those that effect airway protection, such as the intrinsic and extrinsic muscles of the larynx. Contraction of the superior pharyngeal constrictor, styloglossus, palatoglossus, pterygopharyngeal, palatopharyngeal, stylopharyngeal, salpingopharyngeal, stylohyoid, and posterior digastric muscles then occurs. In terms of bolus transportation, this early stage represents the conveyance of the bolus from the oral cavity into the pharynx. This activity is often described as being achieved by the tongue thrust, although a multitude of muscles are involved (McConnel et al. 1988; Cerenko et al. 1989; McConnel 1988). The pharyngeal constrictors give only stability to the gullet—they do not contribute to bolus transportation in other ways (Dodds 1989). In contrast, the late part of the pharyngeal stage consists of contraction of the thyrohyoid, sternohyoid, sternothyroid, and omohyoid muscles (i.e., the strap muscles), and also the middle and inferior pharyngeal constrictors. This latter activity is thought to clear the bolus from the pharynx. The late pharyngeal constrictor activity for clearance of the pharynx is seen as a contracting wave traversing inferiorly from the superior pharyngeal constrictor level. This wave is usually best appreciated on

the anteroposterior view as an inverted V-shape to the tail of liquid or semisolid bolus (Dodds 1989). It is impairment of such clearance that is recognized as retention in the valleculae, piriform sinus, or both.

The exact reason why laryngeal elevation leads to retention in patients with manometrically normal pharyngeal constrictor activity is not clear. It is possible that reduced elevation is caused by impaired function of the suprahyoid muscles and other elevators. Such impaired function might lead to abnormal compliance of the wall, against which the constrictors may then act. As retention was not seen in a location immediately cranial to the cricopharyngeal muscle, it is more likely that a defective opening reflects a more profound and widespread dysfunction in the pharynx. Defective opening may be the sole result of impaired elevation of the pharynx.

2.3 The Pharyngoesophageal Segment

The PES is the transition between the pharynx and the esophagus. Between swallows it is kept closed as a sphincter of circular striated muscles. Anatomically it consists of the cricopharyngeal muscle and the inferior portion of the pharyngeal constrictors and the superior portion of the cervical esophagus. The length of the segment is about 3–4 cm, where the cricopharyngeal muscle makes up 1–1.5 cm. Closure is the effect of muscle tonicity and the pressure from surrounding tissues (Kahrilas et al. 1988). Normal opening, which is crucial for bolus transport, is achieved by relaxation of muscle tone. However, this probably only accounts for 10–20% of the total sphincter tone. More important is the movement of the PES superiorly and anteriorly together with the larynx and the hyoid bone. In addition, intrabolus pressure created mainly by the tongue-base and constrictor activity also helps to open the PES.

2.4 The Esophageal Stage

This is comprehensively presented in Sect. 5.1.

3 The Abnormal Swallow

In terms of what abnormalities can be expected on the four different anatomic levels, a rule of thumb is that dysfunction is by far the principal abnormality in the oral cavity and pharynx. In the PES, dysfunction and structural abnormalities may coexist. In the esophagus, structural abnormalities predominate.

3.1 The Oral Stage

Leaking of barium anteriorly through the lips, laterally into the buccal pouches, or posteriorly into the pharynx is abnormal. An overly large ingestion in a patient with impaired pharyngeal function and misdirected swallowing is also abnormal. This may indicate impairment of bolus sizing. Impaired lingual movement or jerky uncoordinated movements of the tongue during the preparatory phase of swallowing are also abnormal.

In patients with neurologic diseases, oral dysfunction regularly predominates over pharyngeal dysfunction. Radiographically, this can be appreciated as defective containment, i.e., leakage of barium anteriorly through the lips, laterally into the buccal pouches, or posteriorly into the pharynx, where it potentially may reach the airways if the laryngeal vestibule is not closed. If the patient swallows an abnormally large bolus, this may indicate impairment of bolus sizing. Abnormalities in the oral phase of swallowing, i.e., impaired lingual movement or a soft tissue defect, generally lead to delayed oral transit and clearance of the oral bolus with retention of barium. Premature spill of barium into the pharynx may be accompanied by failed initiation of swallowing, aspiration, or both. Impaired oral function is often associated with abnormal pharyngeal swallow (Fig. 3). Normally, the oral phase of swallowing undergoes a smooth transition into the pharyngeal phase with vigorous transport of the swallowed bolus into and through the pharynx. In some patients, however, the pharyngeal phase is delayed but otherwise normal.

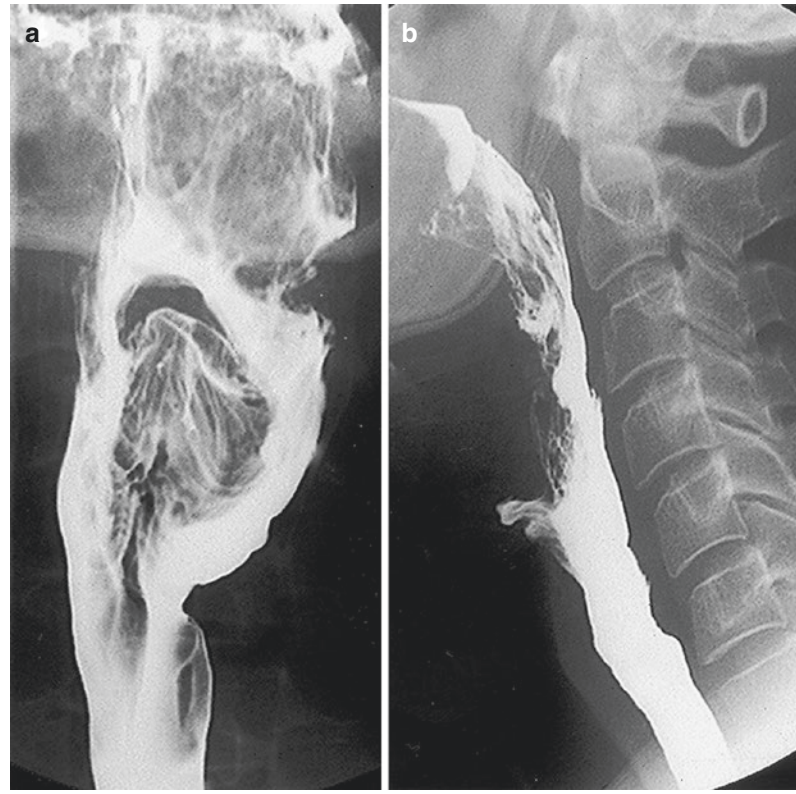

Fig. 3 A 49-year-old man with sudden onset of dysphagia. There is a left-sided weakness of the pharynx. The left side of the pharynx bulges laterally. There is also abnormal opening of the PES, probably due to impaired constrictor strength cranially. The pharyngeal constrictor abnormality is not appreciated in the lateral projection (**a**) and is only appreciated in the frontal projection (**b**)

3.2 The Pharyngeal Stage

Abnormal initiation of the pharyngeal stage of swallowing is easily appreciated when the bolus is conveyed into the pharynx without the pharynx being elevated and without occurrence of constrictor activity. Again, lack of anterior displacement of the hyoid bone is a conspicuous indicator of a serious abnormality. Demonstration of dissociation between the oral and pharyngeal stages depends upon observation of structural displacement. Except for this failure of voluntary elicitation of pharyngeal swallow, the oral and the pharyngeal stages of swallowing basically appear radiologically normal. In borderline cases, in which the bolus is retained in the valleculae or in the piriform sinuses for 2–5 s, the assessment of normalcy is based upon observation of the bolus.

The ultimate consequences of this dissociation are that the bolus reaches the pharynx when the larynx is still open. Even if the barium does not penetrate into the larynx, the delayed initiation is a potential threat to safe swallowing. Even the slightest amount of barium in the vestibule indicates an abnormality (Fig. 4). The wide range of normalcy can be observed during chewing and swallowing of a mixture of solids and liquid, especially during talking, etc., when the barium and/or solids are brought into the pharynx while chewing continues without tongue propulsion being elicited. Again, what happens to the bolus is more important than observing wall displacement in this circumstance. It is even more important to recognize that if pharyngeal swallow is not triggered at the faucial isthmus either by the bolus or by the tongue, swallowing may be elicited from the vallecula or from the posterior pharyngeal wall.

Defective closure of the velopharynx is due to either soft palate dysfunction or defective function in the superior pharyngeal constrictor. Medial movement of the lateral wall is more extensive than the anterior movement of the posterior constrictor wall. Compensation may be in the form of a Passavant's ridge, a protrusion

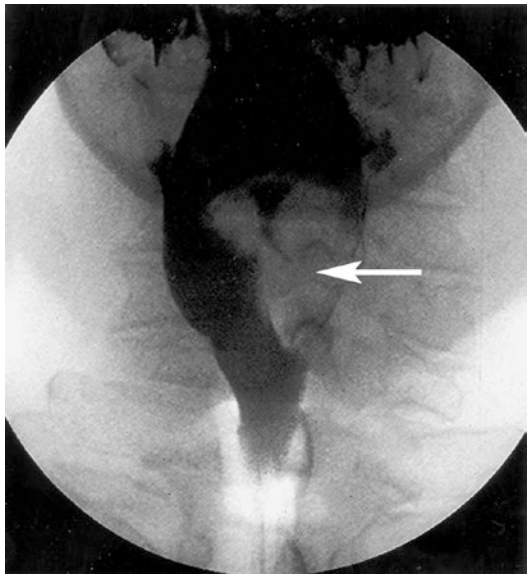

Fig. 4 Another example of a unilateral pharyngeal constrictor paresis, this time on the right side. The deviation of contrast medium into the right side may erroneously give the impression of a tumor on the normal left side (*arrow*). This pseudotumor appearance has led to numerous unnecessary endoscopic examinations

similar to that seen as a compensatory maneuver in speech in individuals with a cleft palate.

The pharyngeal constrictors play a crucial role in swallowing (Ardran and Kemp 1956). If the constrictor muscles are paretic, the pharynx is flaccid and allows an abnormal expansion of the chamber during the compression phase of swallowing (Figs. 3 and 4). Such lack of distensibility may result in impaired transit of bolus from the oral cavity into the esophagus even if the tongue acts normally (Thulin and Welin 1954; Ekberg et al. 1986). This can be seen as a dilated and wide flaccid pharynx, but this is a nonspecific finding. Action of the pharyngeal constrictors is also crucial for clearing barium from the pharynx. However, there are pitfalls (Fig. 5). This constrictor activity is best evaluated in the posteroanterior view (Fig. 2). The consequence of defective constrictor activity is residual barium in the pharynx after swallowing. As the middle pharyngeal constrictor is the pharyngeal constrictor most commonly involved, retention occurs at the level of the laryngeal inlet and may lead to aspiration after swallowing.

In the pharynx, retention of contrast medium may occur and indicate abnormalities in the tongue-base and/or in the pharyngeal constrictors. The finding of any contrast medium that reaches into the laryngeal vestibule and trachea is abnormal (Figs. 1, 2, and 3). This is especially true if the patient does not cough during this event. This indicates desensitization and is seen in patients with impairment lasting for more than about 2 months. Defective tilting down of the epiglottis is also abnormal and is generally seen together with impaired movement of the hyoid bone and larynx. More fundamental abnormalities are impaired elevation of the larynx and pharynx together with the hyoid bone at the initiation of pharyngeal swallow. This is seen in patients who do not elicit the pharyngeal stage of swallowing. We have used the beginning of the anterior movement of the hyoid bone as a key event. During the preparatory stage the hyoid bone and larynx are moving up and down, but at the initiation of the pharyngeal swallow the hyoid bone starts to move anteriorly (from an elevated position). If that movement is missing, the patient does not elicit pharyngeal swallow and is thereby at great risk if fed orally.

3.2.1 Misdirected Swallowing

Confusion exists regarding the terminology confined to barium reaching into the airways. "Penetration" has been used either to describe barium reaching into the airways *during* swallowing or merely to describe barium reaching only into the laryngeal vestibule and not beyond the vocal folds. "Aspiration" has been used either to describe barium reaching into the airways *after* swallowing and usually due to residue in the pharynx or to describe barium reaching beyond the vocal folds. Different use of the terminology has created unnecessary confusion. It is much more rational to describe (1) when the barium reaches into the airways, namely, *before*, *during*, or *after* elicitation of pharyngeal swallow, and (2) how far into the airways the barium reaches, namely, *into the subepiglottic*, *supraglottic portion* of the laryngeal vestibule or *beyond the vocal folds*. There is no consensus regarding the terminology and therefore it is warranted to be precise

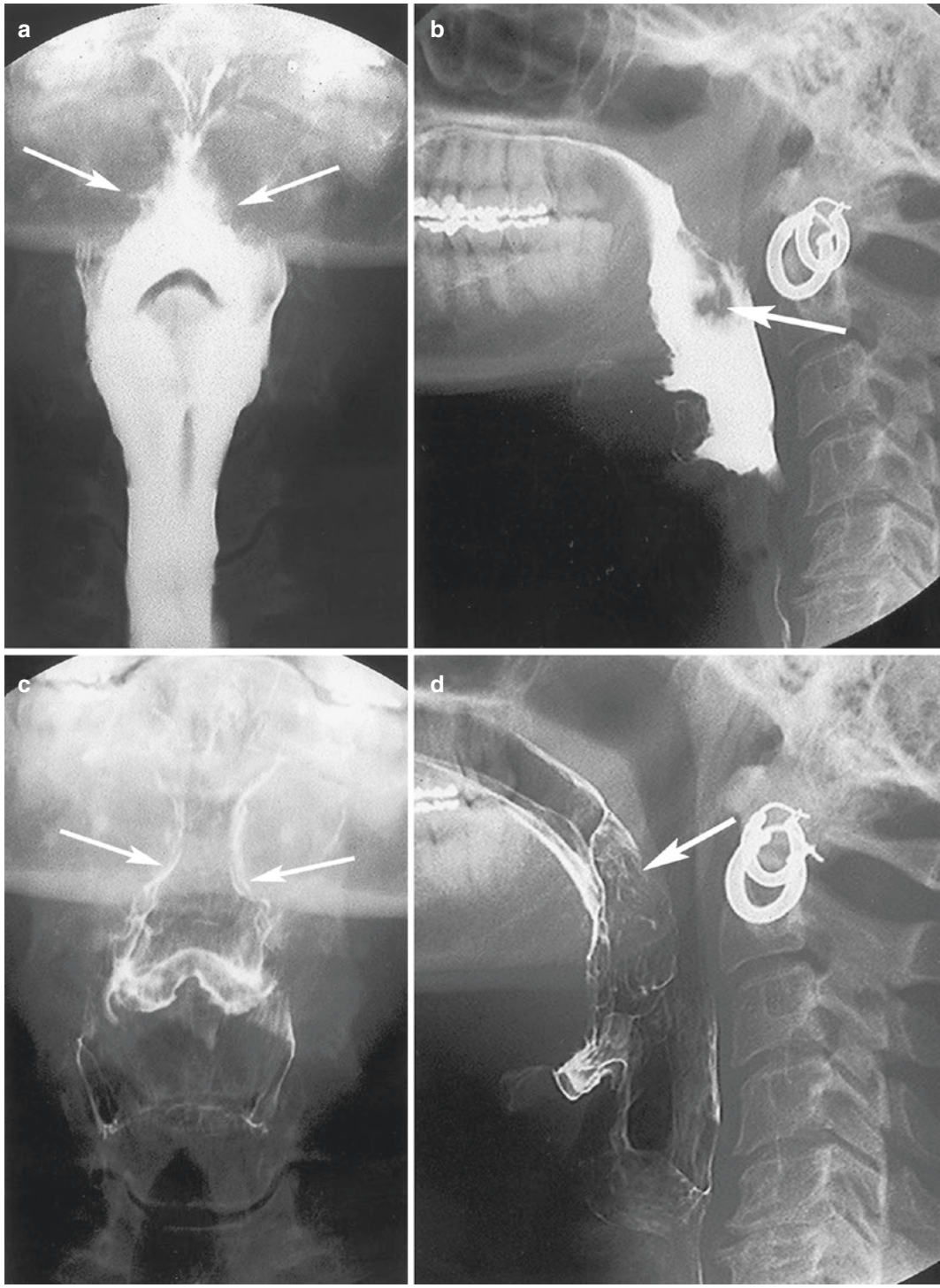

Fig. 5 (**a**, **b**) Barium swallow, single-contrast full column films. (**c**, **d**) Double-contrast films. In this 30-year-old woman there are extremely large tonsils (*arrow*). This finding was seen in both frontal and lateral projection. They may simulate normal or exaggerated function in the constrictor musculature, but they are in fact caused by a morphologic abnormality. Such hypertrophic tonsils may cause dysphagia

as the implicit meaning of "penetration" and "aspiration" is not widely accepted.

Of crucial importance is the coordination between the oral and pharyngeal stages of swallowing. The most common cause of misdirected swallowing is dissociation between the oral and pharyngeal stages of swallowing. This means that those two compartments are acting normally but the synchronization between them is impaired. The oral stage includes propulsion of the bolus into the pharynx. The pharyngeal stage of swallowing includes elevation of the hyoid bone, the larynx, and the pharynx. It is crucial to observe a conspicuous anterior movement of the hyoid bone as this is an indicator of elicitation of pharyngeal swallow. Any patient who does not show such hyoid bone movement potentially has a severe pharyngeal dysfunction. There should also be an approximation between the larynx and the hyoid bone due to contraction of the thyrohyoid muscles. In normal individuals the timing of the oral and pharyngeal stages is tightly coordinated and there is usually a time lag of not more than 0.5 s between when the apex of the bolus passes the faucial isthmus and start of the anterior movement of the hyoid bone. In patients with such a tight coordination, misdirected swallowing is seldom seen. However, the longer the delay, the more likely misdirected swallowing is to occur. Such incoordination between the oral and pharyngeal stages of swallowing is particularly common in the elderly. It is often the sole cause of misdirected swallowing (Fig. 6).

Airway closure and constrictor activity are both important elements of swallowing. Absence of elevation of the pharynx and larynx and failure of anterior movement of the hyoid bone are crucial elements of abnormal function. These are seen not only in the neurologically impaired patient but also after extensive surgery and/or radiotherapy. During barium swallow, the quality of the cough reflex is readily appreciated and can

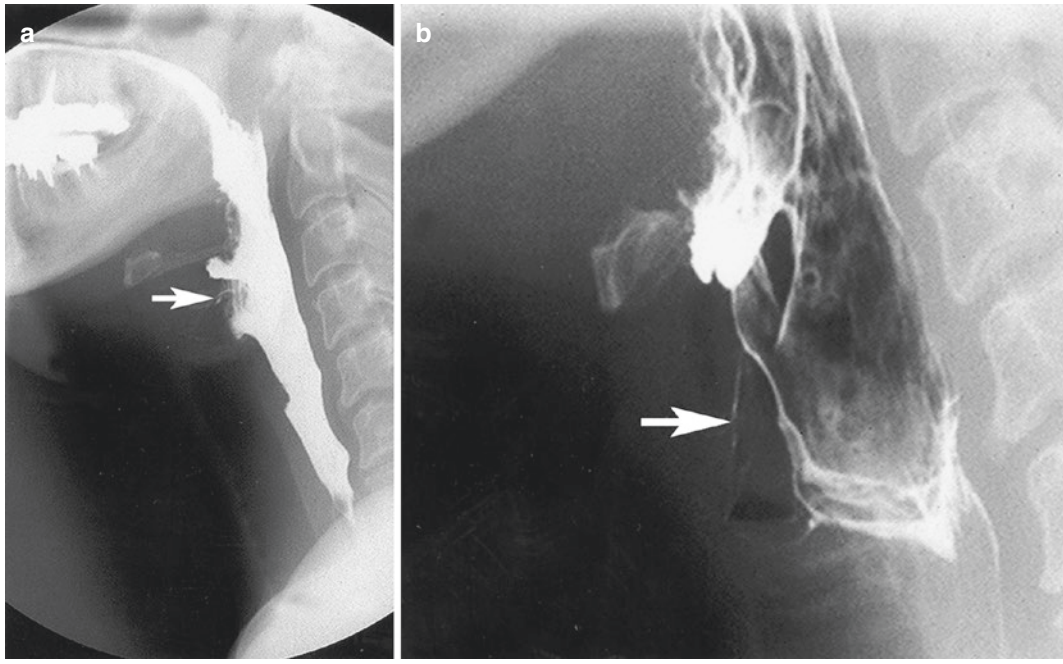

Fig. 6 This patient complained of an occasional sensation of having a foreign body in the neck. She pointed to the lateral part of her neck. Several swallows were normal. However, small amounts of barium eventually reached into the laryngeal vestibule. This was due to a slight dissociation (1.7 s) between the oral and pharyngeal stages of swallowing. This was enough to cause misdirected swallowing into the laryngeal vestibule. The patient then indicated that she had the foreign body sensation in the neck. This was seen both on single-contrast full column films (**a**) (*arrow*) and on double-contrast films (**b**) (*arrow*)

be defined as to the level where it is elicited, as well as roughly how much and for how long the barium must be in contact with the laryngeal and/or tracheal mucosa. However, for proper quantification of misdirected swallowing to the trachea, scintigraphy is more accurate than barium swallow (Muz et al. 1987).

Discovery of misdirection of the barium into the larynx and/or trachea should not lead to the interruption of the study. On the other hand, there are patients with massive penetration into the trachea in whom a very limited study is sufficient for answering the clinician's immediate questions concerning possible oral feeding. It is important to elucidate the underlying pathophysiologic processes in these patients and a few swallows should be observed in lateral projection. However, the risk of acquiring bronchopneumonia secondary to misdirected bolus is probably much less than many would expect (Ekberg and Hilderfors 1985).

According to Kun et al. (1987), elderly patients have misdirected swallowing due to dysfunction in the oral stage or a combination of oral and pharyngeal stage dysfunction. Oral stage dysfunction was due to ingestion of a large volume or rapid acquisition. However, dissociation between the oral and pharyngeal stages was the main finding. It has been shown that thermal stimulation of the faucial isthmus reduces such a dissociation (Logemann 1983; Logemann and Kahrilas 1990). For many years such tactile and thermal stimulation of the faucial isthmus has been a widely used technique for treatment of these patients.

Misdirected swallowing has been considered a major cause of aspiration pneumonia. If major aspiration occurs during barium swallow, it is common for the patient to be fed nonorally. The rationale for such treatment has been questioned (Siebens and Linden 1985). It was shown that patients who were fed nonorally showed more frequent aspiration pneumonia than those who were fed orally. Their explanation was that saliva contaminated with bacteria in the oral cavity caused the pneumonia. The oral hygiene in these patients is usually low. It was concluded that artificial feeding does not seem to be a satisfactory solution for preventing pneumonia in elderly patients with prandial aspiration.

Patients who have defective protection of the airways during swallowing are also at risk of fatal choking episodes. Prandial aspiration most often results in reflexive coughing, gagging, and forced exploration. This is often referred to by the patient as "choking." It is usually uncomfortable but brief and usually familiar in nature to the patient. This is in contrast to airway obstruction during oral intake, which may be fatal unless the occluding material is removed or displaced. Such food asphyxia is an important cause of accidental death in children (Editorial 1981; Lima 1989). It is estimated that 8000–10,000 adults choke to death each year (Donner and Jones 1985). The development of the Heimlich maneuver and its inclusion as part of basic cardiopulmonary resuscitation training has increased public awareness of the problem in the USA (Heimlich 1985). The cause of near-fatal choking episodes has been studied in 58 individuals (Feinberg and Ekberg 1990). Most of these patients who had survived a Heimlich maneuver applied because of food impaction showed abnormalities during the barium swallow. Most of them aspirated liquid bolus. This was due to bolus leak or dissociation. Some patients also showed defective closure of the laryngeal vestibule. However, a subset of patients (14 of 58) were able to vocalize during the near-fatal choking episode and they demonstrated structural abnormalities of the PES and the esophagus. Therefore, patients who have had a near-fatal choking episode should undergo an elective radiologic barium study in order to reveal an underlying cause and prevent new episodes that may otherwise prove to be fatal.

4 Dysfunction of the Pharyngoesophageal Segment

Defective opening of the PES is a common finding. This may be seen as a posterior indentation of the cricopharyngeal muscle. However, it has been shown that the indentation per se does not impinge on the lumen diameter (Olsson and

Ekberg 1995). In fact, the diameter of the PES at the level of the cricopharyngeal muscle is the same in patients with and without that posterior cricopharyngeal bar. Instead the pharynx is dilated above and the cervical esophagus is dilated below the cricopharyngeal bar, thereby giving the false impression of lumen narrowing. Manometrically, the cricopharyngeal muscle in these patients has been shown to act normally, and there are decreased peak amplitudes in the pharynx above. There is also a small subset of patients who have fibrosis of the PES and the cricopharyngeal muscle, but this is rare. Most patients who appear to have an abnormal opening of the PES do have normal morphology and function in that particular segment, and the impairment in fact is defective elevation of the PES and weakness of the pharyngeal constrictors (Olsson and Ekberg 1995). The most common cause of this, in turn, is lack of initiation of the pharyngeal stage of swallowing. Therefore, any surgical procedure on the PES is not likely to be beneficial, the main reason being that only a small fraction of the closure of the PES is due to muscle tonicity.

Failure of the PES to open may be seen in neurologic disease but is generally not accompanied by abnormal pharyngeal bolus transport (Curtis et al. 1984; Ekberg 1986a). Failure of the cricopharyngeal muscle to open or elongate may be due to (1) defective muscle relaxation, (2) defective extensibility, and (3) hypertrophy or hyperplasia. The posterior bar intruding into the barium and created by the cricopharyngeal muscle is seldom an isolated dysfunction. It is commonly associated with abnormal motor function in the segment above (i.e., the inferior pharyngeal constrictor) and/or in the segment below (i.e., the cervical esophageal muscles). Therefore, the cricopharyngeal indentation, though the most conspicuous, is only one aspect of severe motor dysfunction in the adjacent PES (Ekberg 1986a). Cervical esophageal webs are also common in dysphagic patients (Figs. 5 and 7).

Adapted and compensated swallowing basically have the same radiologic appearance and, in most patients, they are notoriously difficult to demonstrate. Therefore, a normal radiologic study does not rule out pharyngeal abnormality.

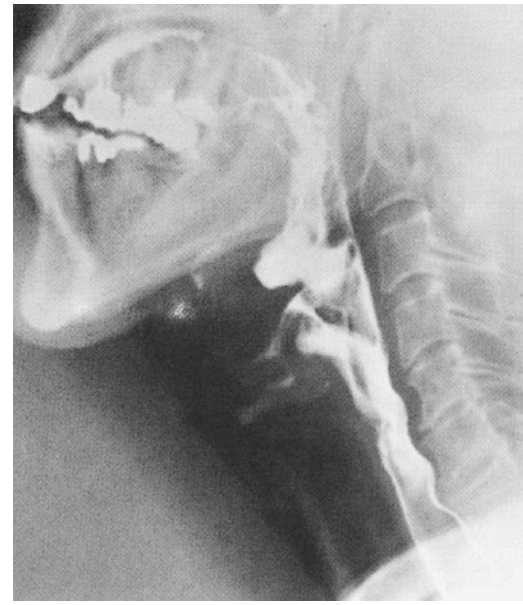

Fig. 7 A 76-year-old woman 2 week after a stroke. Lateral radiogram of the pharynx during swallowing. Contrast medium has reached into the pharynx, through the PES, and into the cervical esophagus. The epiglottis is in a horizontal position. The hyoid bone is elevated and brought slightly forward. However, contrast medium has reached into the laryngeal vestibule to the level of the sinus of Morgagni. No contrast medium is seen in the trachea. The patient did not subjectively experience this misdirected swallowing. There was no cough. This indicates chronic aspiration (see also Fig. 8)

5 Radiologic Evaluation in Specific Disease Entities

Radiologic evaluation of oral and pharyngeal function during swallowing has a high sensitivity but is nonspecific in terms of the type and extent of the underlying abnormality (Figs. 7, 8, and 9). Specific disease is seen to cause pharyngeal dysfunction and dysphagia with varying frequency and the cause of dysphagia during the disease varies. This has been studied radiologically in cerebrovascular disease (Veis and Logemann 1985; Donner and Silbiger 1966), poliomyelitis (Silbiger et al. 1967; Ardran et al. 1957), amyotrophic lateral sclerosis (Bosma and Brodie 1969a), myasthenia gravis (Murray 1962), myotonic dystrophy (Bosma and Brodie 1969b), Parkinson's disease (Calne et al. 1970; Robbins

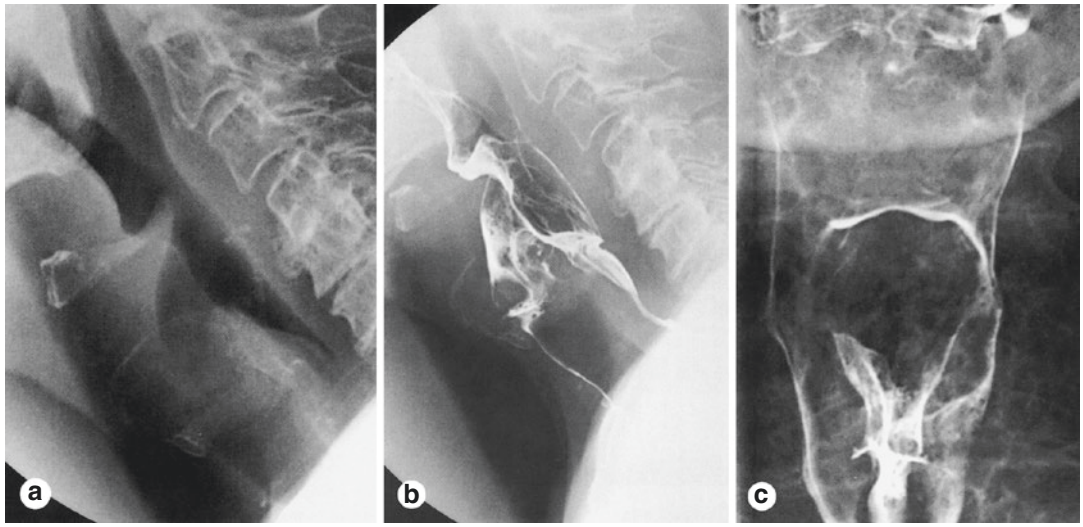

Fig. 8 A 74-year-old man who had undergone radiotherapy to the neck for laryngeal carcinoma 3 year previously. There was no sign of recurrence but the patient now had difficulty swallowing. He had sustained several choking episodes. (**a**) Lateral radiogram of the pharynx. There is thickening of the prevertebral soft tissue and of the epiglottis. (**b**) After barium swallow, there is contrast medium in the laryngeal vestibule and in the trachea, but only minor retention in the piriform sinuses. (**c**) Anteroposterior view of the pharynx. There is minor retention in the effaced valleculae and shallow piriform sinuses. Contrast medium is also seen in the laryngeal vestibule and sinus of Morgagni (see also Fig. 7)

et al. 1986), brainstem tumor (Kun et al. 1987), and multiple sclerosis (Daly et al. 1962). Even the distinction between upper and lower motor neuron disease, e.g., cortical bulbar tract dysfunction (pseudobulbar palsy), and lower motor neuron disease, i.e., pontomedullary dysfunction (bulbar palsy), is ambiguous. However, the latter patients usually have more widespread pharyngeal paresis and they also lack initiation of pharyngeal swallow. Basically, all neurologic impairments lead to the same dysfunction. This is especially so for the "end-stage" dysfunction, which tends to lead all types of disease entities down a common pathway with impaired elevation of the larynx and pharynx and impaired anterior movement of the hyoid bone.

The cause of dysphagia in terms of symptoms and functions often does not match. Deterioration or progression of dysphagia is as a rule compensated. So, if we could decompensate swallowing, this would reveal progression. The radiologist may intentionally elicit the decompensation by extension of the neck by provision of a large bolus and other stresses (Ekberg 1986b; Buchholz et al. 1985).

5.1 Cerebrovascular Diseases

Most patients with pharyngeal dysfunction are patients who suffer from stroke. The prevalence of stroke in the USA has been estimated to be approximately 1.6 million persons, with 250,000 new cases of stroke each year. Of these stroke patients, 30–50% will develop dysphagia. Strokes that are multiple (Veis and Logemann 1985; Rosenbek et al. 1991; Horner et al. 1991; Splainard et al. 1988), bilateral (Logemann 1983), or localized in the brain stem (Veis and Logemann 1985; Horner et al. 1991; Logemann and Kahrilas 1990; Linden and Siebens 1983) are considered to cause severe swallowing impairment. However, even unilateral cortical or subcortical strokes (Veis and Logemann 1985; Robbins and Levine 1988; Robbins et al. 1993; Gordon et al. 1987; Meadows 1973) can cause swallowing problems. Dysphagia in the stroke population may last for weeks or months, but occasionally much longer. Although dysphagia is a subjective symptom, dysfunction of the pharyngeal stage of swallowing can be objectively registered using barium swallow and video recording.

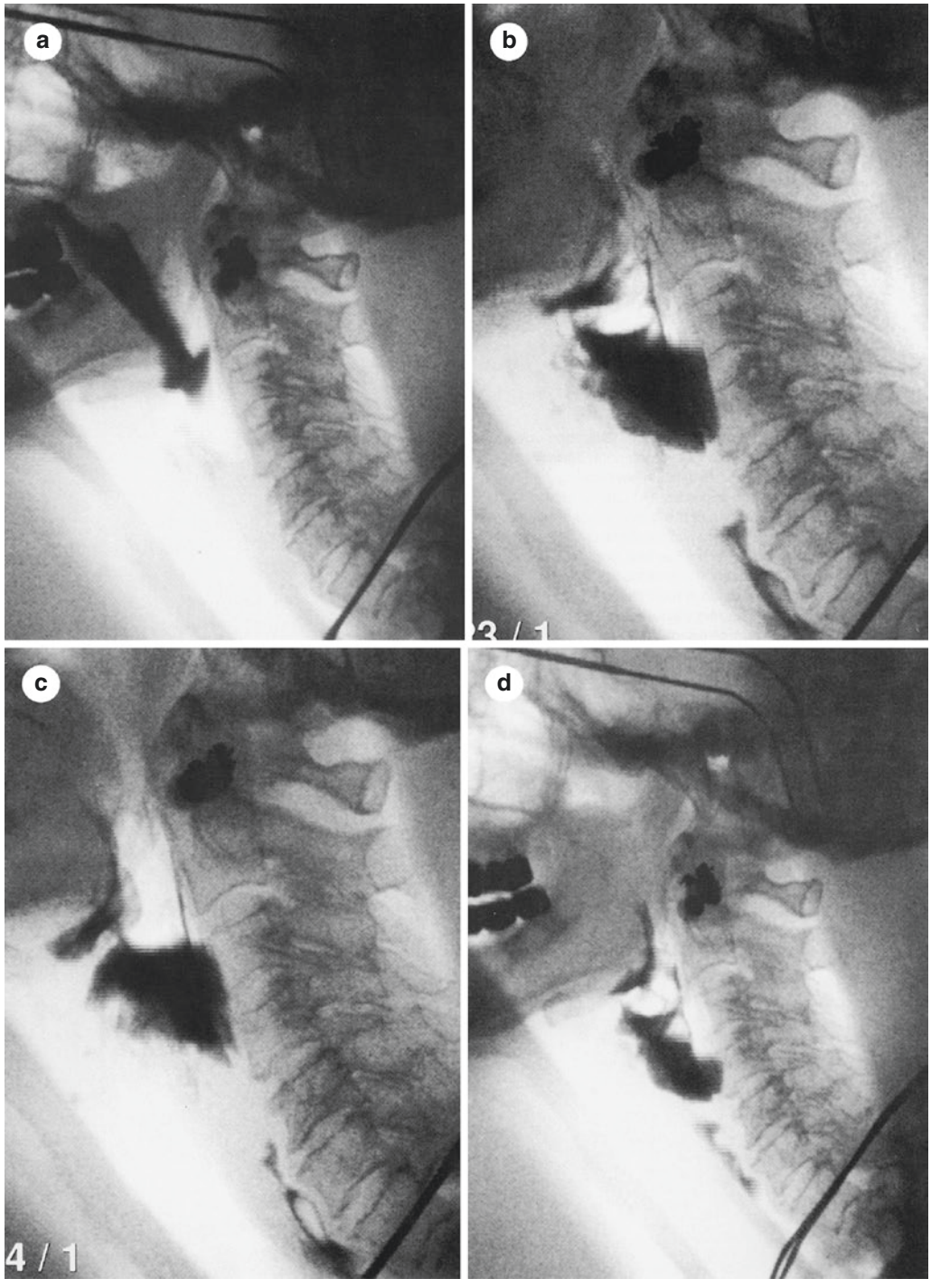

Fig. 9 A 65-year-old woman with no prior history of stroke. She had developed dysphagia 2 year previously. The dysphagia progressed over a couple of weeks. She had difficulty with all kinds of textures and had a very prolonged eating time. (**a**) The contrast medium is brought into the pharynx. (**b**) Pronounced dilatation of the pharynx indicating high compliance secondary to weakness of pharyngeal constrictor musculature. (**c**) Eventually contrast medium reached into the laryngeal vestibule but not further down into the airways. (**d**) Only very tiny streaks of barium reach through the PES during each swallowing attempt. There was minor anterior movement of the hyoid bone that could indicate that pharyngeal swallow had been elicited. However, there was no constrictor activity. The patient spontaneously learned to compensate for the absence of contractility in the constrictors (from Ekberg and Olsson 1997)

This technique is now the gold standard for evaluation of normal and abnormal swallowing.

Oropharyngeal impairment is recognized as a frequent cause of morbidity, disability, and costly dependence in stroke patients (Veis and Logemann 1985). Bolus misdirection into the larynx and trachea is perhaps the most significant abnormality that we routinely observe during barium swallow. Especially in the elderly, swallowing dysfunction is prevalent, particularly in those who are hospitalized, institutionalized, or well advanced in years. These patients represent some of the most challenging cases that clinicians must deal with on a routine basis. The diagnosis is difficult and so is management. However, this is not because of unique abnormalities in swallowing behavior or morphodynamics, but is because of the patients themselves (Veis and Logemann 1985). In fact, swallowing problems may go undetected in these patients because the signs and symptoms are vague, subtle, or unreported by the patients' caregivers. Critical management decisions regarding dietary alterations, degree of oral intake, and institution of artificial feeding often depend on the radiologic assessment of such misdirected swallowing.

Radiologists are important members of multidisciplinary teams that address swallowing disorders. Diagnosis and treatment of dysphagia depend on videofluorographic deglutition examinations during barium swallow. Patients with cerebrovascular disease, Parkinson's disease, and other neurologic conditions, including elderly patients with dementia, need to undergo videofluorographic examination in order to correctly describe functional status and thereby provide a platform for rational therapy. Treatment strategies must be founded on objective grounds (see Sect. 5).

6 The Role of the Radiologist in the Design of Therapy

Treatment of oral and pharyngeal dysfunction strives to correct or compensate for damage to specific neuromuscular components of the oral and pharyngeal swallow, such as reduced tongue movement, delay in triggering the pharyngeal swallow, pharyngeal constrictor paralysis, and defective closure of the laryngeal vestibule. For evaluation of such therapy, successive radiologic evaluations are necessary (see Sect. 5). The radiologic examination must (1) reveal the anatomic and/or physiologic abnormalities causing the patient's dysphagia, and (2) identify those compensatory strategies or therapy techniques which are most effective in improving the efficiency of the patient's oral and pharyngeal swallow. The radiologic examination should start with ingestion and include also the passage of the bolus into the stomach. Following liquid swallows, the patient should be given other food consistencies, particularly pudding consistency materials and food requiring chewing, such as cookies. A variety of foods mixed with barium can be introduced in the radiologic study. The volume of each food or liquid should be measured because the dynamics of normal pharyngeal swallow vary as the volume of the bolus increases.

Two types of therapy techniques are used for reeducation for oral and pharyngeal dysphagia: (1) "direct" swallowing therapy procedures which passively facilitate swallowing by use of particular foods and liquids; and (2) "indirect" therapy techniques designed to compensate for dysfunction by increasing muscle strength, range of motion, or coordination independent of swallowing. The effectiveness of either of these techniques is assessed by observing the transport of the swallowed bolus during radiography.

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Evaluation of Symptoms

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Contents

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1 Introduction

Symptoms of laryngo-/pharyngeal/oesophageal diseases are related to swallowing function, such as dysphagia, odynophagia, globus sensation or heartburn. Patients often do not differentiate between these symptoms and report "swallowing problems". The crossing of airway and digestive tract in the hypopharynx is a critical region for swallowing and respiration: if protection of the airway during swallowing is not secured, aspiration occurs. Moreover, the pharynx is not only part of the upper digestive tract, but also of the vocal tract and therefore influences resonance and articulation.

Swallowing belongs to the most frequent activities in the human body: the human being swallows between 580 and 2000 times a day (Garliner 1974; Logemann 1983, 1998). However, swallowing is not only a vital primary function to ensure adequate nutrition and hydration, but also decisively contributes to quality of life and social integration. Dysphagia may lead to malnutrition and, in the case of aspiration, to potentially life-threatening pulmonary complications, such as aspiration pneumonia. Furthermore, life quality of dysphagic patients is impaired (Ekberg et al. 2002). Dysphagia represents a frequent and severe medical problem. Its prevalence is higher among elderly people and often associated with dementia. For life expectancy the nutritional status, independent oral feeding and prevention of aspiration-related pulmonary complications are of utmost prognostic

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relevance. In acute care hospitals, 13–14% of patients are believed to suffer from dysphagia, and in nursing homes the percentage of dysphagic patients reaches up to 50% (Logemann 1995). Moreover, among patients aged over 65 years, aspiration pneumonia is the fourth most frequent cause of death (Sasaki 1991). Every year, about 50,000 US Americans die from pulmonary complications of aspiration (Jones and Donner 1991). Therefore, in modern, function-orientated medicine, the management of the dysphagic patient has become of great clinical importance and a focus of scientific interest.

Dysphagia and other swallowing complaints necessitate a thorough diagnostic procedure. Only the knowledge of the underlying cause and of the individual swallowing pathophysiology enables appropriate treatment of the patient.

2 Terminology of Dysphagia

The symptom *dysphagia* is defined as disturbance of the intake or transport of food from the mouth to the stomach. Furthermore, it includes behavioural, sensory and motor disorders in preparation for the swallow, e.g. disorders of cognitive awareness, visual and olfactory recognition of food and of the physiologic responses to smell and presence of food (Leopold and Kagel 1996). In the case of *oropharyngeal dysphagia*, the oral preparatory, oral and/or pharyngeal phases of swallowing are afflicted. If the oesophageal phase is disturbed, *oesophageal dysphagia* is present. Both types of dysphagia may influence each other; therefore dysphagia makes the comprehensive evaluation of the aerodigestive tract from the oral cavity to the stomach necessary.

2.1 Components of the Impaired Swallow

To address the pathophysiological aspects, dysphagia has to be regarded as a syndrome. The most important dysphagia-related symptom is *aspiration*, which is defined as the entry of saliva, food or gastric secretion into the airway under the level of the vocal folds. Other components of dysphagia are drooling, leaking, nasal penetration, laryngeal penetration, retention or pharyngeal regurgitation. The swallowing pathophysiology is analysed in relation to the phases of swallowing.

Drooling describes complaints of oral spill, i.e. the falling of food, liquid or saliva from the mouth anteriorly when lip closure is incomplete. *Leaking* is defined as premature loss of the bolus over the tongue base into the pharynx before the swallowing reflex is triggered. Consequently, the risk of aspiration occurs. A *delayed triggering of the swallowing reflex* occurs in neurological diseases (e.g. stroke) or after extensive surgical resection of the trigger points for the pharyngeal swallow.

Retention (pooling) of saliva or food may be localised in the oral cavity, valleculae or hypopharynx (Fig. 1). Retentions in the anterior or lateral sulcus are due to reduced muscle tone in the labial or buccal musculature. Disturbed lingual function may result in retentions on the floor of the mouth and the valleculae. Weakness, paresis or scarring of pharyngeal muscles give rise to pharyngeal retentions.

Nasal penetration (regurgitation) describes the entry of food into the nose and may be caused by incomplete velopharyngeal closure or pharyngeal/esophageal stop of the bolus passage with subsequent overflow into the nasal cavity. In case of *laryngeal penetration*, food or saliva reaches the larynx to the level of the vocal folds.

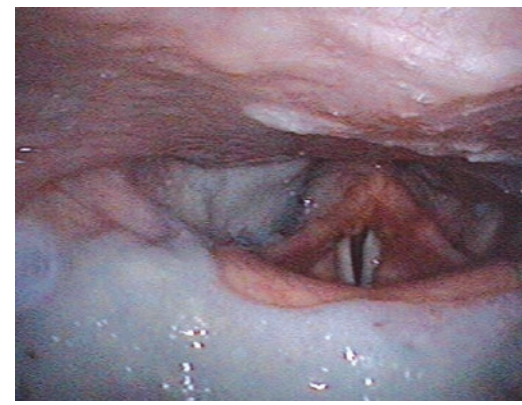

Fig. 1 Retentions of saliva bilaterally in the valleculae and the right pyriform sinus

Pharyngeal regurgitation is characterised by (parts of) the already swallowed bolus flowing back into the pharynx due to a Zenker's diverticulum or a disturbed oesophageal bolus transport.

2.2 Dysphagia and Other Swallowing Complaints

Dysphagia has to be distinguished from other swallowing complaints, such as globus sensation or odynophagia. *Odynophagia* describes the painful swallow, as occurs in inflammatory or tumorous diseases of the upper aerodigestive tract (e.g. acute tonsillitis, peritonsillar abscess, epiglottitis, hypopharyngeal carcinoma).

Globus sensation (*globus pharyngis*) is a feeling of a lump or fullness in the throat and discomfort when swallowing saliva. In contrast to dysphagia, swallowing of food is not disturbed. The symptom mainly occurs during swallowing of saliva and decreases or vanishes while swallowing food. In many patients, an underlying cause can be found, e.g. gastroesophageal reflux disease, oesophageal motility disorders, hypertensive upper esophageal sphincter (cricopharyngeal achalasia), thyroid gland disease, cervical spine syndrome or hyperfunctional voice disorder. Therefore, the obsolete term "globus hystericus" should not be used any more. Only if an exact morphological and functional analysis of larynx, pharynx, oesophagus and neck does not show any medical entity, a psychogenic aetiology can be suspected. Above all, globus sensation and dysphagia may occur in combination.

3 Aspiration

The antero- or retrograde entry of saliva, food or gastric secretion into the airway under the level of the vocal folds is defined as *aspiration* (Fig. 2). To reveal or exclude aspiration is the main goal of the diagnostic procedure in dysphagic patients. The presence/absence of aspiration determines further patient management. In the case of absent or reduced cough reflex, aspiration does not induce cough, but remains "silent" (*silent aspiration*) and is not immediately noticed. About 40% of aspirating patients are so-called silent aspirators.

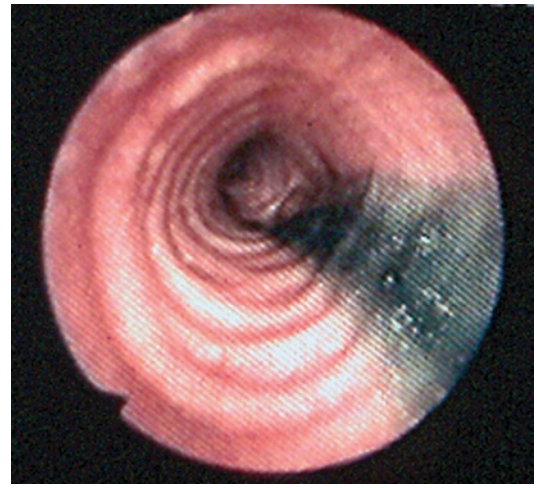

Fig. 2 Aspiration (videoendoscopic view): *blue-coloured* aspirated food in the trachea (from Bigenzahn and Denk 1999)

Aspiration can be classified in relation to the triggering of the swallow reflex. It may occur before (predeglutitive), during (intradeglutitive) and after the swallow (postdeglutitive) or in combined forms (Logemann 1983). *Aspiration before the swallow* may be present when the triggering of the swallow reflex is absent or disturbed, e.g. after stroke. Incomplete laryngeal closure and/or reduced laryngeal elevation may give rise to *aspiration during the swallow*, as is the case, for example, in vocal fold paralysis or in laryngeal defects after partial laryngectomy. Reduced pharyngeal peristalsis, reduced laryngeal elevation and disturbed opening of the pharyngo-oesophageal sphincter possibly result in *aspiration after the swallow* (Fig. 3a, b), e.g. in fibrosis with "frozen" (immobile) larynx after radiation therapy or cricopharyngeal achalasia after stroke.

The severity of aspiration is influenced not only by the amount and type of the aspirated material, but also by the presence of cough reflex and the possibility of voluntary coughing and throat clearing. Several severity scales are used

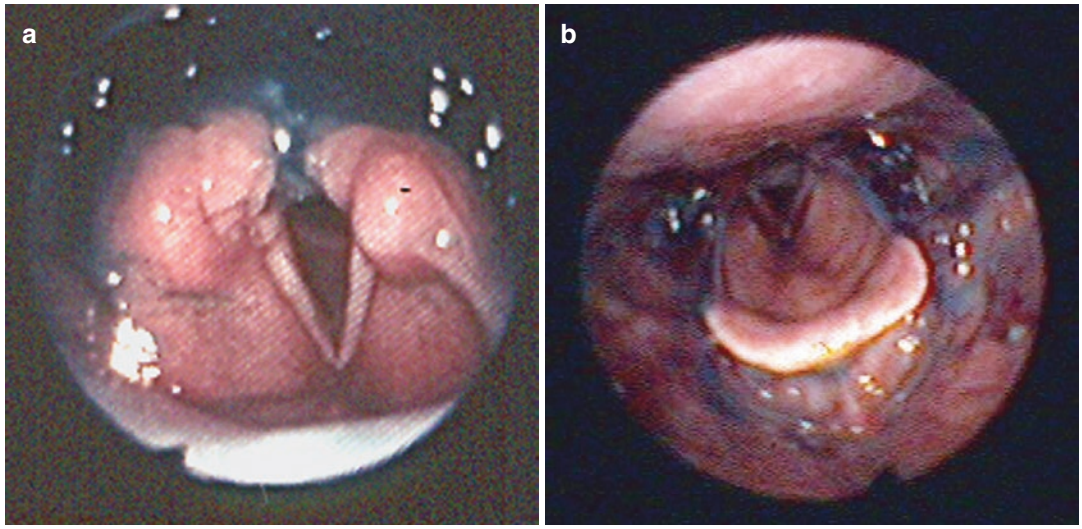

Fig. 3 Aspiration after the swallow (videoendoscopic view): overflow aspiration due to retentions in the hypopharynx (**a**) *blue-coloured* water (from Bigenzahn and Denk 1999) (**b**) jelly

for the grading of aspiration (Table 1). The clinical aspiration scale (Miller and Eliachar 1994) considers possible pulmonary consequences. In the videoendoscopic aspiration scale (Schröter-Morasch 1996) attention is paid to the cough reflex and voluntary coughing. The videofluoroscopic aspiration scale (Hannig et al. 1995) is based on the amount of aspirated material and the presence/absence of the cough reflex. The penetration-aspiration scale by Rosenbek et al. (1996) describes an 8-point scale. The severity of aspiration is determined by the level of entered material in the airway and if this material can be expelled.

The individual tolerance of aspiration varies widely. Some patients tolerate aspiration of more than 10% of the bolus, whereas other patients develop aspiration pneumonia even after aspiration of their saliva. Therefore, not only aspiration but also other additional risk factors play an important role. Langmore et al. (1998) found the following predictors for the development of aspiration pneumonia: dependent for feeding, dependent for oral care, number of decayed teeth, tube feeding, more than one medical diagnosis, number of medications and smoking.

Table 1 Aspiration scales

Clinical scale (Miller and Eliachar 1994)	
I:	Incidental aspiration without complications
II:	Intermittent aspiration of liquids; saliva and solid boluses can be swallowed
III:	No oral feeding possible, intermittent pneumonias
IV:	Life-threatening aspiration; chronic pneumonia/hypoxia
Videoendoscopic scale (Schröter-Morasch 1996)	
I:	Incidental aspiration, intact cough reflex
II:	Incidental aspiration, no cough reflex, voluntary coughing possible or permanent aspiration, intact cough reflex
III:	Permanent aspiration, no cough reflex, voluntary coughing possible
IV:	Permanent aspiration, no cough reflex, no voluntary coughing
Videofluoroscopic scale (Hannig et al. 1995)	
I:	Aspiration of material that has penetrated into the laryngeal vestibule or ventricle, intact cough reflex
II:	Constant aspiration of less than 10% of the bolus, intact cough reflex
III:	Constant aspiration of less than 10% of the bolus, reduced cough reflex or constant aspiration of more than 10% of the bolus, intact cough reflex
IV:	Constant aspiration of more than 10% of the bolus, reduced cough reflex

4 Aetiology of Dysphagia

The aetiologies of dysphagia may be divided into the following groups:

- Diseases of the upper aerodigestive tract (*peripheral "mechanical" dysphagia*)
- Neurological diseases (*neurogenic dysphagia*)
- *Psychogenic dysphagia*

Only if after thorough diagnostics peripheral or neurogenic dysphagia is excluded, psychogenic factors have to be considered. In some cases, the distinction from eating disorders is difficult.

4.1 Mechanical Dysphagia

Diseases of the upper swallowing and respiratory tract or surrounding structures may give rise to dysphagia and aspiration (Table 2). The symptom dysphagia necessitates the exclusion of a malignant tumour in the aerodigestive tract. Moreover, not only a tumorous disease of the oral cavity, pharynx or larynx itself but also the sequelae of therapy—surgical resection, radiation and chemotherapy—can interfere with bolus transfer or airway protection with consecutive dysphagia and aspiration that requires a functional swallowing therapy to regain swallowing function. The

Table 2 Examples of dysphagia aetiologies (modified from Denk and Bigenzahn 1999)

Type of dysphagia	Aetiology
Mechanical peripheral dysphagia	
Oropharyngeal	Inflammatory diseases
	Malignant tumours in the upper aerodigestive tract
	Sequelae after tumour therapy (surgery, radiation, chemotherapy)
	Diseases/surgery of the cervical spine
	Long-term intubation
	Cheilognathopalatoschisis
	Tracheo-oesophageal fistula
	Diverticula (Zenker's diverticulum)
	Goitre
	Systemic diseases (scleroderma, amyloidosis)
	Graft-versus-host disease
Esophageal	Obstructive esophageal diseases (peptic, tumorous stenosis)
	Motility disorders (gastro-oesophageal reflux disease, non-propulsive contractions)
Neurogenic dysphagia	
Central nervous system	Stroke
	Degenerative processes: Amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis
	Cerebral palsy
	Dementia, Alzheimer's disease
	Post-polio syndrome
	Encephalitis
	AIDS
	Posterior fossa tumours
	Head trauma, cervical spine cord injury
	Intoxications
	Drug effects (sedatives, neuroleptics)
	Arnold Chiari malformation

(continued)

Table 2 (continued)

Type of dysphagia	Aetiology
Peripheral nervous system	Skull base tumours (chordoma, meningioma)
	Meningitis
	Guillain-Barré syndrome
	Neuropathy (alcoholic, diabetic)
Neuromuscular junction	Myasthenia gravis
	Botulism
	Lambert-Eaton syndrome
Muscles	Dermatomyositis, polymyositis
	Myopathy (endocrine/metabolic)
	Myotonia, muscular dystrophy
Psychogenic dysphagia	
	Phagophobia

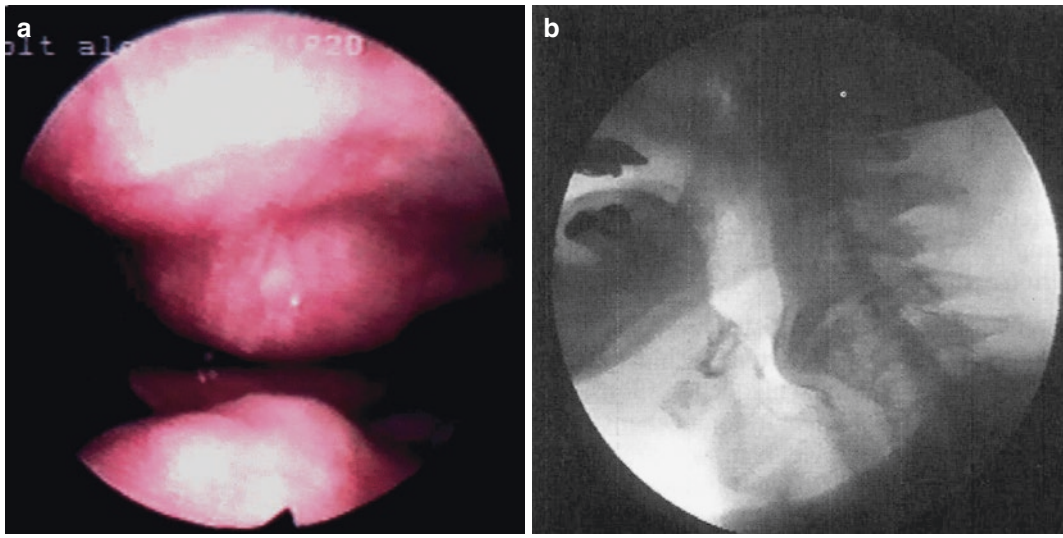

Fig. 4 Diffuse idiopathic skeletal hyperostosis (DISH). (**a**) Endoscopic view. (**b**) Radiologic view (from Bigenzahn and Denk 1999)

different tumour resections in the head and neck are known to create patterns of swallowing disorders, but the same resections need not necessarily result in the same form and degree of dysphagia and aspiration. The extent and localisation of the resections carried out are regarded as determining factors for the severity of dysphagia. Besides these local factors, also general factors, e.g. patients' general condition or therapy-onset postoperatively, influence the outcome of swallowing rehabilitation (Denk and Kaider 1997).

Not only tumours in the pharynx or oesophagus, but also thyroid gland disease or cervical osteophyte compression due to diffuse idiopathic skeletal hyperostosis (DISH) (Marks et al. 1998), may be responsible for obstructive dysphagic symptoms which are typically worse for solid than liquid bolus. Patients suffering from DISH (Fig. 4a, b) become especially symptomatic when an additional disease afflicting swallowing function (e.g. stroke) impairs the patient's functional compensatory capability.

4.2 Neurogenic Dysphagia

Nearly all neurological diseases have the potential to disturb the four levels of sensomotoric control of the swallow (central, peripheral nervous system, neuromuscular junction, muscles) and may cause dysphagia and aspiration (Table 2). For the management of the patients (functional therapy, type of nutrition) it is of utmost importance to distinguish between neurologic lesions with recovery potential (e.g. stroke, head trauma, cervical spine cord injury, etc.) and progressive diseases.

Stroke represents the most frequent cause of dysphagia (25%, Groher and Bukatman 1986). The percentage of dysphagic stroke patients differs with the time from the onset of stroke: in the first 2 weeks after stroke 41%, in the chronic phase 16% of the patients suffer from dysphagia (Kuhlemeier 1994). After all, within the first year after stroke, 20% of patients die from aspiration pneumonia (Brown and Glassenberg 1973).

Besides the swallowing disturbance, neurologic patients possibly show additional symptoms that have to be considered. Disturbances in the motor system bring about impaired posture and head control, and cognitive deficits lead to a lacking awareness of disease. Severely impaired speech and language (e.g. dysarthria, aphasia) impair communication with the patient.

5 Clinical Symptoms of the Dysphagic Patient

Aspiration is well known as the most threatening symptom of dysphagia. Due to disturbed laryngeal sensibility and absent cough reflex, aspiration often occurs silently. Therefore the fact that the patient does not cough/choke while eating cannot be regarded as a reliable "clue" symptom to exclude aspiration. *Indirect and direct symptoms of dysphagia/aspiration* (Table 3) are possible hints to suspect dysphagia and aspiration. Direct symptoms occur during swallowing of food and liquids, whereas indirect symptoms are not directly associated with the swallow as such, but are due to dysphagia.

Table 3 Symptoms of dysphagia/aspiration (from Schröter-Morasch 1993)

Indirect symptoms
Weight loss
Frequent occurrence of fever
Coughing
Bronchitis/pneumonia
Changes of voice, articulation/speech and language
Globus sensation
Heartburn
Non-cardiac chest pain
Direct symptoms
Prolonged duration of swallowing
Pain
Fear of swallowing
Changes of posture
Avoidance of particular consistencies
Drooling
Obstruction
Choking, coughing
Spitting of food
Regurgitation

Among the *indirect symptoms*, weight loss is regarded as a reliable hint to judge the effects of swallowing impairment, because weight is usually directly related to the nutritional state. Frequent occurrence of fever, coughing, bronchitis or pneumonia may be clinical consequences of aspiration. Changes of voice (dysphonia), speech (dysarthria) and language (aphasia) should not be neglected, as they may be related to neurologic diseases. Moreover, anatomical and functional deficits in the upper aerodigestive tract possibly also lead to dysphonia, altered resonance (e.g. hyperrhinophonia = too much nasal resonance) or impaired articulation (e.g. dysglossia = disturbed articulation due to changes in the peripheral organs of speech). Globus sensation, heartburn and/or non-cardiac chest pain often are present in gastroesophageal reflux disease or esophageal motility disorders. Alterations of taste or mucosal dryness impair swallowing function and pleasure from oral intake.

Choking or coughing during or immediately after the swallow due to aspiration, prolonged duration of swallowing, pain (odynophagia) or fear of swallowing belong to the *direct symptoms of dysphagia and aspiration*. Furthermore, changes in posture during oral food intake and changes in eating habits (e.g. avoidance of some food consistency) deserve clinical awareness. Other direct symptoms the patient may report are drooling, nasal regurgitation, spitting of food or regurgitation. The feeling of obstruction may occur not only in patients with tumours, strictures, Zenker's diverticulum, webs or cervical osteophytes (DISH), but also in neurologic diseases because of pharyngeal muscle weakness, lack of coordination of the swallow or oesophageal motility disorder.

6 Screening Procedures

Various screening protocols try to select the patients who need a thorough swallowing diagnostic workup. No gold standard so ever does exist, and the various studies often cannot be compared because of different protocols, lacking validation and small sample sizes.

There is no common consent regarding who should perform the screening (the healthcare team or speech language pathologists?) and how it should be carried out. Is a water swallow sufficient (3-oz water swallow, Suiter and Leder 2008) or should not only water but also thicker consistencies be tested. The Gugging Swallowing screen (Trapl et al. 2007) uses in a direct swallowing test semi-solid, liquid and solid textures. Moreover, an indirect swallowing test as first step observes a saliva swallow, vigilance, voluntary cough and throat clearing. Also the Toronto Bedside Swallowing Screening Test (TOR-BSST, Martino et al. 2009) considers indirect aspects, such as mobility of the tongue and voice quality before and after the water swallows.

To increase the sensitivity and specificity, the combination of two tests is recommended, but the discussion remains controversial. Whereas Lim et al. (2001) believes that a water test in combination with pulse oximetry is an apt tool to detect aspiration, Leder (2000) states that the use of changes in SpO(2), heart rate or blood pressure values as indirect objective markers of aspiration is not suitable. Cervical auscultation did not gain wide acceptance and does not seem to bring any advantage (Al Hawat et al. 2014).

Due to silent aspiration, the dynamic instrumental methods of videoendoscopy and videofluoroscopy can never be replaced by any screening tool to detect or exclude aspiration.

7 Diagnostic Procedure

For adequate management of the patient suffering from swallowing complaints a thorough morphological and functional diagnostic procedure is needed to evaluate the swallow from the oral cavity to the stomach and to reveal the aetiology and individual swallow profile. The diagnostic procedure is summarised in Table 4. To address the complexity of swallowing disorders, an interdisciplinary approach is necessary. Very often, the dysphagic patient first presents to the otorhinolaryngologist/phoniatrician who—after thorough history taking—performs a videoendoscopy of the upper aerodigestive tract and videoendoscopic swallowing study (fibre-optic endoscopic evaluation of swallowing (FEES) (Langmore et al. 1988; Bastian 1991, FEESST (fibre-optic

Table 4 Diagnostic procedure (from Denk and Bigenzahn 1999, 2005)

History
Basic diagnostics (compulsory)
ENT/phoniatric examination
With clinical observation and videoendoscopic swallowing study (= flexible endoscopic evaluation of swallowing, FEES)
Videofluoroscopic swallowing study
In the case of aspiration, chest X-ray
Further diagnostics (optional)
Oesophagogastrodoudenoscopy
Ultrasound of the oral phases of swallowing
Cranial MRI
Manometry, pH-metry
Electrophysiological methods (electromyography)
Scintigraphy

evaluation of swallowing with sensory testing), Aviv 1998), and refers the patient to a videofluoroscopic swallowing study. Depending on the patient's needs and findings, further examinations have to be performed and further medical disciplines need to get involved, such as gastroenterology, pulmunology, neurology, surgery and maxillofacial surgery.

The diagnostic procedure aims at revealing the components of dysphagia, especially proving or excluding aspiration. Moreover, classification and quantification of aspiration have to be performed as well as a prognostic estimate. Further diagnostic goals are recommendations of therapy and type of feeding, as well as indications for emergency therapies (such as tracheostomy) in the case of intractable aspiration.

7.1 Patient History

Patient history provides valuable information that helps to optimise the diagnostic workup. The patient is asked to characterise his or her complaints and to describe their beginning, time characteristics (intermittent or constant occurrence) and influencing factors. However, it is important to know about the influence of bolus consistency on swallowing. In neurologic patients with impaired swallowing reflex and uncoordinated swallow, liquids are more difficult to be swallowed than semi-solids or solids, because they cannot be controlled well. Patients with obstructive diseases (tumours, strictures, web) often report sticking of solid food, whereas patients suffering from oesophageal motility disorders complain about swallowing problems with both liquids and solid food. To estimate the patient's oral intake, a description of his or her meals and weight during the last weeks may be valuable.

Furthermore, information regarding previous diseases and therapies (surgery, radiation—often years ago), as well as medication, needs to be obtained. The side effects of many drugs can impair swallowing: psychopharmacological drugs possibly interfere with the swallow reflex or induce xerostomia, antipsychotic drugs can cause extrapyramidal symptoms and spasmolytics may weaken muscles. It has to be pointed out that changes of voice, speech and language should be carefully noted. Above all, the examiner should also take into consideration the patient's general condition, his or her nutritional status (body weight), posture, cognitive and emotional state. Due to the epidemiological changes dementia will become a challenging problem in our society, and dysphagia may be an early or accompanying symptom. Depending on the patient's needs a holistic approach including the Mini Mental Status (Folstein et al. 1975) or the Mini Nutritional Assessment MNA™ (Nestlé Nutrition Services) can help to judge the patient's clinical condition.

Questionnaires may help to describe the impaired quality of life due to dysphagia (e.g. the MD Anderson Dysphagia Inventory, Chen et al. 2001, the Dysphagia Handicap Index, Silbergleit et al. 2012, the Deglutition Handicap Index, Woisard and Lepage 2010).

7.2 Basic Diagnostic Procedure

The ENT/phoniatric examination plays an important "key" role in the diagnostic workup because it allows a direct morphological and functional analysis of the upper aerodigestive tract. Since clinical observation and palpation of the swallow alone do not meet the diagnostic demands, a videoendoscopic swallowing study (FEES(ST), fibre-optic endoscopic evaluation of swallowing (with sensory testing), see also Sect. 6.2.4, FEES) has to be performed. It is a non-invasive dynamic procedure that delivers an immediate evaluation of the pharyngeal phase of swallowing and directly visualises the upper aerodigestive tract. However, it has the following limitations: no direct visualisation of the bolus on its entire way from the oral cavity to the stomach, no visualisation during the swallow and no visualisation of the oral and oesophageal phases and pharyngo-oesophageal segment. Therefore, a videofluoroscopic swallowing study (Ekberg 1992; Logemann 1993, 1998) has to be carried out routinely as a complementary dynamic diagnostic procedure in many cases.

7.3 Further Examinations

If necessary, further diagnostic methods are used (Table 4). Depending on the results of videoendoscopic and videofluoroscopic swallowing studies, oesophago-gastroscopy can eventually be performed as a first-line diagnostic method to exclude tumorous lesions or reveal disturbances in the oesophageal phase (see also Sect. 6.3, Endoscopy of the Oesophagus). Scintigraphy enables the quantification of bolus transit and aspiration. For an evaluation of neurogenic dysphagia, cranial magnetic resonance imaging (MRI) may detect intracranial lesions responsible for dysphagia. (Impedance) pH-metry represents the gold standard for diagnostics of a suspected gastroesophageal (-pharyngeal) reflux disease. To measure the pressure in the pharynx—especially before surgery of the pharyngo-oesophageal segment—(impedance) manometry is recommended, which allows measurement of the intrabolus pressures and pharyngeal contraction.

Conclusion

Swallowing symptoms necessitate an interdisciplinary, holistic and thorough diagnostic workup which reveals aetiologic factors and pathophysiological components. The patient should be asked precise questions relating to symptoms and valuable information should be obtained, allowing the adequate diagnostic and therapeutic measures to be taken. Above all, the adequacy of oral nutrition and the presence or absence of aspiration are in the focus of diagnostic and therapeutic interests. Due to an absent cough reflex, aspiration may occur silently. Therefore, diagnostic methods must enable direct visualisation of aspiration by videoendoscopy and videofluoroscopy. Aspiration cannot be diagnosed or excluded by patient history or clinical observation alone. However, for an appropriate management, the patient's symptoms should be carefully evaluated.

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Neurology of Swallowing and Dysphagia

Mario Prosiegel

Contents

Abstract

Neurogenic dysphagia is difficulty swallowing due to neurological diseases and compromises especially the oral and/or pharyngeal stage. The first section of this chapter deals with neuroanatomy and neurophysiology of swallowing as a basis for a better understanding of neurogenic dysphagia. Then diagnostic approaches are described comprising history taking, screening examinations, comprehensive clinical swallowing examination, and instrumented methods. The third section focuses on those neurological diseases which are frequently associated with dysphagia and ends with the description of the problem that only few pharmacological and invasive therapeutic interventions against neurogenic dysphagia exist. This expressly underlines the need for swallowing therapy and the development of new therapeutic approaches such as electrical pharyngeal or noninvasive magnetic and electrical brain stimulation.

1 Neuroanatomy and Neurophysiology

This section deals with neuroanatomical and neurophysiological basics of normal and abnormal swallowing: Which role do the cerebral hemispheres and the brainstem play in deglutition? How can the pathogenesis of pseudobulbar as well as of bulbar palsy be explained?

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Besides such topics, one focus lies also on the upper esophageal sphincter (UES), because opening deficits of the UES are very frequent in neurogenic dysphagia (for other swallowing muscles, see "Anatomy and Physiology" in the chapter by O. Ekberg and G. Nylander, this volume).

1.1 Cerebral Hemispheres

In their pioneering work, Penfield and Boldrey (1937) from the Montreal Neurological Institute in Canada performed intraoperative electrical stimulations of the cerebral cortex in awake patients. Thereby, they found certain sensorimotor representational areas with the net result of the well-known sensorimotor homunculus (the "little man inside the brain"). With regard to swallowing, the researchers could elicit deglutition by stimulation of the *frontoparietal operculum*, i.e., the lower portion of the precentral gyrus (primary motor area), of the premotor cortex and of the postcentral gyrus (primary sensory area)—corresponding to Brodmann areas (BA) 4 (motor), 6 (premotor) and 3, 2, 1 (sensory), respectively.

Magnetic resonance imaging (MRI) and functional imaging of the brain including functional MRI (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) confirmed these earlier findings and showed that also the *anterior insula* (BA 14–16) is involved in volitional swallowing (Barritt and Smithard 2009; Hamdy et al. 1999; Humbert and Robbins 2007; Riecker et al. 2009). Furthermore, by use of transcranial magnetic stimulation (TMS) it was found that the esophageal, pharyngeal, and oral muscles are discretely represented within the motor cortex in a rostrocaudal direction, with esophageal muscles being situated more rostral than the pharyngeal muscles, which in turn are more rostral than the oral muscles (Hamdy et al. 1996) (Fig. 1).

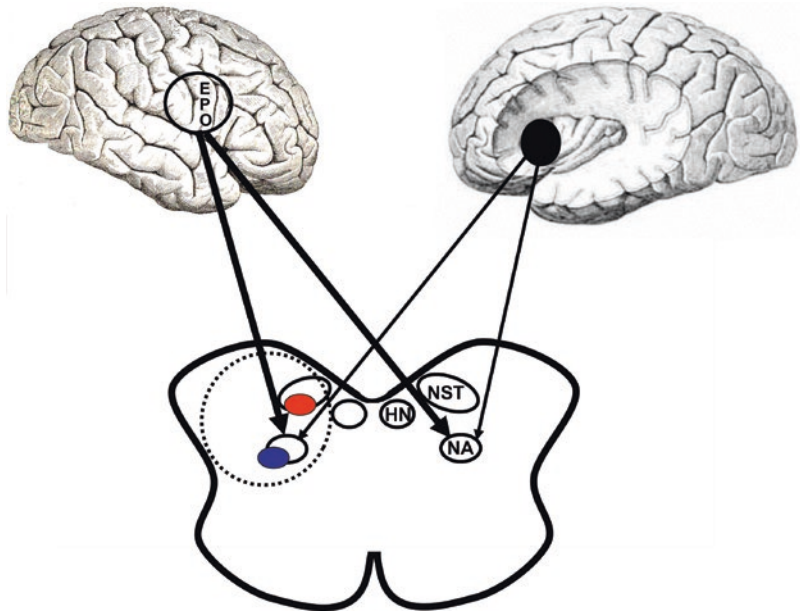

Fig. 1 Swallowing cortex, corticobulbar fibers, and lower brainstem. *Top left*: Right cerebral hemisphere with the frontoparietal operculum (*closed circle*) and the representational areas of the esophagus (*E*), pharynx (*P*), and oral region (*O*). In this example, the right hemisphere is swallowing-dominant, with more corticobulbar fibers (*long thick arrows*) projecting to the ipsilateral and contralateral medulla. *Top right*: Left hemisphere after removal of the operculum; the insula with its anterior swallowing-relevant part (*black area*) can therefore be seen. *Bottom*: Axial view of the lower brainstem (medulla; lower part = anterior, upper part = posterior). On the *right side* (left side of the medulla) the nucleus of the solitary tract (NST), the nucleus ambiguus (NA), and the hypoglossal nucleus (HN) are shown. On the *left side* (right side of the medulla) the dorsomedial and ventrolateral central pattern generators for swallowing are shown (*red area* and *blue area*, respectively). The *horizontally lined area* corresponds to the site of a dorsolateral medullary infarction with consecutive Wallenberg syndrome. For details, see the text

Functional brain imaging studies could also show that the swallowing cortex is represented bilaterally, but asymmetrically, i.e., it is (in most people) bigger on one side as compared to the other one. The bigger swallowing cortex is called the dominant one. *Swallowing dominance* is independent of the language-dominant side or of handedness (Barritt and Smithard 2009; Hamdy et al. 1999).

The fibers which project from the motoneurons of the swallowing cortex to both sides of the brainstem are called *corticobulbar fibers* and constitute the *corticobulbar (corticonuclear) tract* (Fig. 1). When the dominant swallowing cortex and/or its corticobulbar fibers are affected, a significant hemispheric dysphagia occurs (hemispheric dysphagia means swallowing problems caused by cortical and/or subcortical lesions such as ischemia or hemorrhage of the left or right cerebral hemisphere, i.e., supratentorial stroke). Additionally, right-sided cortical lesions are often associated with "neglect for swallowing," "food stuffing," and consecutive problems in the pharyngeal phase (Robbins and Levin 1988), whereas left-sided lesions may cause swallowing apraxia with corresponding problems in the oral phase (Daniels 2000). Independent of these behavioral/neuropsychological problems, left-sided and right-sided areas of the swallowing cortex seem to play different roles during the early and later phase of swallowing, respectively (Teismann et al. 2009).

Besides the abovementioned swallowing areas, other cortical and subcortical regions are involved in swallowing function such as the *supplementary motor area (SMA)* corresponding to the medial part of BA 6, the *basal ganglia*, the *cerebellum,* and *many other parts of the brain*. The SMA is responsible for the generation of the readiness potential ("Bereitschaftspotential"), which arises about 1 s before a volitional motor action. It could be shown that also a *swallowing potential ("Schluckpotential")* exists, which is generated in the SMA too, but spreads to both primary motor areas (whereas the readiness potential spreads to the motor area which is contralateral to the innervated extremity) (Huckabee et al. 2003).

According to Mosier and Bereznaya (2001) *two swallowing networks* can be distinguished: (1) an "insular loop" including the insula, the primary sensorimotor motor cortex, premotor cortex, posterior parietal cortex, and the SMA/cingulate gyrus; (2) a "cerebellar loop" comprising the cerebellum, the SMA/cingulate gyrus, the inferior frontal gyrus, the secondary sensory cortex, the corpus callosum, and the basal ganglia as well as the thalamus. The influence of the "insular loop" might be necessary to synchronize the kinematics of the swallowing movements, whereas the "cerebellar loop" might optimize and modulate movements using feedback information.

As could be shown by Power et al. (2007), swallow response time (SRT) is prolonged in dysphagic patients due to unilateral hemispheric stroke as compared to healthy volunteers. Interestingly enough, in these stroke patients a sensory deficit of the faucial pillars could be found bilaterally in 66% and the duration of SRT as well as the degree of the sensory deficit were associated with the severity of predeglutitive aspiration.

Since the cortical swallowing network comprises many sensorimotor areas, sensory input seems to be very critical for an intact swallowing. This view was confirmed by a recent study in decerebrate pigs: The sensory threshold for the swallowing response was increased since the facilitatory pathways descending from cerebral structures to the brainstem had been lost (Thexton et al. 2007). *Therefore, important roles of the cerebral cortex in deglutition seem to be initiation of swallowing, direct modulation of swallowing, and modification of brainstem swallowing responses—in each case mainly dependent on sensory inputs (see also* Sect. 1.2*).*

1.2 Brainstem

Doty and Bosma (1956) conducted a pioneering study on the role of the brainstem in swallowing: By electrical stimulation of the superior laryngeal nerve (SLN) with 30 Hz in different animals including monkeys, they could elicit the complete

sequential pattern of activation or inhibition of swallowing muscles of the pharyngeal phase. Therefore, they postulated the existence of a swallowing center in the medulla oblongata; this view was confirmed later on (review: Jean 2001). There are four swallowing centers—two on each side of the brainstem—for which the term *central pattern generators (CPGs) for swallowing* was coined. The dorsomedial CPGs (dmCPGs) are situated besides the nucleus of the solitary tract (NST); they contain so-called master neurons which generate the temporal-spatial sequence of pharyngeal swallowing muscle activation or inhibition. This information is transmitted to ventrolateral CPGs (vlCPGs) situated near the nucleus ambiguus (NA); switching neurons of the vlCPGs distribute the timed output to the cranial nerve nuclei V and VII in the pons as well as to the cranial nerve nuclei IX, X, and XII in the medulla oblongata (Fig. 1). The most probable site of the dmCPGs and vlCPGs is the parvocellular reticular nucleus (PCR) of the lateral reticular formation according to the nomenclature of Olszewski and Baxter's brainstem atlas (Büttner-Ennever and Horn 2014). *The functioning of the brainstem central network can be influenced by peripheral inputs—e.g., from oropharyngeal mucosal receptors and muscle spindles of the tongue and jaw muscles—as well as by central inputs from the cortex; both inputs converge at the NTS and serve in particular to adapt the swallowing drive to properties of the bolus to be swallowed. The brainstem is also important for coordinating interactions between respiration and swallowing* (Jean 2001; Miller 1993).

Due to the role of the brainstem in swallowing, unilateral lesions of the medullary region—such as in Wallenberg syndrome caused by unilateral infarctions in the supply area of the posterior inferior cerebellar artery—affecting both ipsilateral CPGs as well as the NA and the NTS, cause complex swallowing disturbances including: unilateral pharyngeal and laryngeal paresis (NA), impaired pharyngeal peristalsis (NA and dmCPG), sensory deficits in the oropharyngeal region (sensory trigeminal nucleus and NTS), secondary UES opening deficit due to impaired hyolaryngeal excursion, and/or primary UES opening disturbance due to impaired sphincter relaxation (dmCPG) (Prosiegel et al. 2005a). Besides dysphagia and hoarseness, other characteristics of Wallenberg syndrome are nystagmus, ipsilateral Horner syndrome, ipsilateral ataxia, and contralateral dissociated sensory disturbances (hypalgesia and thermhypesthesia).

1.3 Pseudobulbar and Bulbar Palsy

Two frequently occurring syndromes associated with dysphagia are pseudobulbar and bulbar palsy. *Pseudobulbar palsy is caused by bilateral lesions of the cerebral cortex and/or its corresponding corticobulbar fibers including those passing through the brainstem*. On the contrary, *bulbar palsy* ("bulbus" is an outdated term formerly used for the lower brainstem) *is due to bilateral lesions of pontine and medullary cranial nerve nuclei or their axons or due to bilateral lesions of the cranial nerves themselves.*

1.3.1 Pseudobulbar Palsy

The motoneurons of the swallowing cortex are called first or upper motoneurons (UMNs). When the *swallowing cortex itself and/or its axons, i.e., the corticobulbar fibers, are lesioned bilaterally*, there is diminished input to the brainstem. The consequence is severe dysphagia which affects predominantly the volitional oral phase. Due to impaired cortical input, the membrane of the motoneurons in the brainstem lowers its electrical threshold with consecutive *hyperreflexia* (e.g., enhanced masseter reflex) and *muscle stiffness in terms of spasticity*. There are no muscle atrophies, since the second/lower motor neurons (LMNs) in the brainstem are intact and, therefore, able to supply the corresponding muscles with the transmitter acetylcholine. *This syndrome is called pseudobulbar palsy and occurs in UMN diseases (UMNDs)*; examples are amyotrophic lateral sclerosis (ALS) due to bilateral degeneration of the UMNs or bilateral subcortical infarctions affecting the corticobulbar tracts. In most cases of pseudobulbar palsy, *besides dysphagia also dysarthria and chewing problems* occur;

pathological crying or laughing is often associated with pseudobulbar palsy, too. Bilateral lesions of the corticobulbar tract in the brainstem (e.g., in bilateral anterior mesencephalic infarctions) may also cause pseudobulbar palsy. Very typical for pseudobulbar palsy is *automatic-voluntary dissociation*: *Emotional or reflex responses are intact or enhanced (e.g., enhanced palatal or masseter reflex), whereas volitional activities are disturbed (e.g., no elevation of the soft palate during phonation of /A/ or chewing problems due to weakness of the masseter muscles*). One of the classic findings of pseudobulbar palsy during videomanometry is also spasm of the cricopharyngeal muscle with subsequent UES opening disturbance.

1.3.2 Bulbar Palsy

In contrast to pseudobulbar palsy, *muscle atrophy* occurs when the cranial nerve nuclei in the brainstem (or the motoneurons in the spinal cord)—i.e., the *second or lower motor neurons (LMNs)*—are affected. Because of diminished input to the corresponding muscles, the muscular membrane develops a decreased electrical threshold with consecutive *pathological spontaneous activity*. This can be assessed electromyographically or seen clinically in the form of *fibrillations of the atrophic tongue (jerks of muscle fibers) or fasciculations of the face or body musculature (jerks of groups of muscle fibers)*. Other features comprise *weakness of the oro-facio-pharyngeal muscles* and *decreased muscle tone in terms of hypotonia with diminished reflexes* as well as *bulbar (slurred) speech*. This syndrome, which is caused by affection of the LMNs, is called bulbar palsy and occurs in *LMN diseases (LMNDs)* such as ALS (ALS is an example of a combined UMND and LMND). Bulbar palsy may also be caused by lesions of the fibers of the cranial nerve nuclei or of the cranial nerves themselves.

1.4 Upper Esophageal Sphincter

The upper esophageal sphincter (UES) is defined as a *high pressure zone* with a rostrocaudal extension of 2–6 cm, which maintains a closed pharyngo-esophageal junction and opens phasically during various physiological states (Lang and Shaker 1997). It consists of *striated muscles comprising the caudal part of the inferior pharyngeal constrictor (IPC), the cricopharyngeus muscle (CP), and the uppermost esophageal musculature (UE)*. In contrast to the other swallowing muscles, the UES forms a network together with connective tissue (~40%) and consists of more than 70% of slow twitch (tonic, type I) fibers. The number of these tonic fibers is especially high in the horizontal part of the CP (CPh) as compared to its oblique part (CPo) as well as in the slow inner layer (SIL) as compared to the fast outer layer (FOL) of the UES and the pharyngeal constrictors. The SIL is innervated by the IX. cranial nerve (N. glossopharyngeus), whereas the FOL is supplied by different branches of the X. cranial nerve (N. vagus) in the following manner: (1) IPC—pharyngo-esophageal nerve (PEN) forming the pharyngeal plexus; external superior laryngeal nerve (ESLN); (2) CP—pharyngeal plexus; ESLN; recurrent laryngeal nerve (RLN); (3) UE—RLN. Whereas the FOL is adapted for sphincteric and peristaltic functions, the SIL is assumed to act also as a tensor and shaper, i.e., the inner muscular layer of the pharyngeal constrictors is able to "maintain the stiffness of the pharyngeal walls during respiration and to shape the walls for speech articulation" (Mu and Sanders 2007).

UES opening is a very complex event. Firstly, *relaxation of the UES* muscles occurs (as can be shown electromyographically). Secondly, about 100 ms later, there is a *reduction of UES pressure* (as can be shown by use of manometry). Thirdly, again about 100 ms later, *UES opening* occurs caused by two forces which have to overcome the resistance of the sphincter: (1) *Traction forces, exerted by the suprahyoidal muscles during anterior-superior hyolaryngeal excursion*, widen the CP, since the CP originates from the arch of the cricoid cartilage; (2) *tongue base retraction with approximation of the base of tongue (BOT) to the posterior pharyngeal wall (PPW)* generates the *force responsible for the primary pressure on the descending bolus* (shortening of the pharynx helps to meet the bolus with the UES).

These forces can be described mathematically as follows: $F_{\text{Traction}} + F_{\text{Bolus (approximation of BOT to PPW)}} > R_{\text{UES}}$ (review: Lang et al. 1991). Pharyngeal peristalsis is also important, but its predominant role is to clear pharyngeal bolus residuals.

Impaired opening of the UES occurs frequently in patients with dysphagia due to medullary lesions (such as in Wallenberg syndrome), Parkinson disease (Williams et al. 2002), or myositis (Oh et al. 2007) and is sometimes called cervical achalasia. Defective tonicity of the UES (cervical chalasia) may occur in myotonic dystrophy, myasthenia gravis, during "off" periods of Parkinson disease, and after radiotherapy of the neck (Ekberg and Olsson 1995).

2 Examinations

Diagnostics in (suspected) neurogenic dysphagia comprise clinical examinations and instrumental methods. Bedside screening tests are necessary in certain cases, which are described in Sect. 2.1.2. Special diagnostic approaches such as laboratory examination and MRI are dealt with in Sect. 3.6.

2.1 Clinical Examinations

They comprise history taking, bedside screening examination, and comprehensive clinical dysphagia assessment.

2.1.1 History Taking: Signs and Symptoms in Neurogenic Dysphagia

In many textbooks or articles one can find the statement that dysphagia for liquids is typical for neurogenic dysphagia. Although often occurring, it is, however, not a pathognomonic symptom for dysphagia of neurogenic origin. In reality, there is a broad range of different signs and symptoms occurring in patients with neurogenic dysphagia. *During history taking it is helpful to use a checklist of questions and to ask the patient and his/her relatives to try to answer them as accurately as possible*. Interestingly enough, in many cases the relatives may observe, e.g., disturbances of feeding behavior or postural changes, which are not or not to the same extent realized by the patients themselves.

Some of the most important signs and symptoms are listed in the following: abrupt or gradual beginning of swallowing problems; difficulty with control of saliva; problems with liquids and/or thick consistencies; problems with warm, hot, or cold liquids and/or food; involuntary weight loss; eating and/or drinking slower as compared to the time before symptom-onset; eating and/or drinking smaller portions as compared to the time before symptom-onset; unexplained fever and/or pneumonia; coughing and/or choking and/or voice change (e.g., wet, hoarse, nasal) after eating and/or drinking; drooling and/or sialorrhea; increase of secretions; dry mouth; articulation problems (e.g., slurred speech); feeling of a "lump in the throat"; fear of swallowing; pain during swallowing (where?); change of head or trunk posture during swallowing; chewing problems; problems to propel the bolus from the mouth backwards into the pharynx; problems to hold the bolus in the mouth during chewing or swallowing; residuals of food in the mouth after swallowing; nasal regurgitation of food or liquids; feeling of "food stucking" (where?); need for repetitive swallowing in order to remove all residues; breathing problems; prior or current disease such as chronic obstructive pulmonary disease; prior surgery/medical therapy such as anterior cervical surgery, carotid endarterectomy or radiochemotherapy of head and neck cancer; current status such as dependence on percutaneous endoscopic gastrostomy (PEG), nasogastric tube or tracheal cannula; prior and current medication.

2.1.2 Bedside Screening Examination

Bedside screening examination (BSE) should be simple in format and quick to administer by trained clinicians (including nurses). It aims at predicting the presence or absence of dysphagia or aspiration with sufficient sensitivity and specificity and identifying "individuals who require a comprehensive assessment of swallowing

function or a referral for other professional and/or medical services" (Donovan et al. 2013). BSE seems to be especially helpful in acute illnesses such as stroke since rapid therapeutic decisions have to be made in those situations with regard to oral administration of food and water versus nil per os (NPO). In acute stroke, BSE should be performed during the first 4 h and patients with pathological BSE should proceed to comprehensive clinical swallowing examination at least within 24 h after stroke (see Sect. 2.1.3).

With regard to acute stroke, Hinchey et al. (2005) could convincingly demonstrate the importance of an early screening procedure which is reflected by the title of their article: "Formal dysphagia screening protocols prevent pneumonia." Indeed, the most dangerous complication of dysphagia is aspiration pneumonia, but also malnutrition—defined as a body-mass index (BMI) <18.5 kg/m^2 (or <20 kg/m^2 in elderly persons)—is an important variable since its occurrence during the acute stroke phase correlates with a poor clinical outcome and with a prolonged length of stay in the hospital (Bray et al. 2017).

Based on a systematic review of 35 protocols, Schepp et al. (2012) found only two screening examinations which met certain inclusion criteria (e.g., high sensitivity and specificity): the Toronto Bedside Swallowing Screening Test (TOR-BSST) and the Barnes-Jewish Hospital Stroke Dysphagia Screen (BJH-SDS). The TOR-BSST has one major disadvantage over the BJH-SDS, since it is copyrighted and requires purchase for training, implementation, and administration. Therefore, the BJH-SDS is shortly presented here (Edmiaston et al. 2014). It comprises four yes-no-items: score on the Glasgow coma scale <13, facial or tongue or palatal asymmetry/weakness. If one of these items is answered with "yes", the test is pathological; if all items are normal ("no"), the examiner has to proceed to a 3-ounce water test (see below): if throat clearing or cough or change in vocal quality (wet, gurgly, breathy, or hoarse) occurs immediately after or 1 min following the swallow, the test is pathological. The BJH-SDS is easy to perform, time to administer is 2 min on average, online evaluation is possible (www.mdcalc.com/barnes-jewish-hospital-stroke-dysphagia-screen). Sensitivity and specificity values for dysphagia are 94% and 66% and for aspirations 95% and 50%, respectively. The high negative predictive value for dysphagia and aspiration (93% and 96%, respectively)—i.e., a high probability that dysphagia (or aspiration) is absent in case of a normal test—is helpful for the decision whether or not oral feeding is possible.

With regard to aspiration risk and feeding recommendations, the clinical utility of the *3-ounce water swallow test* was examined by Suiter and Leder (2008) in 3000 patients. The diagnostic categories comprised 850 neurological (most frequently stroke) and 232 neurosurgical disorders. The patients were required to drink 3 ounces (90 ml) of water without interruption; criteria for referral for further assessment of swallowing included inability to complete the task, coughing, choking, or a wet-hoarse vocal quality exhibited either during or within 1 min of test completion. Sensitivity and specificity for assessing the risk of aspiration were 96.5% and 48.7%, respectively. Due to a high negative predictive value of 98.3%, passing the 3-ounce water swallow test was a good predictor for the ability to tolerate oral diet without further dysphagia testing.

For further reading, the articles by Donovan et al. (2013) and by Schepp et al. (2012) are recommended.

2.1.3 Comprehensive Clinical Swallowing Examination

Comprehensive clinical swallowing examination (CSE) is usually performed by speech and language therapists. It aims at detecting disturbances of specific swallowing components as a basis for adequate therapeutic interventions. It comprises—in descending order of cranial nerves (CNs) V, VII, IX, X, and XII—the following examinations: decreased strength of chewing muscles, asymmetry of the mandible, sensory impairment of the facial and oral region—V. CN; decreased strength and/or motility of facial muscles, fasciculations of the facial musculature,

hypogeusia of the anterior two-thirds of the tongue—VII. CN; decreased or absent palatal and pharyngeal reflex, unilateral pharyngeal wall paresis (paralyzed side moving towards the healthy side, also called "Vernet's mouvement de rideau"), sensory impairment of the pharyngeal mucosa, impaired phonation (e.g., wet, hoarse, nasal), disturbed breathing (e.g., stridor), impaired volitional cough, hypogeusia of the posterior third of the tongue—IX. and X. CNs; fibrillations and/or atrophy of the tongue, decreased strength and/or motility, asymmetry of the tongue during rest (to the healthy side) and protrusion (to the affected side)—XII. CN.

Other findings may include: dyskinesia or dystonia of the face, jaw, head, and neck; dysarthria; buccofacial apraxia; neglect; attention or memory deficits; impaired vigilance. Of special importance are pseudobulbar and bulbar signs (see Sect. 1.3).

Recently, Bray et al. (2017) performed a multicentre study on 63,650 acute stroke patients of England and Wales. They examined the association between BSE, comprehensive CSE, and stroke-associated pneumonia (SAP) within the first 7 days after stroke onset. The authors found an increased risk of SAP (overall incidence 8.7%) with delays in BSE and comprehensive CSE; the absolute increase of SAP incidence was 1% per day of delay.

It has to be emphasized that BSE can never replace comprehensive CSE or instrumented methods such as FEES or VFSS, since the latter ones are necessary for the assessment of the individual swallowing disturbance patterns and thus for applying the corresponding therapeutic interventions.

2.2 Instrumented Methods

The two most important instrumented methods are *F*lexible *E*ndoscopic *E*valuation of *S*wallowing (FEES) and *V*ideo*f*luoroscopic *S*tudy of *S*wallowing (VFSS). Only the special role of FEES and VFSS in neurogenic dysphagia is shortly described hereafter.

During *FEES*, the pharyngeal stage is the center of attention with regard to: (1) structural abnormalities and sensory deficits—by touching the pharyngeal wall, the epiglottis, and the aryepiglottic fold or by air pulse stimuli (FEES with sensory testing, abbreviated as FEEEST); (2) disturbances of control of saliva and/or the ability to swallow real food, liquids, and pills; (3) response to therapeutic interventions such as postural changes. Additionally, showing the video images to the patient and/or to the relatives makes FEES an ideal biofeedback method. In neurological patients with dysphagia, patient outcome with respect to development of pneumonia seems to be similar whether dietary or behavioral management is guided by FEES or VFSS (Aviv et al. 2000). Since with FEES there is no time constraint (because of lacking radiation exposure), FEES can be performed or be repeated as long and as often as necessary. Recently, Pisegna and Langmore (2016) compared diagnostic parameters as assessed with FEES and VFSS; they found that "clinicians visualized more pharyngeal and laryngeal structures and detected residue in more locations on FEES" and "provided more severe impressions of residue amount on FEES." In the authors' view, this is a "diagnostic dilemma" since pharyngeal residues are interpreted as more severe with FEES in comparison to VFSS.

VFSS has many advantages as compared to FEES, among which the most important ones are: (1) evaluation of the oral, the pharyngeal, and the esophageal stage; (2) direct visualization of UES opening deficits; (3) accurate measurement of the swallowing reflex/oropharyngeal transition time/swallow response time—usually defined as the interval (in ms) between the first frame showing the apex of the bolus passing the faucial isthmus to the first frame showing anterior moving of the hyoid bone (an interval >500 ms is usually interpreted as oropharyngeal dissociation which is an important cause of leaking); (4) visualization of the approximation of the BOT to the PPW, which is an important event in the generation of the bolus pressure (see Sect. 1.4).

Manometry of the esophagus and pharynx is dealt with in "High resolution manometry of the pharynx and esophagus" in the chapter by

N. Rommel, this volume. In neurogenic dysphagia, pharyngeal manometry/videomanometry is of special value in patients with opening deficits of the UES. By use of pharyngeal manometry it can be differentiated between primary UES dysfunction (impaired or absent relaxation) and secondary UES opening deficits due to reduced hyolaryngeal excursion and/or impaired bolus pressure. Based on certain manometric findings, the indication for interventions such as cricopharyngeal myotomy, botulinum neurotoxin injection into the cricopharyngeal muscle or dilatation of the UES can be made in primary UES dysfunction (see Sect. 3.7.1).

3 Diseases Associated with Neurogenic Dysphagia

This section deals mainly with diseases, which are frequently associated with neurogenic dysphagia. For rare causes of dysphagia, the book "Dysphagia in Rare Conditions" edited by Jones and Rosenbek (2010) is recommended.

3.1 Diseases of the Central Nervous System (CNS)

3.1.1 Stroke

Stroke is the most frequent cause of dysphagia. The *incidence of stroke*—comprising brain infarction (80%), intracerebral hemorrhage (15%), and subarachnoidal hemorrhage (5%)—accounts for over 200/100,000 persons per year in industrial countries of the western hemisphere (Hankey and Warlow 1999). According to Mann et al. (2000), dysphagia and aspirations occur in 64% and 22%, respectively, of acute stroke patients as shown videofluoroscopically. About half of these dysphagic patients recover or die within 2 weeks; therefore, about 30% of stroke survivors suffer from chronic dysphagia (Bath et al. 2000). The prognosis is worse in brainstem stroke as compared to hemispheric stroke: Among dysphagic patients with Wallenberg syndrome due to dorsolateral medullary infarction, who need enteral feeding at onset, about 30% remain dependent on enteral feeding tubes (Prosiegel et al. 2005b). Whereas in supratentorial stroke leaking of liquids (due to a delayed swallow reflex) is the predominant finding, in medullary stroke various disturbances occur including unilateral pharyngeal paresis, decreased hyolaryngeal excursion with subsequent secondary opening deficits of the UES as well as primary UES dysfunction caused by insufficient relaxation.

A very severe dysphagia develops in bilateral infarctions of the frontoparietal operculum (*bilateral anterior opercular syndrome* or *Foix-Chavany-Marie syndrome*) with predominant problems in the oral phase.

Subcortical arteriosclerotic encephalopathy (SAE)—formerly called Binswanger disease—refers to a combination of periventricular white matter lesions (leukoaraiosis) and lacunar infarctions (<2 cm in diameter). It is most frequently caused by high blood pressure and/or diabetes mellitus; in the case of dementia, it is called *Subcortical Ischemic Vascular Dementia (SIVD)*. The severity of SAE/SIVD is positively correlated with an increase in bolus transit times (Levine et al. 1992) and may, therefore, aggravate or cause swallowing disturbances.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a genetic variant of SIVD and a rare cause of stroke, which occurs mainly in younger persons with a history of migraine. This autosomal dominant genetic disease is associated with mutations in the NOTCH 3 gene on chromosome 19. When the subcortical infarctions are bilaterally situated in the region of the corticobulbar fibers, a severe pseudobulbar palsy may be the consequence (Fig. 2). The diagnosis is made by molecular genetic examination and/or skin biopsy (granular osmiophilic material [GOM] in dermal arteries as shown by transmission electron microscope).

Vasculitides are a group of diseases in which inflammatory destruction of vessel walls occurs with consecutive thrombosis or stenosis of (large or small) vessels of the CNS (and in some types also of the peripheral nervous system). *Primary vasculitides* comprise giant cell arteritis (temporal arteritis; see below), Takayasu arteritis (granulomatous arteritis of the aortic arch and its branches, also called "pulseless disease"), polyarteritis nodosa,

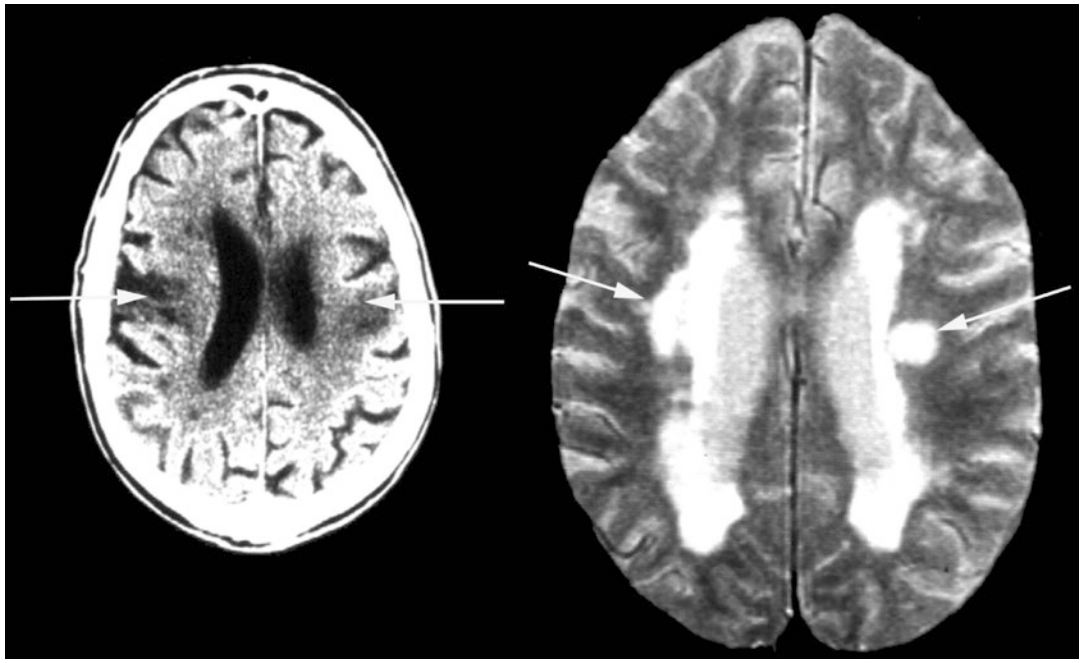

Fig. 2 *Left*: Cranial computed tomography showing bilateral infarctions (*arrows*) in the supply area of the middle cerebral artery affecting the frontoparietal operculum bilaterally causing the so-called bilateral anterior frontoparietal opercular syndrome (Foix-Chavany-Marie syndrome). *Right*: T2-weighted magnetic resonance imaging showing bilateral subcortical infarctions (*arrows*) in a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and severe dysphagia; for details, see the text

Wegener granulomatosis (granulomas affecting the kidneys, lungs and upper respiratory tract, skull base, etc.), Churg-Strauss syndrome (allergic granulomatosis with a history of asthma or allergy), Behçet disease (uveitis, aphthous ulcers of the mouth and genitals), and *primary central nervous system vasculitis* (see below). In *giant cell arteritis/temporal arteritis*, besides headache and visual loss also jaw claudication (pain in the jaw when chewing) as well as tongue claudication (pain in the tongue when moving) and tongue necrosis may occur. *Primary central nervous system vasculitis (PCNSV)/primary angiitis of the CNS (PACNS)* is a rare vascular inflammatory disease restricted to the brain and spinal cord of unknown cause; the mean age is 42.48 years at onset of symptoms; the diagnosis of PCNSV/PACNS is made clinically (headache, cerebral infarctions, cognitive dysfunction) by positive leptomeningeal or brain biopsy and/or cerebral angiography (alternating dilatations and narrowings—also called "beading"—, aneurysms and other irregularities within blood vessels) (review: Kraemer and Berlit 2010). When the infarctions of PCNSV/PACNS affect the dominant swallowing cortex and/or corticobulbar fibers, dysphagia may occur. *Secondary vasculitides* may complicate other diseases such as connective tissue diseases (see Sect. 3.4.2). For laboratory testing of vasculitides see Table 1.

When there is a need for *enteral feeding in the acute stroke phase*, a PEG should not be inserted to early, i.e., not before about 2 weeks after disease onset: A multicenter RCT (Dennis et al. 2005) found that early PEG insertion is associated with an increased risk of death or poor outcome (as measured after 6 months with the modified Rankin scale) of 7.8% as compared to early nasogastric feeding. A single-center RCT could show that *early beginning of high-intensity swallowing therapy after stroke* (within 7 days) is associated with an increased proportion of patients who returned to a normal diet ($p = 0.04$) and recovered swallowing ($p = 0.02$) by 6 months as compared to "usual care" or low-intensity therapy (Carnaby et al. 2006).

Table 1 Checklist for dysphagia of unknown cause

CIP/CIM, myotonia, myasthenia gravis, LEMS, GBS	Electromyography, repetitive nerve stimulation, motor and sensory nerve conduction studies
MS, neuroborreliosis, CPM/EPM, skull base tumors, Chiari malformation	Cranial CT or MRI
Eagle syndrome, ventral osteophytes, and/or complications after anterior cervical spine surgery	Lateral cervical radiography, (three-dimensional) CT
Myasthenia gravis	Anti-AChR abs, anti-MuSK abs, anti-LRP4 abs
LEMS	Anti-VGCC abs
Myositides	Myositis-associated antibodies
– DM	– Anti-Mi-2 abs
– PM	– Anti-synthetase (anti-Jo-1) abs
– sIBM	– Anti-cN1A (anti-Mup44) abs
Connective tissue diseases	Anti-nuclear abs (ANAs)
– Sjögren syndrome	– Anti-SSA/Ro abs, anti-SSB/La abs
– Systemic sclerosis	– Anti-scl70/topoisomerase abs, anti-PM-Scl abs
– MCTD/Sharp syndrome	– Anti-U_1-RNP abs
– SLE	– Anti-dsDNA abs
Vasculitides	Anti-neutrophil cytoplasmic abs (ANCAs) (c = cytoplasmic, p = perinuclear)
– Wegener granulomatosis	– c-ANCA (antigen: proteinase 3 [PR3])
– Microscopic polyangiitis	– p-ANCA (antigen: myeloperoxidase [MPO])
– Churg-Strauss syndrome	– p-ANCA (antigen: myeloperoxidase [MPO])
– Panarteritis nodosa	– HBsAg
Polyneuritis cranialis, Miller-Fisher syndrome	Anti-ganglioside (GQ1b or GT1a) abs
Paraneoplastic syndromes	
– LEMS	– Anti-VGCC abs
– Brainstem encephalitis	– Anti-Hu abs, ant-Ri abs, anti-MA2 abs
– Stiff-person syndrome	– Anti-amphiphysin abs, anti-gephyrin abs, anti-Ri abs
Idiopathic stiff-person syndrome	GAD abs
Neuroborreliosis, MS, meningitis	Cerebrospinal fluid (CSF) examination
CADASIL	Skin biopsy: granular osmiophilic material (GOM) in dermal arteries
Myositides, rare myopathies	Muscle biopsy
CADASIL, SBMA/Kennedy disease, OPMD	Molecular genetic examination
PCNSV/PACNS	Brain biopsy

CIP critical-illness polyneuropathy, *CIM* critical-illness myopathy, *LEMS* Lambert-Eaton myasthenic syndrome, *GBS* Guillain-Barré syndrome, *MS* multiple sclerosis, *CPM* central pontine myelinolysis, *EPM* extrapontine myelinolysis , *DM* dermatomyositis, *PM* polymyositis, *sIBM* sporadic inclusion body myositis, *MCTD* mixed connective tissue disease, *SLE* systemic lupus erythematosus, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *SBMA* spinobulbar muscular atrophy, *OPMD* oculopharyngeal muscular dystrophy, *PCNSV* primary central nervous system vasculitis, *PACNS* primary angiitis of the central nervous system, *CT* computed tomography, *MRI* magnetic resonance imaging, *AChR* acetylcholine receptor, *abs* antibodies, *MuSK* muscle-specific tyrosine kinase, *LRP4* lipoprotein receptor-related protein 4, *VGCC* voltage-gated calcium channels, *cN1A* cytosolic 5′-nucleotidase 1A, *dsDNA* double-stranded DNA, *HBsAg* hepatitis B surface antigen, *GAD* glutamic acid decarboxylase

3.1.2 Idiopathic Parkinson Syndrome

The morphologic substrate found in idiopathic Parkinson syndrome (IPS)/Parkinson disease (PD) (with high incidence and prevalence rates of 15/100,000/year and 150/100,000, respectively) are intracellular Lewy bodies consisting mainly of the protein α-synuclein; therefore, IPS belongs to the α-synucleinopathies. These inclusion bodies do not only affect neurons of the dopaminergic substantia nigra, but also non-dopaminergic cells in other brainstem regions (e.g., the pedunculopontine nucleus) as well as parasympathetic cells of the esophageal Auerbach plexus. Therefore, dopaminergic drugs are effective in only 30–50% of parkinsonian dysphagia. In IPS, only one-third

of the patients report spontaneously on swallowing problems; the objective prevalence of dysphagia is, however, higher and accounts for about 80%, of whom about the half are (silent) aspirators; aspiration pneumonia is one of the most frequent causes of death in IPS. IPS-specific questionnaires are useful, since they may stimulate patients' awareness of swallowing symptoms; an example is the Munich Dysphagia Test-Parkinson's disease (MDT-PD) by Simons et al. (2014), which comprises 26 items and has high sensitivity and specificity for dysphagia (90% and 86%) and aspiration (82% and 71%); online evaluation of the MDT-PD is possible (www.mdt-parkinson.de). Predictors of dysphagia in IPS comprise disease severity (score of the Hoehn and Yahr scale >3), recent loss of weight or body mass index <20 kg/m^2, dementia and drooling. The spontaneous swallowing frequency is often decreased and mainly responsible for sialorrhea and (besides hypokinesia of the mimic muscles) for drooling. Oral and pharyngeal symptoms occur often in combination comprising oral residuals, repetitive pumping motions of the tongue, leaking, piecemeal deglutition, residuals in the piriform sinuses, prolonged triggering of the swallow reflex, as well as UES opening deficits. Manometric studies have shown various esophageal motility disorders in 61–73% of persons with IPS including decreased peristalsis and diffuse esophageal spasm. The symptoms due to these esophageal disturbances may resemble oropharyngeal problems and should always be kept in mind.

Pharmacotherapy comprises oral application of L-Dopa, non-ergot dopamine agonists, inhibitors of monoamine oxidase-B (MAO-B) or catechol-o-methyltransferase (COMT), anticholinergics, and amantadine. Transdermal application of the dopamine agonist rotigotine can be helpful in patients with gastroparesis. Dysphagia during "off" periods may respond to subcutaneous apomorphine (intermittent injections or continuous therapy via pump). In patients with severe fluctuations, continuous delivery of L-dopa via a jejunal tube (gel suspension; Duodopa pump) may be indicated. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) with 130 Hz alleviates many symptoms of persons with IPS, but does not influence dysphagic symptoms at all; lower stimulation frequencies (e.g., 60 Hz) may, however, be effective in dysphagia. DBS of the internal pallidum may even cause or aggravate swallowing symptoms (reviews: Pfeiffer 2003; Suttrup and Warnecke 2016).

As a rule, the diagnosis of IPS is improbable when oropharyngeal dysphagia occurs within the first year after the first symptoms; in those cases, atypical Parkinson syndromes (APS) are the probable cause; they are dealt with in the next Sect. 3.1.3.

3.1.3 Atypical Parkinson Syndromes

Atypical Parkinson syndromes (APS) comprise progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies, and corticobasal degeneration.

Progressive supranuclear palsy (PSP) is characterized by axial rigidity, dementia, vertical gaze paralysis, postural instability with falls, and dysarthria. Dysphagia occurs initially in about 16% and during the course of the disease in about 83% (Litvan et al. 1996).

Multisystem atrophy (MSA) comprises two types: In MSA-P (P for Parkinson; about 80%) Parkinsonian symptoms predominate, whereas in MSA-C (C for Cerebellar; about 20%) cerebellar symptoms such as gait ataxia are typical. In both types, autonomic disturbances occur, e.g., orthostatic hypotonia and bladder dysfunction. In MSA, neurogenic dysphagia occurs in over 70% (Higo et al. 2005; Müller et al. 2001; O'Sullivan et al. 2008) and laryngeal stridor in over 30% (Yamaguchi et al. 2003).

Dementia with Lewy bodies (DLB) comprises motor features of Parkinsonism, dementia, visual hallucinations, fluctuating course, and hypersensitivity against certain drugs such as neuroleptics. Neurogenic dysphagia occurs in over 20% (Müller et al. 2001).

As compared to IPS, where dysphagia occurs rarely in the first years after disease onset, swallowing problems develop earlier in APS (PSP: 42 months, MSA: 67 months, DLB: 43 months). After onset of dysphagia, survival time is very similar in MSA and PSP (15–24 months) (review:

Müller et al. 2001). In contrast to IPS pharmacological interventions against APS symptoms are not very effective

3.1.4 Huntington Disease

Huntington disease is an autosomal dominant genetic neurodegenerative disease with a prevalence of 2–7/100,000 and disease-onset in most cases between the ages of 30–45 years. Besides choreatic movements, personality changes, and cognitive decline, neurogenic dysphagia occurs frequently (in over 80%; Edmonds 1966). *Tachyphagia and problems with chewing and bolus transfer* may be found in *the oral phase,* but pharyngeal and esophageal disturbances also occur. A differential diagnosis is *chorea-acanthocytosis*. In this autosomal recessive genetic disease including chorea, epilepsy, cognitive decline, and thorny erythrocytes, swallowing problems are characterized by an action-induced tongue protrusion dystonia with widened jaw. Therefore, eating and drinking are very effortful and the patients try to compensate the problem, e.g., by pressing the lips strongly together (for details, see Bader et al. 2010). Pharmacologic therapy against choreic movements includes typical and atypical neuroleptics, benzodiazepines, and the monoamine depleting agent tetrabenazine.

3.1.5 Dystonia

Among the various types of dystonia, *torticollis* (cervical dystonia or spasmodic torticollis) is one of the most frequent causes of dysphagia; according to Ertekin et al. (2002) dysphagia occurs in about 70%. In torticollis, the muscles controlling the neck cause sustained twisting. The *combination of oromandibular dystonia and blepharospasmus* is called *Meige* or *Brueghel syndrome*, which is often associated with dysphagia. Therapy of choice for the abovementioned dystonias are botulinum neurotoxin injections in the corresponding muscles (neck, M. masseter, M. temporalis, M. pterygoideus lateralis).

3.1.6 Wilson Disease

Wilson disease is a rare (prevalence 1–3/100,000) autosomal recessive genetic disorder with accumulation of copper in various tissues such as liver, cornea, and brain. Clinical symptoms and signs comprise psychiatric problems, cognitive decline, personality changes, symptoms of parkinsonism including a typical hand tremor or dystonia. According to Machado et al. (2006) dysphagia occurs in 50%; the oral, pharyngeal, and esophageal phases may be affected in isolation or in combination. An early diagnosis (low serum copper, high urine copper, liver biopsy, genetic testing) is important, since pharmacological interventions are available with the main aim of removing copper from the body. Liver transplantation may be lifesaving in patients who are unresponsive to drugs.

3.1.7 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common degenerative motor neuron disease of adulthood with a prevalence of about 7/100,000. It is a disease of unknown etiology with combined degeneration of the upper motor neuron (UMN) and the lower motor neuron (LMN), which occurs in most cases between 50–70 years of age; about 90% are sporadic and 10% genetic (mainly autosomal dominant). UMN disease (UMND) causes supranuclear symptoms, also termed pseudobulbar palsy. LMN disease (LMND) affects (besides spinal motoneurons) the motor cranial nuclei in the pons and medulla oblongata innervating the muscles of the jaw, face, tongue, pharynx, and larynx with subsequent bulbar symptoms of chewing, swallowing, speech, and voice. Survival time varies on average between 3 and 5 years; in about 25% of cases, the onset is bulbar (bulbar type of ALS; progressive bulbar palsy) with an even worse prognosis. Causal therapy does not exist, but the glutamate antagonist riluzole increases survival time by some months. The frequency of neurogenic dysphagia is very frequent in the course of the disease and occurs in all patients with the bulbar type of ALS. Dysphagic symptoms include problems of the oral phase (with tongue paresis), disturbed pharyngeal peristalsis, as well as primary or secondary opening deficits of the UES. Swallowing therapy must take into account that too many or long-lasting exercises may exhaust the weakened muscles. Many ALS patients need thickening of liquids, especially in

the case of severely impaired oral control; it has, however, to be considered that thickening may sometimes enhance the swallow effort. When UES dysfunction is a significant problem, thickening may even be dangerous. Since the insertion of a PEG is associated with increased morbidity and mortality in patients with a forced vital capacity (fVC) <60%, patients and relatives have to be informed on the necessity to insert a PEG not too late (Kühnlein et al. 2008).

Since Chiari I malformation, syringobulbia, tumors of the skull base, inclusion body myositis, and spinobulbar muscular atrophy may mimick ALS symptoms, these diseases are important differential diagnoses and mentioned in this chapter.

3.1.8 Spinal Muscular Atrophies

Spinal muscular atrophies (SMAs) are diseases, which cause degeneration of spinal and sometimes also of bulbar motor neurons with flaccid pareses, muscular fasciculations or tongue fibrillations, respectively. There are *four types of autosomal recessive SMAs affecting the proximal musculature* (the distal types are not dealt with hereafter), called SMA types I, II, III, and IV. Dysphagia occurs in SMA types I, II, and III; patients with SMA type I die before the age of 10. Messina et al. (2008) reported on 122 persons with SMA type II (age between 1 and 47 years) and found chewing problems in 34 patients (28%), impaired jaw opening in 36 patients (30%), and dysphagia in 30 patients (25%). Similar frequencies of dysphagia were reported for SMA type III (Chen et al. 2012).

Spinobulbar muscular atrophy (SBMA) or *Kennedy disease* is an X-linked genetic disease (hyperexpansion of CAG repeats) which, therefore, occurs almost only in men. As compared to ALS, with which it shares some similarities such as bulbar symptoms and fasciculations of the facial and body musculature, sensory impairment of spinal and cranial nerves may occur and the course of the disease is slow. Nevertheless, aspiration pneumonia seems to increase the mortality risk in SBMA patients. Laryngeal stridor is much more frequent in SBMA (about 50%) as compared to ALS (initially 2%, in the course about 19%) (Kühnlein et al. 2008). Because the androgen receptor gene is affected, gynecomastia and testicular atrophy may also occur.

3.1.9 Ataxias

Spinocerebellar ataxias (SCA) are rare autosomal dominant genetic diseases. According to the chronological order of detection of the gene loci, 40 SCA can be differentiated (SCA1 till SCA40). Dysphagia occurs most frequently in SCA1, SCA2, SCA3, SCA6, and SCA7; in the four last-mentioned types, widespread neurodegeneration of swallowing-relevant brainstem nuclei was found (Rüb et al. 2006). *Friedreich ataxia (FRDA)*, the most frequent inherited ataxia, is an autosomal recessive genetic disease (hyperexpansion of GAA repeats) with a prevalence of about 3/100,000. The onset is usually before the age of 20 years. Characteristic features are gait ataxia, dysarthria, sensory symptoms, flaccid pareses of the distal muscles, scoliosis, foot deformity, and hypertrophic cardiomyopathy. In the study performed by Dürr et al. (1996) on 140 persons with FRDA, dysphagia occurred in 27%. *Sporadic ataxias* comprise, e.g., alcoholic or paraneoplastic cerebellar atrophy. In sporadic ataxia of unknown origin, the frequency of dysphagia accounts for 38% (Abele et al. 2002).

3.1.10 Tumors of the Brain or the Skull Base

Whether or not a brain tumor causes neurogenic dysphagia depends on many variables such as the exact site of the tumor, pressure exerted by the tumor on neighboring structures, and radiation injury of the brain. In the prospective study performed by Newton et al. (1994) on 117 patients with primary brain tumors, dysphagia occurred in 14.5% (30% were present before the operation, 30% developing immediately after the intervention, and 40% in the course afterwards). In a retrospective study, Wesling et al. (2003) studied 38 patients with brain tumors as compared with a sample of stroke patients who were matched for age, site of lesion, and initial composite cognitive functional independent measure (FIM) score. Primary (80% malignant) and secondary (metastatic) brain tumors accounted

for 83% and 17%, respectively. With regard to outcome—length of stay, total hospital charges, and swallowing status—, no statistically significant difference between the tumor and stroke patient groups was found. The authors' conclusion was that *patients with brain tumors including malignant ones "should be afforded the same type and intensity of rehabilitation for their swallowing that is provided to patients following a stroke."*

Tumors of the posterior fossa (IV ventricle) such as ependymomas or cerebellar pilocytic astrocytomas may cause neurogenic dysphagia after neurosurgical intervention, since during detaching these tumors from the posterior region of the medulla oblongata, medullary (venous?) bleedings may occur. Due to consecutive bilateral affection of the dmCPGs, the resulting dysphagia is often very severe (Prosiegel et al. 2005a, b).

The outcome of 12 patients with dysphagia after excision of *tumors of the skull base* was described by Jennings et al. (1992) (five glomus jugulare tumors, one glomus vagale tumor, three acoustic neuromas, and three meningiomas). Aspiration occurred in 75%, and after 2 weeks 58% of the patients were able to tolerate oral intake by use of compensatory swallow techniques and diet modifications.

3.1.11 Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory CNS disease with high incidence and prevalence rates of about 6/100,000/year and 100/100,000, respectively, in industrial countries of the northern hemisphere. Although the etiology is still unknown, the autoimmune pathogenesis may be shortly described as follows: Activated lymphocytes penetrate the blood brain barrier and initiate immunological events such as activation of certain pro-inflammatory cytokines. Besides demyelination of axons in the white (and grey) matter of the brain and spinal cord, even axonal loss occurs. In about 80% the disease shows a relapsing-remitting onset (RRMS), whereas 20% of patients suffer from a primary-progressive course (PPMS). After some years, about one-half of the patients with RRMS develops a secondary-progressive MS (SPMS). Pharmacological approaches include intravenous glucosteroid treatment, intravenous immunoglobulins, or plasmapheresis in the case of relapses; chronic treatment comprises immunotherapy with interferon-beta preparations, glatiramer acetate, natalizumab, mitoxantrone, and many new drugs such as orally administered dimethyl fumarate and fingolimod. In PPMS, the monoclonal antibody ocrelizumab seems to be effective. Dysphagia is rarely an isolated, predominant symptom in MS. The prevalence of dysphagia accounts for about 30% of persons with MS and is associated with overall disability and with brainstem signs; about 15% of persons with mild disability may, however, also suffer from dysphagia. There are no swallowing disturbance patterns which are typical for MS; aspiration pneumonia due to dysphagia is among the leading causes of death in persons with MS (Prosiegel et al. 2004).

3.1.12 Central Pontine and Extrapontine Myelinolysis

In central pontine myelinolysis (CPM), a so-called osmotic demyelination of white matter in the central pons occurs due to rapid correction of hyponatremia. Also brain areas outside the pons (basal ganglia, cerebellum, thalamus, etc.) may be affected, which is called extrapontine myelinolysis (EPM). The most frequent disease underlying CPM or EPM is alcoholism. But also liver transplant patients may develop CPM or EPM; in these cases the development of the disease is particularly attributed to the immunosuppressive agent cyclosporine (Lampl and Yazdi 2002). Besides spastic tetraparesis with dysarthria, neurogenic dysphagia occurs very frequently and has usually a good prognosis.

3.1.13 Infectious Diseases of the CNS

In herpes simplex encephalitis, dysphagia rarely occurs, since the virus affects predominantly the temporal lobes. Stickler et al. (2003) described a patient with dysphagia due to bilateral lesions of the insula and the adjacent operculum caused by viral encephalitis of unknown origin.

Acute encephalitis of the lower brainstem (rhombencephalitis) caused by Listeria monocytogenes—a food-borne gram-positive bacillus—is commonly

associated with severe dysphagia. Overall mortality is about 50%, 100% of untreated patients die and more than 70% of patients treated early with ampicillin or penicillin survive; neurological sequelae develop in about 60% of survivors (Armstrong and Fung 1993; Smiatacz et al. 2006).

Poliomyelitis is a viral disease affecting the motor nuclei of the brainstem and/or the spinal cord. Global polio immunization resulted in eradication of the disease caused by wild-strained polio virus type 2 (WPV2), which could not be detected worldwide since 1999. In the polio-free countries, cases and outbreaks are reported due to imported WPV1 or WPV3 because of unbroken localized circulation of these types in three polio-endemic countries (Afghanistan, Nigeria, and Pakistan). *Post-polio syndrome (PPS)* is a condition, which develops about 30–40 years after an acute paralytic polio infection in about 50% of formerly affected people. PPS is characterized by exacerbation of preexisting symptoms or development of new symptoms including muscle weakness, general fatigue, pain, cold intolerance, and swallowing problems. Sonies and Dalakas (1991) examined 32 patients with PPS, among whom 14 persons had new swallowing difficulties; 12 persons had bulbar involvement during acute polio infection. Interestingly enough, 31 patients had "some abnormality on detailed testing of oropharyngeal function" and "only 2 patients had any signs of aspiration." The authors' conclusion is that "in patients with the post-polio syndrome, the bulbar muscles often have clinical or subclinical signs of dysfunction. These abnormalities suggest that in bulbar neurons there is a slowly progressive deterioration similar to that in the muscles of the limbs."

Human Immunodeficiency Virus (HIV)—with its two types HIV-1 and HIV-2—belongs to HTLV-III (human T-cell lymphotropic virus type III) retroviruses. Dysphagias may be due to many causes in infected persons: (1) directly by HIV-based diseases such as HIV-associated encephalopathy, AIDS dementia complex, HIV neuropathy, and HIV myopathy; (2) indirectly by meningitis/encephalitis/encephalopathy caused by fungi (e.g., *Cryptococcus neoformans* and *Candida albicans*), toxoplasma gondii, cytomegaly virus (CMV), herpes simplex virus (HSV), varizella-zoster virus (VZV), mycobacterium, treponema pallidum or by the JC virus (JCV) causing progressive multifocal leukoencephalopathy (PML). One should also keep in mind primary CNS lymphomas, which are often associated with the Epstein-Barr virus (EBV), and esophagitis due to candida, CMV, and/or HSV.

Neuroborreliosis is caused by *Borrelia burgdorferi* transmitted by ticks. In the second and third stage of the disease, dysphagia may occur (Velázquez et al. 1999). Neuroborreliosis can mimick symptoms of other diseases such as MS and is, therefore, an important differential diagnosis. It can successfully be treated by use of antibiotics.

3.1.14 Chiari Malformations

Most important in the context of adult patients with dysphagia is Chiari I malformation with herniation of the cerebellar tonsils below the foramen magnum and elongation of the medulla oblongata. Dysphagia may occur as the sole manifestation of adult Chiari I malformation and mimick a bulbar palsy in amyotrophic lateral sclerosis; probably, in those cases dysphagia is caused by pressure exerted by the cerebellar mass on the hypoglossus nuclei and/or on the dorsomedial central pattern generators for swallowing (Paulig and Prosiegel 2002). Neurosurgical posterior fossa decompression is necessary in symptomatic cases.

3.1.15 Syringomyelia and Syringobulbia

Syringomyelia is a congenital or acquired (e.g., after trauma) cavitation of the central region of the spinal cord, in most cases in its cervical part; *syringobulbia* may be an isolated idiopathic form or caused by the extension of a cervical syrinx (Greek word for "flute") into the medulla oblongata. In syringobulbia, the most frequent symptoms are headache, vertigo, dysphonia, dysarthria, trigeminal paraesthesia, diplopia, and dysphagia; dysphagia is caused by atrophy and weakness of the soft palate, the pharynx, or the tongue due to pressure exerted by the syrinx on the ambiguous or hypoglossal nuclei. Neurosurgical intervention is necessary depending on the severity of symptoms.

3.1.16 Paraneoplastic Syndromes of the CNS

With respect to dysphagia, *paraneoplastic brainstem encephalitis* is of special importance. Most frequently in patients with small cell lung carcinoma (SCLC), an anti-Hu syndrome may occur with positive anti-Hu antibodies—also called antineuronal nuclear autoantibody type 1 (ANNA-1). Saiz et al. (2009) reported on 22 patients with Anti-Hu-associated brainstem encephalitis, of whom seven suffered from dysphagia. Paraneoplastic brainstem encephalitis due to anti-Ri antibodies (ANNA-2) is in most cases found in women with breast cancer or persons with SCLC and may also cause dysphagia (Pittock et al. 2003). Patients with anti-Ma2-associated (brainstem) encephalitis suffer frequently (>50%) from testicular germ-cell tumors. *Stiff-person syndrome (SPS)* is characterized by rigidity of the trunk and proximal limb muscles, intermittent spasms, and increased sensitivity to external stimuli. Antibodies against glutamic acid decarboxylase (GAD) are frequently found. SPS of paraneoplastic origin accounts for about 5% of cases and is associated with anti-amphiphysin, anti-gephyrin, and anti-Ri antibodies. Dysphagia may occur in SPS, but reports on its prevalence are lacking (Bhutani 1991; Chen 1992).

3.2 Diseases of the Cranial Nerves

3.2.1 Guillain-Barré Syndrome (GBS) and Variants

Guillain-Barré syndrome (GBS) is an acute, acquired, monophasic autoimmune disorder of peripheral nerves including cranial nerves (CNs) such as the VII. CN. GBS develops frequently about 2 weeks after respiratory (e.g., caused by cytomegaly virus) or gastrointestinal infections (e.g., caused by campylobacter jejuni), operations or, less frequently, after vaccination (influenza, hepatitis B or rabies vaccine) (Souayah et al. 2007). GBS is the most common cause of acute ascending flaccid sensorimotor paralysis. An elevated CSF protein without elevation of lymphocytes is typically found (albumino-cytological dissociation). The most frequently occurring type of GBS is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). After campylobacter-jejuni enteritis, the prognosis of GBS seems to be worse than after other infections, since there is acute motor axonal damage (acute motor axonal neuropathy, abbreviated as AMAN). Chen et al. (1996) found in a videofluoroscopic study on 14 GBS patients neurogenic dysphagia in all cases; five patients with moderate-severe dysphagia were re-examined and showed a light-moderate dysphagia 4–8 weeks later. *Variants of GBS* (1–5%) are *Miller-Fisher syndrome (MFS)* and *polyneuritis cranialis*. MFS is characterized by an external ophthalmoplegia, cerebellar ataxia, areflexia, and frequently also by neurogenic dysphagia. In polyneuritis cranialis, a bilateral affection of the caudal cranial nerves with consecutive neurogenic dysphagia occurs. In MFS and polyneuritis cranialis, serum antiganglioside antibodies (against GQ1b or GT1a) are often positive. In a chronic variant of GBS, the so-called *chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)*, cranial nerves are involved in up to 20%, but neurogenic dysphagia occurs rarely (Mazzucco et al. 2006). Therapeutic options in GBS and its variants include intravenous immunoglobulins (5-day course of daily 0.4 g/kg/day) and plasma exchange.

3.2.2 Tumors

Tumors of the IX, X, or XII cranial nerve (CN) such as glossopharyngeal, vagal, or hypoglossal neurinomas cause mild–moderate dysphagia including palatal, pharyngeal, or lingual hemiparesis, respectively (Prosiegel et al. 2005b). Dysphagia may be more severe in cases with affection of more than one caudal CN; examples are tumors of the skull base including the region of the jugular foramen (Oestreicher-Kedem et al. 2010) such as meningeomas, chondromas, and glomus jugulare tumors (see Sect. 3.1.9). Collet-Sicard syndrome is characterized by palsy of the CNs IX, X, XI, and XII and may be caused by tumors or trauma of the base of the skull, but also by carotid artery dissection.

3.2.3 Eagle Syndrome

An elongated styloid process (unilaterally or bilaterally) occurs in about 2–4% of healthy persons; only 4–10% of these persons are, however, symptomatic (Murtagh et al. 2001) and develop symptoms of the so-called Eagle syndrome: masticatory pain, globus sensation, neuropathic pharyngeal or facial pain, odynophagia and dysphagia. Eagle syndrome may follow tonsillectomy or trauma. Diagnosis is confirmed by lateral cervical radiograph, (three-dimensional) CT-scan, palpation of the styloid process in the tonsillar fossa, and/or infiltration with anesthetic. Therapy depends on the predominant symptoms, i.e., analgetic therapy in the case of pain or—provided that pain relief by local anesthesia is proven—surgical removal of elongated styloid processes. Severity of symptoms seems not to correlate with the degree of elongation of the styloid processes (review: Piagkou et al. 2009; case report with CT-scan: Akhaddar et al. 2010).

3.3 Diseases of the Neuromuscular Junction

The two most important types are myasthenia gravis and Lambert-Eaton syndrome.

3.3.1 Myasthenia Gravis

Adult-onset myasthenia gravis (MG) is an acquired autoimmune disorder. *Antibodies against the acetylcholine receptor (AChR) of the muscle endplate* are present in 80–90% of patients with generalized MG. These anti-acetylcholine receptor antibodies (anti-AChR abs) do not only block the AChRs, but are also able to destroy them. Incidence and prevalence of MG are about 0.8–1/100,000/year and 15–25/100,000, respectively. The characteristic features are muscle weakness worsening on exertion/during the course of the day and improving with rest; typically, proximal muscles, muscles of the eyes as well as chewing and swallowing muscles are predominantly affected. Therefore, besides proximal weakness also ptosis, diplopia, and dysphagia are frequent findings. Dysphagia occurs in about 20% as initial symptom and in about 50% in the course of MG. In most cases, MG can be treated successfully by use of cholinesterase inhibitors such as pyridostigmine (increasing the concentration of acetylcholine with the aim of improving neuromuscular junction transmission), corticosteroids, immunosuppressants and (in very severe cases) intravenous immunoglobulins or plasma exchange. Subgroups without antiAChR abs, but with antibodies against muscle-specific tyrosine kinase (MuSK) are called seronegative and show predominant bulbar symptoms including dysphagia. In these anti-MuSK-positive patients, the response to the abovementioned pharmacological interventions is often less favorable and the monoclonal antibody rituximab may be effective. Thymectomy is indicated in patients with thymomas or with early onset (age <50 years); thymectomy is not recommended in seronegative cases. Meanwhile other antibodies have been detected such as anti-Agrin abs or anti-LRP4 abs; their pathogenetic role is still unclear (review: Gilhus 2016).

3.3.2 Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is rare and occurs more frequently in men than in women. Its etiology is paraneoplastic in over 60% (small cell lung cancer [SCLC] in most cases) and then caused by *antibodies against voltage-gated calcium channels (VGCC)* at presynaptic nerve endings with consecutive impaired synaptic release of acetylcholine. Proximal lower limb girdle weakness is a typical finding. In the course of the disease, ptosis, double vision, and dysphagia may occur. *The frequency of dysphagia varies in the literature between 24% and 34%* (Payne et al. 2005). 3,4-Diaminopyridine, intravenous immune globulin, immunosuppressants, plasma exchange, and the removal of an underlying tumor are therapeutic options.

3.4 Diseases of the Muscles

This section deals with muscle diseases which are frequently associated with dysphagia (for rare types of myopathies including those due to mitochondrial respiratory chain disorders, see special literature).

3.4.1 Muscular Dystrophies

The most frequent late-onset muscular dystrophies are myotonic dystrophies. *Myotonic dystrophy type 1 (DM1)* is an autosomal dominant disorder and caused by an expansion of a CTG trinucleotide repeat (chromosome 19q13.3); the European prevalence is 3–15/100,000. The disease affects distal skeletal muscles, smooth muscles, the eyes, the heart, the endocrine system, and the central nervous system. Depending on the severity of DM1, symptoms comprise cataract, myotonia (sustained muscle contraction), muscle atrophy, cardiac conduction abnormalities, and dysphagia. *Myotonic dystrophy type 2 (DM2)* is also an autosomal dominant genetic disorder and caused by an expansion of the CCTG repeat (chromosome 3q21), but occurs rarer than DM1. *DM2* affects predominantly proximal muscles and is, therefore, also called PROMM (for *pro*ximal *m*yotonic *m*yopathy). Dysphagia is common in DM1 with reported frequencies of about 70% and frequently occurring UES opening deficits (Ertekin et al. 2001); esophageal motility disorders may also occur in DM1 (Eckardt et al. 1986). In DM2, dysphagia occurs in about 40% and is milder than in DM1 (Tieleman et al. 2009).

The rare *autosomal dominant oculopharyngeal muscular dystrophy (OPMD)* is caused by expansion of GCG repeats (chromosome 14q) and begins in the fifth or sixth decade of life (Brais et al. 1999). OPMD is characterized by slowly progressive ptosis and dysphagia. The severity of dysphagia correlates positively with the progression of ptosis. This is mainly caused by retroflexion of the neck which compensates the ptosis ("astrologist's view"), but aggravates dysphagia (de Swart et al. 2006).

The *X-linked Duchenne muscular dystrophy* (DMD) affects male children and is associated with high frequencies of dysphagia in the advanced stage—30 of 31 patients with a mean age of 19.9 year in the study performed by Hanayama et al. (2008). The *X-linked Becker muscular dystrophy (BMD)* is rarer than DMD and has a much more benign disease course; according to Yamada et al. (2017) "swallowing problems in BMD are similar to those observed in patients with DMD." The *autosomal dominant facioscapulohumeral muscular dystrophy* is a rare muscular dystrophy with slow disease progression and predominant affection of the muscles of the face and shoulder; according to the study performed by Stübgen (2008), dysphagia occurred in 8 out of 20 patients—with oropharyngeal in five and esophageal symptoms in three persons.

3.4.2 Inflammatory Muscle Diseases

In adult patients, the most frequent inflammatory muscle diseases are polymyositis, dermatomyositis, and sporadic inclusion body myositis (review: Dalakas 2015).

Polymyositis (PM) and *dermatomyositis (DM)* belong to the so-called connective tissue diseases (CTD) comprising also systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), diffuse systemic sclerosis/scleroderma, and Sjögren syndrome. In mixed connective tissue disease (MCTD; Sharp syndrome, overlap syndrome) features of various connective-tissue diseases coexist and overlap. PM and DM are more frequent in women than in men and their onset is acute or subacute with weakness of proximal muscles (e.g., shoulder region); various types of antinuclear antibodies (ANAs) can be found. A paraneoplastic pathogenesis is more frequent in DM as compared to PM.

Sporadic inclusion body myositis (sIBM), the most frequent myositis in adulthood, is associated with weakness and atrophy of distal muscles, a feature which may initially mimick ALS. In muscle fibers of sIBM patients, "rimmed vacuoles" can be found; they contain amyloid-β42 (Aβ42), which may play a pathogenic role. Dysphagia is very frequent in IBM, where it occurs in over 50% (Houser et al. 1998).

The response of PM and DM to corticosteroids, immunosuppressants, and intravenous immunoglobulin is good as compared to IBM with poor response.

Other inflammatory muscle diseases are rare at least in industrial countries of the western

hemisphere. Examples are trichinosis or cysticercosis as well as viral (e.g., HIV myositis) or bacterial causes.

3.4.3 Complications of Prolonged Mechanical Ventilation and/or Sepsis

Ajemian et al. (2001) examined 48 patients by use of videoendoscopy, in whom *prolonged mechanical ventilation* was performed for at least 48 h; 56% suffered from dysphagia with silent aspirations in 25%. These results are similar to those of the study performed by Tolep et al. (1996), who found dysphagia in 80% of 35 patients with prolonged mechanical ventilation. The cause of dysphagia in these patients is unclear until now.

Critical-illness polyneuropathy (CIP) and/or *myopathy (CIM)* are monophasic and self-limited diseases occurring in about 50–70% of patients treated on intensive care units because of sepsis or systemic inflammatory response syndrome (SIRS). Characteristic features of CIP/CIM are delayed weaning from the respirator due to weakness of respiratory musculature, flaccid tetraparesis, and a prolonged mobilization phase. In the pathogenesis, inflammatory factors mediating SIRS as well as drugs such as steroids and neuromuscular blocking agents seem to be involved (review: Hund 2001). Dysphagia occurs in CIP/CIM, but there are no reports on incidence or prevalence rates. Complete recovery of swallowing problems occurs in a high percentage of patients with CIP/CIM (Ponfick et al. 2015).

3.5 Iatrogenic Causes

3.5.1 Drugs

A lot of pharmacological interventions may cause dysphagia or aggravate preexisting swallowing problems. *Sedatives* such as benzodiazepines may suppress cortical or brainstem control of swallowing. *Drugs which impair neuromuscular junction transmission* can cause weakness of swallowing muscles or aggravate myasthenic symptoms; examples are aminoglycosides and D-penicillamine. A *drug-induced myopathy* may be caused, e.g., by corticosteroids, colchicine, the antiretroviral drug ziduvidine, cholesterol-lowering agents such as statins, amiodarone, and cyclosporin (Walsh and Amato 2005). Certain neuroleptics (e.g., haloperidol) or the antiemetic agent metoclopramide may cause dysphagia via extrapyramidal symptoms due to *dopamine antagonistic* action. Anticholinergic agents or drugs with *anticholinergic side effects* (e.g., the antidepressant amitriptyline) may influence swallowing by CNS effects (e.g., confusion) or via xerostomia. Drug-induced *esophageal injury* may be induced by tetracyclines, nonsteroidal anti-inflammatory agents, potassium chloride, quinidine sulfate, and biphosphonates (Zografos et al. 2009). *Botulinum neurotoxin (BoNT)* may cause dysphagia after injection into neck muscles, e.g., in patients with torticollis, into the thyroarytenoid muscle in the case of adductor spasmodic dysphonia or into the cricopharyngeal muscle because of primary UES dysfunction, into the lateral pterygoid muscle in patients with oromandibular motor disorders and into the tensor veli palatini muscle in the case of essential palatal tremor. The probability of these complications is injection site-specific (e.g., more common with injection into pterygoid or palatal muscles as compared to neck muscles). In the case of torticollis, BoNT-induced dysphagia occurs in about 6% on average 9.7 days after injection with a duration of about 3.5 weeks (Kessler et al. 1999).

3.5.2 Carotid Endarterectomy

According to the study of Cunningham et al. (2004) on 1739 patients undergoing carotid endarterectomy (CEA), cranial nerve (CN) injuries occurred in 65 patients: 27 hypoglossal, 17 marginal mandibular branch (of the facial nerve), 17 recurrent laryngeal, one accessory, and three Horner syndrome; in nine patients the deficit was present at 4-month follow-up examination; none of these persisting deficits (0.5%) resolved during the subsequent follow-up (1 year); duration of operation longer than 2 h was associated with an increased risk of CN injury. In the case of a postoperative combination of ipsilateral

vocal cord and pharyngeal hemiparesis (with consecutive dysphagia), the term "double trouble" is used (hoarseness and dysphagia). According to a study on 14 patients with "double trouble" (AbuRahma and Lim 1996), after Teflon injections to medialize the paralyzed vocal cord and a cricopharyngeal myotomy to restore swallowing and alleviate aspiration, "13 of 14 patients had satisfactory outcomes, including normal voice and swallowing."

3.5.3 Anterior Cervical Spine Surgery

Martin et al. (1997) studied retrospectively 13 patients with new-onset dysphagia after anterior cervical spine surgery (ACSS). They found the following dysphagia patterns: prevertebral soft tissue swelling near the surgical site with deficient posterior pharyngeal wall movement and impaired upper esophageal sphincter opening in two patients, absent or weak pharyngeal phase in five patients (with consecutive aspiration in three cases), problems in the oral preparatory and oral stages of swallowing including deficient bolus formation and reduced tongue propulsive action in four persons and impaired oral preparatory and oral phases with a weak pharyngeal swallow combined with prevertebral swelling in two patients. Due to postoperative swelling/edema or hematoma, transitory odynophaga is frequent. The study performed by Lee et al. (2007) is very interesting, since the authors examined 310 patients over a period of 2 years. The frequencies of dysphagia were 54.0%, 33.6%, 18.6%, 15.2%, and 13.6% after 1, 2, 6, 12, and 24 months, respectively; three negative predictors with regard to the onset of dysphagia within 2 years were found: female gender, revision surgeries, and multilevel surgeries. During history taking, it is important to ask for cervical spine surgery, even when performed many years ago: Vanderveldt and Young (2004) described a patient in whom many months after ACSS a symptomatic esophageal stricture at the level of the cervical hardware was found (scar? graft extrusion?); in addition, the authors mention cases in the literature with new-onset of dysphagia due to various complications after ACSS.

3.5.4 Radiochemotherapy of Head and Neck Cancers

Irradiation of oropharyngeal tumors often causes xerostomia, mucositis, altered taste, edema and indurations of the soft tissue, altered sensation, and trismus. These side effects may lead to dysphagia or aggravate preexisting swallowing problems. Especially, subcutaneous indurations impair hyolaryngeal excursion with consecutive UES opening deficits and other problems.

In the pathogenesis of neurogenic dysphagia, however, radiation-related cranial nerve palsy plays the most important role. It is assumed that irradiation-induced fibroses of the affected tissue cause nerval lesions directly via pressure and/or secondarily by reduced vascular supply. Lin et al. (2002) studied 19 patients in whom tumors of the nasopharynx were irradiated. The XII. (hypoglossal) cranial nerve (CN) was affected most frequently (n = 17, bilaterally: n = 7); the X. (vagal) CN was lesioned in 11 cases (bilaterally: n = 2); affection of the recurrent laryngeal nerve occurred in six patients (bilaterally: n = 5) and of the XI. (accessory) CN in two cases (bilaterally). The latency between irradiation and affection of CNs showed a range between 12 and 240 months (!). An additional chemotherapy enhances the severity of radiation-related sequelae (Caudell et al. 2009). Nguyen et al. (2004) studied 55 patients with combined radiochemotherapy due to cancers of the oropharynx (29), larynx (11), oral region (6), hypopharynx (5), and nasopharynx (4); the frequencies of dysphagia and aspirations were 45% and 36%, respectively. New methods of radiation therapy such as *intensity-modulated radiation therapy (IMRT)* reduce the frequency and severity of chronic dysphagia and via parotid gland sparing also of xerostomia (Anand et al. 2008; van Rij et al. 2008).

3.6 Special Diagnostic Approaches

In neurogenic dysphagia of known origin, laboratory findings and other diagnostic results may help to confirm the diagnosis and more importantly to monitor the treatment. For example, in

polymyositis serum creatine kinase (CK) is usually elevated and the dosage of corticosteroids and other drugs can be lowered in the case of normalization of this muscle enzyme.

In some cases the *origin of neurogenic dysphagia is unknown*; this occurs frequently, when swallowing problems are the sole symptoms at disease onset, e.g., in inclusion body myositis (IBM); in suspected IBM, a muscle biopsy would be the next diagnostic step. In such situations it is highly recommended to use a *checklist in order not to forget any of the many etiologies and the corresponding diagnostic tools*.

In clinical routine, the following blood/serum parameters should be assessed: complete blood counts; besides routine serum values also creatine kinase (CK; e.g., elevated in myositis, temporal arteritis), calcium, potassium, sodium and copper, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (both, e.g., usually elevated in temporal arteritis), vitamin B_{12} and folic acid, thyroid screening, serologic tests for syphilis and Lyme disease (please note: elevated IgG or IgM levels in the serum do not prove neuroborreliosis, which can only be confirmed by cerebrospinal fluid [CSF] examination).

For details see the checklist in Table 1, which does of course not comprise all possible etiologies, but at least the most frequent ones.

3.7 Therapy

3.7.1 Interventions Against Dysfunction of the Upper Esophageal Sphincter

Primary UES dysfunction is caused by impaired/lacking relaxation of the UES, which occurs most frequently in brainstem lesions, Parkinson disease and myositis (Oh et al. 2007; Williams et al. 2002). In such cases, *cricopharyngeal myotomy (CPM)* may be indicated dependent on certain videomanometric findings (Kelly 2000; Williams et al. 2002). *Botulinum neurotoxin (BoNT) injection into the cricopharyngeal muscle (CP)* is a reversible alternative approach. The available data pool is much better with regard to CPM as compared to BoNT: In BoNT studies, the patient groups were small; the largest and most recent prospective study (Alfonsi et al. 2010) consisted of 34 patients with quite different neurological diseases (stroke = 10, PSP = 9, IPS = 7, MSA = 5, MS = 2, Ataxia telangiectasia = 1); the dose of BoNT varied in different studies between 30 and 360 Dysport equivalent units (Chiu et al. 2004). The assumption that effective cricopharyngeal BoNT injection might predict good results after CPM seems logic, but is not confirmed by study results.

Recently, Kocdor et al. (2016) published a systematic review comparing outcomes of CPM, BoNT injection, and *dilatation*. Among 34 articles, which met eligibility criteria, there were 16 on CPM, 12 on BoNT injection, and six on dilatation. The authors found a statistically significant difference between success rates of cricopharyngeal myotomy (78%) and BoNT injection (69%); endoscopic CPM had a higher success rate than open CPM (odds ratio 2.2). The intermediate success rate of dilatation (73%) was not statistically different from CPM or BoNT injection, respectively. Although the results of this study are very interesting, they must be interpreted with caution, since a systematic review does not replace a randomized controlled study comparing the different interventions. There is still a need for such studies.

3.7.2 Pharmacotherapy and New Therapeutic Approaches

When *causal therapy of the underlying disease* (e.g., myasthenia gravis) is possible, dysphagia responds in most cases to about the same extent as the other symptoms. An exception is, e.g., idiopathic Parkinson syndrome (IPS): dysphagia responds in only 30–50% to dopaminergic drugs as compared to other symptoms of the disease, since besides dopaminergic neurons also non-dopaminergic swallowing-relevant cells of the brainstem are affected in IPS (see Sect. 3.1.2).

Unfortunately, specific pharmacological interventions against neurogenic dysphagia are not available until now. But since some years, research focuses on substance P (SP) and on drugs which enhance its concentration, because SP facilitates protective cough and swallowing; its concentration

is decreased in many body compartments (e.g., sputum, serum) in silent aspirators. Therefore, drugs such as angiotensin-converting enzyme (ACE) inhibitors which inhibit degradation of SP and thus cause an increase of its concentration may be effective (review: Ramsey et al. 2005). Also dopamine stimulates the synthesis of SP and amantadine acts by releasing dopamine from dopaminergic nerve terminals. In a randomized placebo-controlled multicenter-trial (RCT) on 6105 patients with a history of stroke, the ACE inhibitor perindopril was compared to placebo with regard to pneumonia rate after a median follow-up of 3.9 years: in the whole study population, the frequency of pneumonia was 3.8% in the perindopril group and 4.7% under placebo (relative risk reduction [RRR] = 19%; p = 0.09), whereas in participants of Asian origin there was a significant RRR of 47% (p = 0.009); this difference seems to be caused by ACE allele polymorphismus (Ohkubo et al. 2004). In a randomized, but not placebo-controlled study (100 mg amantadine per day versus no therapy) on 163 dysphagic stroke patients, Nakagawa et al. (1999) compared the frequency of aspiration pneumonia 3 years after disease-onset: the frequencies were 6% versus 28% in the treated versus the untreated group. Besides ACE inhibitors and amantadine, capsaicin may have favorable effects on prophylaxis of aspiration pneumonia. In a systematic review on pharmacological prevention of aspiration pneumonia (El Solh and Saliba 2007), the authors conclude that ACE inhibitors may be beneficial in selected patients at high risk for aspiration; since capsaicin is a low-risk approach to stimulate swallowing and cough reflexes, it can be recommended; the routine use of amantadine is not recommended because of possible serious adverse events. According to the principles of evidence-based medicine, drugs such as ACE inhibitors, capsaicin, and amantadine can, therefore, be applied in individual patients and with a low grade of recommendation.

With regard to pharmacotherapy, the main problem is that multicenter RCTs in large patient populations are still lacking. This underscores the necessity of swallowing therapy (see "Behavioural Treatment of Oropharyngeal Dysphagia" in the chapter by R. Speyer, this volume) and of new approaches such as transcutaneous neuromuscular electrical stimulation of the neck, pharyngeal electrical stimulation, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation (see "Direct and Indirect Therapy: Neurostimulation for the Treatment of Dysphagia after Stroke" in the chapter by S. Mistry, this volume).

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Gastroesophageal Reflux Disease, Globus, and Dysphagia

Jacqui Allen and Peter C. Belafsky

Contents

Abstract

Gastroesophageal reflux disease (GERD) is a highly prevalent disorder in Western society and closely linked with the production of two common symptoms—dysphagia and globus pharyngeus. The interrelationship of these symptoms with GERD and with each other is complex but critical to an understanding of patients' complaints, underlying pathological mechanisms, and appropriate treatment planning. In this chapter, we explore these relationships, related diagnostic methodology, and options for treatment of reflux disorders, dysphagia and globus.

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1 Introduction

As the population continues to age and medical science enables longevity of life that has previously been unheard of, we are now seeing the emergence of chronic disease processes.

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Prominent among these are diseases affecting deglutition. Largely (but not exclusively) experienced by our elderly community, dysphagia and its consequences have a marked effect on quality of life. Almost one in two adults over the age of 65 years will complain of swallowing problems (Meng et al. 2000; Robbins et al. 2002; Belafsky 2010). The incidence is much higher in those with neurologic disease and head and neck cancer (Altman et al. 2010; Ramsey et al. 2003; Nguyen et al. 2004, 2006). Dysphagia is the most common symptom following stroke and was estimated to be present in 16.5 million Americans in 2010 (Belafsky 2010). It is associated with mortality in rest home residents and people in long-term care (Belafsky 2010; Altman et al. 2010). Dysphagia, however, is only a symptom and may range from the isolated sensation of a lump in the throat to profound oropharyngeal dysphagia and complete dependence on nonoral tube feeding. Dysphagia may be mild or severe, temporary or permanent, improve or progress over time, and may be due to solids, liquids, or pills alone or any combination of these. Swallowing is an extraordinarily complex function that integrates centers from the brainstem and spinal cord with vagally controlled musculature and the neurenteric plexi of the gut. Dysfunction at any point in the pathway or task will impact function proximally and distally and may lead to symptoms. One of the most common causes of dysphagia is gastroesophageal reflux (GER).

GER disease (GERD) has increased in prevalence dramatically over the past 50 years, outstripping even the obesity epidemic, with which it is closely correlated (Lien et al. 2010; He et al. 2010; Tutuian 2011). Estimates of prevalence in Western populations exceed 20% (Orlando 2011). Population studies have reported that more than 6% of the population of the Western world suffer daily heartburn or regurgitation, with 14% having symptoms weekly (Ronkainen et al. 2006; Lacy et al. 2010). Prevalence estimates in China range from 3.1 to 5.2% using the symptom-based Montreal definition of GERD (He et al. 2010; Vakil et al. 2006). Although 20% of the population in Western societies are said to suffer from GERD, in most cases it is an intermittent phenomenon, which waxes and wanes in a seemingly random fashion (Lacy et al. 2010; Chassany et al. 2008). The relationship between GERD and dysphagia is well established. Over 35% of patients with esophagitis report dysphagia. The presence of swallowing impairment has been associated with the severity of esophageal erosion, and dysphagia resolves in over 80% of patients with erosive esophagitis who are treated with a proton pump inhibitor (PPI) for with 4 weeks (Vakil et al. 2004). It has become clear that GER affects not only the esophagus but also extraesophageal sites. A wide range of symptoms are now attributed to reflux-mediated mechanisms from heartburn and regurgitation (so-called typical symptoms) to dysphonia, dyspnea, postnasal drip, cough, and pharyngeal irritation (atypical symptoms). Reflux has been implicated in disorders including sinusitis, otitis media, globus pharyngeus, pharyngitis, hyperactive airway disease, chronic cough, chronic laryngitis, and laryngeal cancer (Johnston et al. 2003; Pearson and Parikh 2011; Allen et al. 2011; Wilson 2005; Wight et al. 2003; Ozulgedik et al. 2006). The lifetime point prevalence of globus pharyngeus alone is nearly 50%. Despite improved understanding of reflux-mediated injury, controversy still remains over diagnosis, classification, and treatment of GER. The rapidly expanding prevalence of reflux and swallowing dysfunction demands that the clinician has an advanced understanding of these disorders. The purpose of this chapter is to review the current understanding of GERD, dysphagia, and globus and the interrelationship between these disorders.

2 Dysphagia

Difficulty swallowing (dysphagia) affects all ages. Dysphagia may be due to food, fluid, or pills or any combination of these. Dysphagia impacts food choices, meal durations, and quality of life (Meng et al. 2000; Altman et al. 2010). Many patients complaining of dysphagia believe their condition to be untreatable. Patients experience embarrassment and social isolation owing to inability to eat normally (Meng et al. 2000; Altman et al. 2010; Farri et al. 2007). Swallowing

disorders are associated with serious health consequences including malnutrition, weight loss, aspiration, pneumonia, pulmonary abscess, and even death (Meng et al. 2000; Robbins et al. 2002; Altman et al. 2010). In the elderly, the prevalence of dysphagia approaches 50% (Schroeder and Richter 1994). High-risk groups include those with neurologic disease, including stroke and progressive neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, inclusion body myositis, and multisystem atrophy. Poststroke dysphagia is reported in more than 80% of patients (Meng et al. 2000). Sufferers of head and neck cancer and treatment thereof also exhibit increased prevalence of dysphagia, with prolonged feeding tube dependence in 45% of patients and detectable aspiration in up to 59% of patients (Nguyen et al. 2004, 2006).

3 Etiology

The cause of dysphagia is expansive (see Table 1). Dysfunction may be central or peripheral. Central neurologic insults will affect afferent and efferent inputs, disrupt central patterning and processing, affect coordination, and result in end-organ neuromuscular deficits. Peripheral disruption will affect local tissue, peripheral neuromuscular connections and functions, and sensation. These are not mutually exclusive, and different disorders may have both central and peripheral consequences. The cause of acute-onset dysphagia differs with age. The most common pediatric disorders causing sudden-onset dysphagia are infectious pharyngitis and tonsillitis, foreign body ingestion, caustic ingestion, and Guillain–Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy). Chronic dysphagia is uncommon in children but may be due to an inherited condition such as muscular dystrophy or metabolic disorders such as lipid and lysosomal storage diseases, e.g., Gaucher's disease, Neimann–Pick disease, Hunter's syndrome, and Hurler's syndrome. Eosinophilic esophagitis may cause prolonged and recurring dysphagia in both children and adults and is one of the most prevalent swallowing disorders in children (Furuta et al. 2007; Hurtado et al. 2011; Ricker et al. 2011). The population-based prevalence is estimated between 0.003 and 0.06%, whereas the prevalence in symptomatic adults and children ranges between 6.5 and 22.5% (Furuta et al. 2007; Ricker et al. 2011; Sealock et al. 2010; Prasad et al. 2009; Kanakala et al. 2010). Misdiagnosis and underdiagnosis may occur because the diagnosis requires biopsy of esophageal mucosa and some debate remains regarding diagnostic criteria (Furuta et al. 2007; Kanakala et al. 2010).

Adults presenting with acute-onset dysphagia may have a variety of underlying conditions. Painful swallowing (odynophagia) is usually associated with infective causes, e.g., deep neck space abscess, tonsillitis, or quinsy. Infective esophagitis, for example, candidal or herpes esophagitis,

Table 1 Causes of dysphagia

Cause	Example	Type
Neurologic	Cerebrovascular accident	A, C
	Parkinson's disease	C, P
	Cranial nerve injury, e.g., postschwannoma resection	A, C
Autoimmune/ neurologic	Guillain–Barré disease	A, C
Neuromuscular	Myasthenia gravis	A, C
Muscular	Muscular dystrophy	C, P
	Myopathies	A, C
Metabolic	Lysosomal storage disorders, e.g., Hunter's/ Hurler's syndrome	C, P
Neoplastic	Oropharyngeal cancer	C, P
	Postradiation therapy	A, C, P
Infectious	Tonsillitis and pharyngitis	A
	Viral—Cytomegalovirus, HSV	A
	Candidiasis	A, C
Inflammatory	Gastroesophageal reflux	C, P
	Caustic ingestion	A, C
Traumatic	Postsurgical defect, e.g., tumor resection	A, C
	Blunt force trauma, e.g., motor vehicle accident	A, C
Allergic	Eosinophilic esophagitis	C, P

A acute, *C* chronic, *P* progressive, *HSV* herpes simplex virus

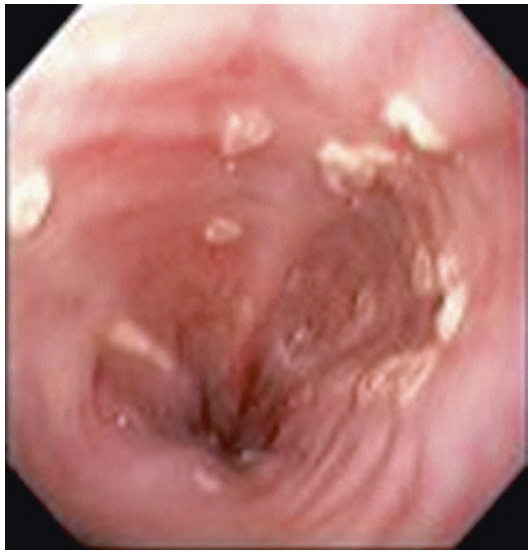

Fig. 1 Endoscopic view of herpetic viral esophagitis. Multiple macular lesions are seen across the esophageal mucosal surface

may result in odynophagia with localization of pain to both the chest and the cervical region (Fig. 1). Both immune-competent and immunocompromised individuals may present with infective esophagitis. Painless acute dysphagia is often neurologic in origin—acute cerebrovascular event (stroke), neoplastic neural invasion or compression, postsurgical defects or injuries. Eosinophilic esophagitis in adults presents with solid food impactions in otherwise healthy adults. It is now the most common cause of solid food impaction in adults (Furuta et al. 2007; Sealock et al. 2010). Diabetes mellitus negatively impacts esophageal motility. This may result in delayed bolus transit and significant reflux and dysmotility (Kinekawa et al. 2008). The presence of diabetic neuropathy increases the prevalence of GERD symptoms and chronic cough (Wang et al. 2008). Here the interrelationship between reflux and dysphagia is well illustrated. GER may cause or exacerbate dysphagia through multiple pathways—by induced esophageal dysmotility secondary to prolonged exposure to refluxate, by pharyngoesophageal mucosal inflammation and esophageal stricture formation, or through cricopharyngeal dysfunction and pharyngeal outlet obstruction. Slow-onset dysphagia in adults may be due to progressive neurologic conditions, among them Parkinson's disease being most common, neoplastic growth, posttreatment changes, e.g., after radiotherapy to the head and neck, or intrinsic muscular conditions, e.g., myasthenia gravis. At times, malignancy may also cause odynophagia, particularly when there is surface ulceration or erosion, or neural invasion. Other features may be present, such as change in voice, airway compromise, and difficulty managing secretions. Dysphagia may be a predictable consequence of treatment or disease progression. In these cases, early intervention, rehabilitation, or frequent reassessment is suggested to limit the negative consequences of dysphagia.

4 Assessment of Dysphagia

4.1 History and Patient-Reported Measures

Clinical history is crucial in understanding both the possible cause of dysphagia and its impact. Which types of food or fluid are difficult to manage, how long the symptom has been present, its onset, aggravating or alleviating factors, self-modification of diet, weight loss, and hospitalizations with pulmonary problems are all relevant in assessing the type of dysphagia and its impact. A patient self-assessment tool can be helpful for assessing self-perceived impairment and change over time. Several self-assessment tools are available, including the 40-item SWAL-QOL and the MD Anderson Dysphagia Inventory, which is specific for dysphagia related to head and neck cancer (McHorney et al. 2000a, b, 2002, 2006; Chen et al. 2001). Because of its brevity and extensive validation studies, we use the ten-item Eating Assessment Tool (EAT-10). The EAT-10 is a validated, self-administered symptom questionnaire for dysphagia (Belafsky et al. 2008) (see Appendix 1). Items are rated on a five-point Likert scale (0 for no problems, 4 for severe problem), and the sum total is calculated for an estimation of severity. Validation studies in both

dysphagic subjects and normal adults identified a score greater than 3 as lying more than two standard deviations outside the normal range. The survey takes just a couple of minutes to complete, is easy to interpret, and has been demonstrated to be responsive to treatment intervention and to be able to differentiate patient groups on the basis of disease (Belafsky et al. 2008).

4.2 Examination and Instrumental Assessment

Examination must include cranial nerves, neck architecture, and visualization of the laryngeal apparatus. A simple bedside examination of swallowing involves feeding patients and observing them. A palpation of laryngeal structures during swallowing will allow the clinician to evaluate laryngohyoid elevation. Listening to vocal quality and auscultating for fluid in the trachea may help improve the sensitivity to detect swallowing dysfunction (Leslie et al. 2004; Borr et al. 2007). The bedside examination is inexpensive and requires no specialized instruments. Although it can be helpful in guiding dietary recommendations, it is limited by its inability to detect silent aspiration, which may be present in more than 30% of neurologically impaired patients (Ramsey et al. 2003; Bours et al. 2009). Instrumental examinations are more sensitive and specific for detecting violation of the airway and offer increased information regarding anatomical, mechanical, and physiological aberrations. This may be achieved by videoendoscopy, which gives magnified images of pharyngeal and laryngeal structures, enables laryngeal function testing (motor and sensory), and may incorporate a functional endoscopic evaluation of swallowing (FEES) with sensory testing (FEESST) or without sensory testing. FEES involves administering small measured quantities of food and fluid (usually colored with food dye to improve visualization) to the patient while maintaining endoscopic views of the pharynx during deglutition. Despite a short period of "whiteout" when the endoscopic view is obscured by pharyngeal contraction and

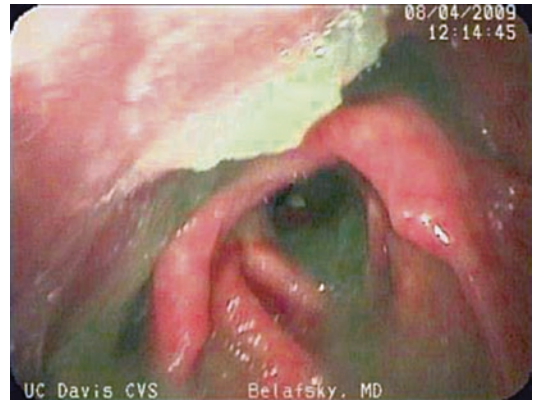

Fig. 2 Endoscopic view during functional endoscopic evaluation of swallowing in a patient with gross aspiration of puree into the subglottis and trachea

epiglottic retroversion, this is a very sensitive method for identifying airway violation and observing completeness of bolus transfer (Langmore et al. 1991; Langmore 2003) (Fig. 2). Additionally, the anatomy of the vocal folds may be seen, and compensatory maneuvers may be tested with immediate feedback to the patient. Endoscopic examination may also demonstrate signs of laryngeal inflammation that in combination with the history may suggest reflux-mediated damage. FEESST allows quantitative testing of laryngopharyngeal sensation by delivering controlled puffs of air to the mucosa at selected sites in the laryngopharynx (Aviv et al. 2000a, b). Sensory deficiencies are correlated with swallowing problems and with reflux injury, and FEESST may provide a way to document improvement over time.

The most commonly used instrumental assessment of deglutition is a videofluoroscopic swallowing study (VFSS). Various quantities and consistencies of barium contrast material are administered to the patient, and real-time dynamic fluoroscopic images are obtained of the passage of the contrast material during the swallow, from the oral cavity to the stomach (Fig. 3). This technique is sensitive and specific for violation of the airway and excellent for delineating anatomical features such as cricopharyngeal impressions or bars, webs, strictures, rings, hypopharyngeal diverticuli, hiatal herniae, esophageal dysmotility,

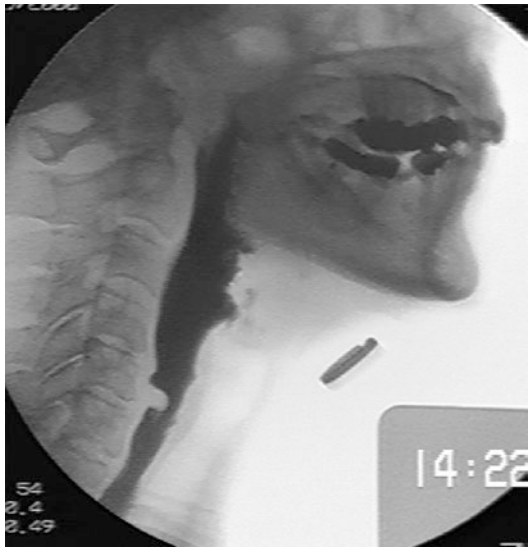

Fig. 3 Lateral videofluoroscopic image demonstrating a moderately obstructing cricopharyngeal bar

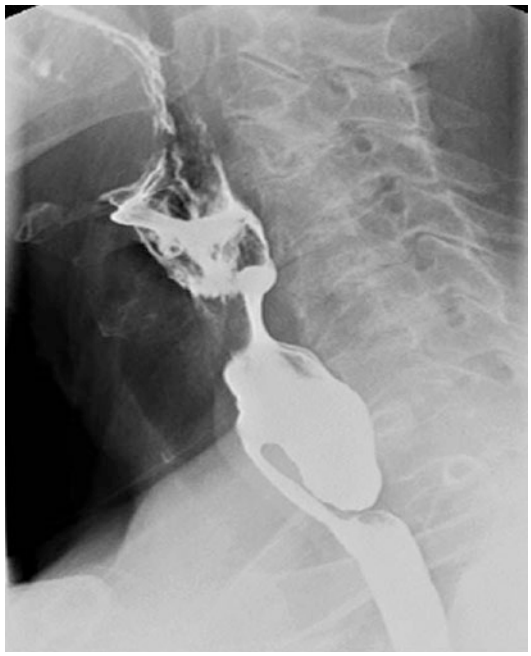

Fig. 4 Lateral videofluoroscopic view of a hypopharyngeal (Zenker) diverticulum. Note the pouch filled with barium posteriorly and the narrowed pharyngoesophageal segment anteriorly

and gastroesophageal, intraesophageal, and occasionally esophagopharyngeal reflux (Figs. 4 and 5). Disadvantages of VFSS include radiation exposure, expensive machinery needed to perform the study, and lack of anatomical detail of the vocal folds.

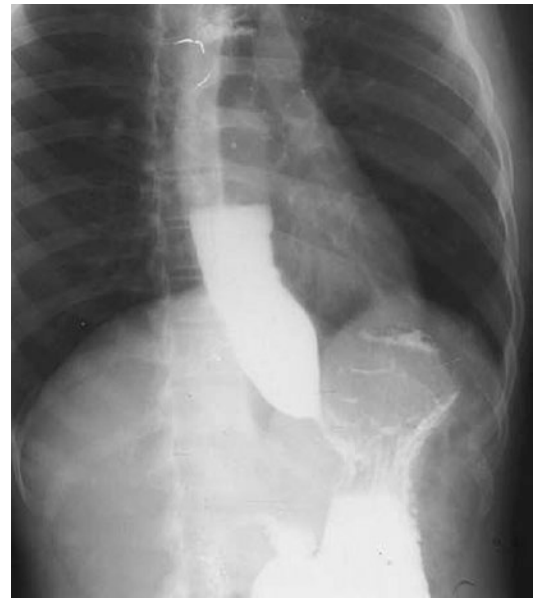

Fig. 5 Videofluoroscopic image demonstrating typical findings in achalasia with a barium air–fluid level in the distal esophagus and a "bird's beak" tapering at the lower esophageal sphincter

4.3 Advanced Endoscopic Evaluation

Endoscopic techniques have advanced significantly in recent years. The development of thin-caliber endoscopes with working channels has ushered in an era of unsedated, in-office transnasal esophagoscopy (TNE). Endoscopes with 5.5-mm outer diameter and 2-mm working channels can be passed through the nasal cavity and into the pharynx, then through the esophageal inlet, esophagus, and ultimately to the stomach. In-office TNE has demonstrated equivalent diagnostic precision when compared with traditional sedated esophagogastroduodenoscopy, but has the advantages of avoiding sedation (and its attendant problems), being performed in an upright patient (anatomical position); being cheaper, faster, and safer; and being preferred in most patients (Postma et al. 2002, 2005; Rees 2007; Belafsky and Rees 2009). Biopsies may be obtained, and therapeutic procedures are also possible using TNE (e.g., balloon dilatation of strictures and rings, botulinum toxin injection) (Belafsky and Rees 2009). A guided observation of swallowing in the esophagus allows the

clinician to observe transit of bolus through the pharyngoesophageal segment and into the stomach using TNE. Administering different food textures may identify areas of functional stenosis or holdup and affords the opportunity for targeted biopsies (Belafsky and Rees 2009). The authors employ early TNE in the assessment of patients presenting with dysphagia (and/or GERD as detailed later), as it is a safe, expeditious, and cost-effective method to rule out organic disease and guide further investigation and management.

4.4 Additional Studies

Additional studies that may be relevant to assessment of dysphagia include esophagram; computed tomography of the neck, chest, and brain; MRI of the neck and brain; ultrasonography of the neck and thyroid; and pH and manometry testing. These will each have a role depending on the presenting symptoms of the patient in addition to dysphagia and relevant earlier examination findings.

5 Treatment

Treatment of dysphagia will depend on the cause and the specific characteristics of each patient, i.e., age, comorbidities, dietary goals, and cognition. The treatment plan should progress in a stepwise fashion and is greatly enhanced by multidisciplinary cooperation and input. Vital members of the swallowing team include the speech–language pathologist, respiratory therapist, dieticians, geriatricians, otolaryngologists, nursing staff, rehabilitation service, and occupational therapist. Many other services may also be involved. Patients with significant swallowing dysfunction need frequent reassessment and review to ascertain the benefit of therapy and diet allocation.

Where possible, direct amelioration of causative factors is preferred, e.g., oral antifungal medication to treat *Candida* pharyngitis/esophagitis, and topical steroid treatment in allergic eosinophilic esophagitis. In most cases, however, it is a combination of symptomatic treatment and compensatory or rehabilitative strategies that offers the best outcomes. For example, in patients who have received radiotherapy and surgery for head and neck cancer, a combined approach is required. Dietary modifications plus swallowing rehabilitation during and after treatment can be combined with directed balloon dilatation of strictures. Consideration of dysphagia and planning prior to treatment are also important, e.g., use of intensity-modulated radiotherapy or conformal radiotherapy protocols that spare noninvolved and critical tissue such as the pharyngeal constrictor muscles. Peponi et al. (2011) reviewed 82 patients with advanced head and neck cancer treated with primary and postoperative radiotherapy with or without chemotherapy using an intensity-modulated radiotherapy protocol. At a mean of 32 months after treatment, only a single patient had persisting grade 3 (moderate) dysphagia, with no medial marginal failures seen due to sparing tissue (Peponi et al. 2011).

Intervention can be considered (1) prior to treatment or procedures, (2) during treatment, and (3) after treatment. It may be behavioral, medical, or surgical, often combining several therapies which are complementary.

5.1 Behavioral Therapy

Behavioral strategies include modification of diet, reformulation of medications, positioning strategies, compensatory maneuvers, and targeted rehabilitative exercises. Often patients will be treated by speech–language therapists and dieticians during this aspect of treatment. Biofeedback through endoscopic guidance or transcutaneous electrical stimulation has also been used with variable success (Ryu et al. 2009; Lim et al. 2009; Lin et al. 2011; Ludlow 2010). Positioning such as side lying to gravity-assist the food bolus, maneuvers such as chin tuck or head turn to exclude the bolus from the airway, and dietary manipulation such as thickening of fluids or soft, slippery diets may be helpful in maintaining oral intake. Ames et al. (2011) reported that continued oral intake of some sort during and after radiotherapy for head and neck cancer was associated with shortened gastrostomy tube duration and increased overall survival. A wide variety of targeted exercises and maneuvers can be utilized to increase safety of

the swallow (particularly in preventing airway violation) and improve swallow efficiency (Table 2). Exercises may be tried out with the patient during FEES or videofluoroscopy to ensure safety and adequate response.

Table 2 Targeted maneuvers and exercises for dysphagia management

Maneuver	Method
Supraglottic swallow	Hold liquid in your mouth. Take a breath in and hold it and bear down. Swallow while holding your breath. Immediately after swallowing, exhale with a cough, then swallow again
Massako maneuver	Bite your tongue between your teeth (gently) and while holding it between your teeth, swallow
Mendlesohn maneuver	Palpate thyroid notch anteriorly. During swallow, when the larynx is at maximal elevation, hold this position for 10 s (or as long as instructed)
Shaker exercises	1. Lie supine without a pillow. Lift your chin off the bed, flexing your neck to look at your toes, keeping your shoulders on the bed. Hold your head in this position for 60 s (or as long as instructed). Relax your head back to the bed and rest for 60 s. Repeat as instructed 2. Lie supine without a pillow. Lift your chin off the bed, flexing your neck to look at your toes, keeping your shoulders on the bed. Immediately relax your head back to the bed. Repeat this 30 times in quick succession, then rest for 2 min
Effortful swallow	Moisten your oral cavity. Swallow as hard as possible, imagining you are swallowing a grape whole
Head turn and chin tuck	Turn your head to the side that is affected (as instructed by your clinician) and tilt your chin down as low as possible. Swallow in this position
Tongue resistance exercises	1. Tongue against fingers on cheek (both sides) for 10 s (or as long as instructed) 2. Tongue against roof of mouth for 10 s (or as long as instructed) 3. Hold a spoon in front of your mouth. Push your tongue against the bowl of the spoon for 10 s (or as long as instructed)
Tongue range of motion exercises	Holding your chin steady, protrude your tongue as far as possible and hold, then move your tongue from side to side to each commissure or as far as possible on each side

5.2 Medical Therapy

Directed medical therapy for an underlying condition may help symptoms of dysphagia. Antiparkinsonian medications, antibiotics, antifungals, or antivirals may be employed in particular cases. Reducing polypharmacy is important, particularly in the elderly, where multiple medications may cause xerostomia and difficulty handling a bolus. Supportive nutrition by oral supplements or nasogastric tube is sometimes required. Tactile stimuli in the oral cavity and transcutaneous electrical stimulation have been used to enhance sensory detection and to increase efficacy of exercise regimes (Ryu et al. 2009; Lim et al. 2009; Lin et al. 2011). There is some debate regarding transcutaneous stimulation of suprahyoid muscles for assisted swallowing, with recent evidence suggesting that instead of the desired laryngeal elevation, stimulation results in net downward motion of the larynx. Although this might provide "resistance training" to those with some residual swallow function, in patients unable to overcome this descent effect there is a risk of increased airway exposure and potential penetration or aspiration (Ludlow 2010).

5.3 Surgical Therapy

Surgical management of dysphagia is diverse, but broadly speaking is directed at improving bolus transit or preventing aspiration (or both) (Table 3). Intervention may be preoperative and preventative, incorporated into surgical plans, or instituted after onset of symptoms or progression of disease. A preventative approach is useful if one is embarking on a procedure known to cause dysphagia or that might have consequences for swallowing. The surgical plan may incorporate procedures to minimize postoperative dysphagia, protect the airway, or both. Early rehabilitation and swallowing therapy may help minimize post-treatment dysfunction. A slightly different surgical approach may be taken when a patient presents with dysfunctional swallowing due to disease progression or previous intervention. The time after injury and previous efforts at rehabilitation then need to be taken into account in making the treatment plan.

Table 3 Surgical treatment of dysphagia

Reconstruction	Replace lost tissue with tissue of similar characteristics Preplan defect reconstruction Preserve superior laryngeal nerves if possible Sensate if possible Static vs. dynamic reconstruction Prostheses Anastomotic closure considerations (tension-free)
Laryngeal suspension	Resuspension under neotongue helpful after resection Suspension in patients with abnormal hyolaryngeal elevation
Vocal fold medialization	Injection laryngoplasty Type I thyroplasty Arytenoid adduction Combination
Partial laryngeal surgery	Preserve competent valve mechanism
Cricopharyngeal procedures	Dilatation Botulinum toxin injection Myotomy—Endoscopic (laser/stapler/harmonic scalpel) vs. open Zenker diverticuli—Excision, pexy, myotomy
Dental appliances	Dentures Dental implants Prostheses
Pharyngeal procedures	Tonsillectomy Pharyngoplasty (cleft lip) Hypopharyngeal pharyngoplasty (unilateral closure of piriform fossa) Cervical osteophytectomy or metalware removal
Laryngeal separation procedures	Total laryngectomy Biller laryngectomy/steamboat laryngectomy Laryngotracheal separation
Nonoral feeding	Percutaneous or open feeding tube placement
Esophageal procedures	Dilatation of strictures/rings/webs Botulinum toxin injection into UES/LES Heller myotomy Esophagectomy and gastric pull-up Esophageal stent
LES procedures	Fundoplication (Nissen, Toupet) Endoscopic suture plication Radio-frequency application
Novel procedures	Swallow expansion device Neuromuscular stimulation and pacing Deep brain stimulation

LES lower esophageal sphincter, *UES* upper esophageal sphincter

Established surgical management options for improving bolus transit include cricopharyngeal muscle procedures such as dilation, botulinum toxin injection, myotomy with or without diverticulum management, pharyngoplasty, laryngeal suspension, and cervical osteophytectomy. Various laryngoplasty techniques and laryngeal framework surgery, tracheostomy and gastrostomy tube placement, laryngeal closure procedures, laryngotracheal separation, and total laryngectomy have been employed for prevention of aspiration. Innovative new techniques reported include hypopharyngeal pharyngoplasty, neuroprosthetic device implantation and cortical stimulation, and the swallowing expansion device (SED). We discuss selected procedures below.

5.3.1 Treatment of the Upper Esophageal Sphincter

The upper esophageal sphincter (UES), also called the pharyngoesophageal segment, acts as the valve mechanism between the hypopharynx and the cervical esophagus. Opening of this region is crucial to bolus transport. It also plays a protective role preventing reflux or regurgitation of esophageal contents back into the pharynx. Reflux may result in cricopharyngeal hypertension. This may be expressed as globus or dysphagia. Reflux treatment may help ameliorate dysphagia, but if cricopharyngeal muscle hypertrophy becomes severe, surgery may be indicated. The cricopharyngeal muscle is often the target—by dilatation, chemical paralysis, or permanent surgical division. This region may also be the site of anastomotic strictures and posterior cricoid webs, which respond well to balloon dilation. Allen et al. (2010) demonstrated the effectiveness of balloon dilatation and botulinum toxin injection in relieving dysphagia due to cricopharyngeal bar. Although measured opening of the UES was less than that in patients treated surgically, patients treated with conservative therapies still noted improved swallowing (Allen et al. 2010). Lawson et al. (2003) reported success with CO_2 laser assisted cricopharyngeal myotomy in all of 29 patients with cricopharyngeal dysfunction. Kos et al. (2010) demonstrated resolution of dysphagia in 20 of 28 patients with chronic oropharyngeal dysphagia who underwent

external cricopharyngeal myotomy. Ozgursoy and Salassa (2010) reported increased cricopharyngeal opening area and decreased intrabolus pressures after laser myotomy in 14 patients with radiographic cricopharyngeal bars. Despite concerns that division of the muscular sphincter may increase reflux in some patients, this does not appear to be borne out in practice. In patients with Zenker diverticulum, the common denominator is a dysfunctional cricopharyngeal muscle, and cricopharyngeal myotomy is the most effective symptomatic treatment. Myotomy can be accomplished by endoscopic or open techniques. Risks of open procedures include recurrent laryngeal nerve injury, mediastinitis, and esophageal perforation. Endoscopic techniques are well tolerated. Patients demonstrate excellent symptomatic improvement, minimal complications, and shortened hospital stays. The greatest drawback of endoscopic approaches is difficult access. In a small number of patients, endoscopes cannot be placed to give adequate views. When visible, division of the party wall is accomplished by electrocautery, laser, stapler, or more recently, by the harmonic scalpel, particularly in shallow pouches or difficult anatomy (Allen et al. 2010; Lawson et al. 2003; Ozgursoy and Salassa 2010; Pitman and Weissbrod 2009; Wirth et al. 2006; Allen and Belafsky 2010) (Fig. 6).

Laryngeal elevation or suspension procedures help dysphagia in two ways. Suspension improves protection by moving the airway anterosuperiorly and assists pharyngoesophageal segment opening by anterosuperior distraction. Combined with a myotomy, the UES will open, facilitating bolus transfer and reducing dysphagia. Suspension of the larynx involves mandibular anchoring, either in the midline or laterally. Suspension has been performed in patients with dysphagia after resection of cancer, trauma, and neurogenic dysphagia (Meurmann 1957; Herrmann 1992; Aviv et al. 1997; Fujimoto et al. 2007). Surgical suspension of the remaining laryngeal or hyolaryngeal apparatus under the neotongue assists in diverting material from the airway. Fujimoto et al. (2007) reported 62 patients with extensive oropharyngeal cancers who underwent resection with flap reconstruction, laryngeal suspension, and cricopharyngeal muscle myotomy. More than 85% achieved an oral diet. In all patients, the superior laryngeal nerves were preserved bilaterally.

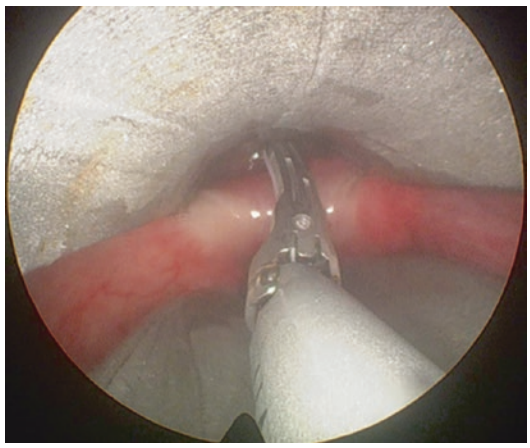

Fig. 6 Endoscopic image of harmonic scalpel across a cricopharyngeal bar

5.3.2 Laryngeal Procedures

A paralyzed or lateralized vocal fold inhibits closure of the airway and can allow material into the airway. It also reduces effect cough responses. Repositioning of the vocal fold by augmentation or medialization helps to close the glottal gap and restore competence. Depending on the time since injury, a temporary or permanent implant may be chosen. Temporary implants allow spontaneous resolution of impaired vocal fold mobility, while helping achieve closure (and improve dysphagia) in the early postinjury phase. Hendricker et al. (2010) reported 20 patients treated with Gore-Tex thyroplasty for aspiration. Eleven of twenty were able to discontinue g-tube use postoperatively. Carrau et al. (1999) reported an 83% success rate in resolving aspiration and dysphagia in a series of 70 patients with unilateral vocal fold paralysis and dysphagia treated with silastic medialization. In some cases, medializing the musculomembranous fold is inadequate to effectively close large gaps. These patients may benefit from repositioning of the arytenoid cartilage in combination with augmentation or medialization. Woodson (1997) described combined type I thyroplasty, arytenoid

adduction, and cricopharyngeal myotomy in ten patients with severe unilateral vagal injury. All patients demonstrated improved swallow and resolution of aspiration.

When dysphagia leads to intractable aspiration, surgical options for treatment include laryngotracheal separation and narrow-field laryngectomy. During laryngotracheal separation, the trachea is closed at the level of the second or third ring, creating a blind superior pouch, and requiring a tracheostoma for respiration. Phonation is severely affected. More recently, "steamboat laryngoplasty" has been described by Ku et al. (2009). This is a modification of a Biller laryngoplasty wherein the aryepiglottic folds are bisected along their length and approximated to each other in the midline, effectively closing off the airway below from the pharynx above except for a small hole for phonation. Leaving a small outlet passage allows continued glottal speech production, but prevents gross aspiration (Ku et al. 2009). Narrow-field laryngectomy is considered for end-stage intractable dysphagia and aspiration with no hope of recovery. In all cases of total laryngectomy, the ultimate aspiration protection is installed—that of a separated airway and digestive tract. This is a permanent ablative surgery, also limiting phonation, and is only considered after failure of all conservative management protocols. In planned total laryngectomy, cricopharyngeal myotomy may be helpful in minimizing postoperative dysphagia.

5.3.3 Novel Procedures

In (2010), Belafsky reported a novel device for treatment of oropharyngeal dysphagia. The SED allows manual control of the UES via an implanted shim that is attached to the anterior cricoid ring. The implant may be manipulated either by use of an external magnet or by traction on a projecting rod (Fig. 7). The average distraction possible in cadaver studies was 11.6 mm and in an ovine model was 14.2 mm. These are supraphysiologic values for adults on small boluses. Assisted opening of the UES eliminated aspiration of barium in the sheep model (Belafsky 2010).

The advantages of this device are that it is easy to implant, through a small skin incision, maintains reflux protections, and appears to result in minimal gross disturbance to the cricoid cartilage. However, as yet it is unclear whether this device would be accepted in irradiated tissue with the same success, the magnet is not compatible with MRI, there is a small infection risk, and some degree of manual dexterity and cognitive function is required to use it. The research group has now produced a modified device which lacks the iron core and instead has a projecting rod which passes transcutaneously and may be used to manipulate the implant. Human trials are pending (Fig. 7) (Belafsky 2010).

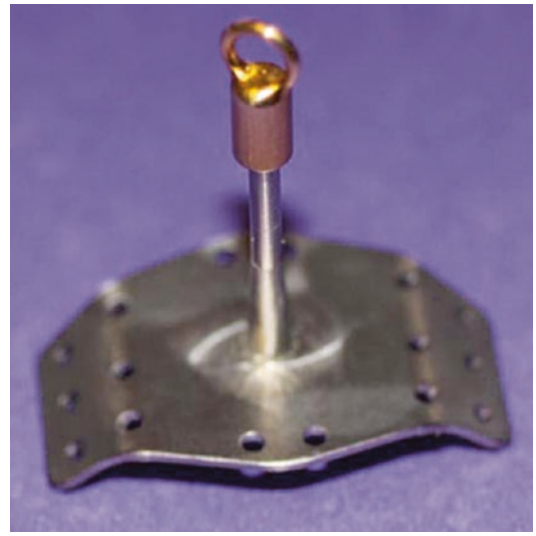

Fig. 7 Swallowing expansion device

Several groups are looking at novel electrical stimulation devices that can elicit aspects of the swallow patterns. Lowell et al. (2008) and Broniatowski et al. (2010) have investigated myostimulation and triggered vocal fold closure through neurostimulation of the larynx, respectively. Triggering of action coordinated to the rest of swallow, particularly aimed at preventing aspiration, is still in progress. These novel avenues will offer new options for patients otherwise unresponsive to treatment.

In summary, the surgical management of dysphagia is extremely diverse. Treatment may be preventative and proactive or rehabilitative and restorative. Treatment is largely dependent on the cause, and identification of the cause will guide

targeted therapy. Most importantly, successful management of dysphagia is best achieved in a multidisciplinary setting, where tailored treatment plans can be developed and implemented.

6 Gastroesophageal Reflux Disease

GER is the retrograde transit of material from the stomach into the esophagus. The Montreal Consensus meeting agreed that GERD was present when symptoms resulted from this transit or there was endoscopically discernable mucosal damage (Vakil et al. 2006). The prevalence of this disorder is estimated at greater than 20% of Western adults (Orlando 2011; Francis et al. 2011). The estimated costs of diagnostic efforts and medical treatment are in the billions of dollars, and yet we still lack a gold standard diagnostic test and gold standard treatment. GERD is one of the most common causes of dysphagia.

7 Pathophysiology

Reflux occurs in almost everyone to some degree. Physiological reflux is usually dealt with by intrinsic mechanisms. The esophagus has a three-tiered system of protection beginning with lower esophageal sphincter (and UES) closure resisting retrograde transit under neurohormonal control. This is supported by the extrinsic diaphragmatic pinch mechanism and differential pressures between intrathoracic and intra-abdominal portions of the esophagus. Material left in the esophagus or refluxed into its lumen is cleared by a combination of primary and secondary peristalsis. Primary peristalsis occurs with a swallow, begins in the pharynx, and will clear most of the bolus into the stomach. Secondary peristalsis is triggered by material left in the esophagus or refluxed into its lumen and may begin in the esophagus. Saliva buffers material by a dilution effect, and owing to its bicarbonate content helps neutralize acid reflux (Orlando 2011; Pearson and Parikh 2011). The esophagus is protected, in part, by an ill-defined coating of mucus and water rich in bicarbonate that resists penetration of acid and pepsin. The most robust barrier function is in the epithelium itself, which is specialized at the apical membrane. This membrane consists of a hydrophobic lipid bilayer and pH-sensitive cation channels that limit acid diffusion into the cell. The intercellular space is protected by apical junctional complexes consisting of tight junctions, adherens junctions, and desmosomes (Orlando 2011). Bridging proteins link cells at these junctions, and these intercellular bridges prevent diffusion of ions and fluid into the space. Additionally, the intercellular space contains buffering substances such as carbonic anhydrase enzyme that can respond to esophageal acidification by increasing neutralization (Orlando 2011; Rees and Belafsky 2008; Gill et al. 2005). Prolonged acid contact time or injury by other substances may disrupt these intercellular defenses, leading to ion diffusion accompanied by water and giving rise to dilated intercellular spaces—the pathognomonic sign of reflux damage on electron microscopy (Orlando 2011; Pearson and Parikh 2011). In laryngopharyngeal reflux (LPR), these protective mechanisms are lacking. The larynx lacks mucosal protection and peristalsis and demonstrates depletion of carbonic anhydrase and elevation of stress hormones when exposed to acid and pepsin (Johnston et al. 2004, 2007). This suggests that far fewer episodes of exposure to refluxate are required to cause tissue damage and symptoms (Little et al. 1985; Aviv et al. 2000a, b; Postma 2000). Aviv et al. (2000a, b) have demonstrated sensory deficits in patients with LPR and dysphagia. Furthermore, acid is not the only injurious substance present. Other factors contributing to tissue damage include pepsin, bile acids, and trypsin (Pearson and Parikh 2011; Wight et al. 2003; Galli et al. 2002; Johnston et al. 2004, 2006; Tack 2005; Strugala et al. 2009; Tang et al. 2005; Del Negro et al. 2008; Samuels and Johnston 2009). Prolonged or repeated exposures to activated pepsin, bile acids, and hydrochloric acid lead to inflammation, ulceration, metaplasia, dysplasia, and even frank carcinoma.

Recent work has examined the role of pepsin in esophageal and laryngeal injury (Allen et al.

2011; Gill et al. 2005; Johnston et al. 2006, 2007; Samuels and Johnston 2009; Samuels et al. 2008; Knight et al. 2005). Pepsin is the major enzyme in gastric juice and may reach concentrations of 1 mg/mL in the stomach. Pepsin is activated by acid and is most potent in a low-pH environment, but can retain proteolytic effect up to pH 6.5, and is not irreversibly inactivated until pH > 8 (Del Negro et al. 2008; Altman et al. 2010; Tack 2005; Nguyen et al. 2004). Some authors now support pepsin as the main etiological factor in esophageal and laryngeal reflux damage (Pearson and Parikh 2011; Johnston et al. 2006; Tack 2005; Strugala et al. 2009; Samuels and Johnston 2009; Samuels et al. 2008). Pepsin can adhere to the laryngeal mucosa or be absorbed into pharyngeal secretions. It may be inactive at that time, as the typical pH of the pharyngolarynx is 6.8; however, later exposure to low pH, as happens with a reflux episode, can reactivate sequestered pepsin, promoting inflammation and cell damage (Johnston et al. 2004, 2007; Tack 2005; Samuels and Johnston 2009). The laryngeal mucosa actively endocytoses pepsin, and the pepsin may remain viable within the cell cytosol or may be transported to the Golgi apparatus and late endosomes. Pepsin can induce gene activation for inflammatory cytokines in human hypopharyngeal cells and alter the production of protective mucus in these cells (Johnston et al. 2007; Samuels et al. 2008). Depletion of protective proteins such as carbonic anhydrase isoenzyme III and squamous epithelial stress protein Sep70 has been found in pepsin-exposed laryngeal tissue (Johnston et al. 2004, 2006). These findings strongly implicate pepsin as a key mediator in reflux-related tissue damage and suggest a pathway through which pepsin/reflux injury may inhibit the cell's ability to cope with mutagenic insults.

8 Diagnosis

In adults, GERD is characterized by the symptoms of heartburn and regurgitation, but numerous other symptoms have been attributed to the effects of reflux, including chest pain, bloating, hoarseness, chronic cough, throat clearing, throat irritation, postnasal drip, globus sensation, and shortness of breath (Wilson 2005; Wight et al. 2003; Park et al. 2010; Frye and Vaezi 2008). Disorders in which reflux is suspected to contribute to the cause include Barrett's esophagus, esophagitis, esophageal carcinoma and strictures, esophageal dysmotility, laryngeal edema, laryngeal cancer, cough, asthma and reactive airway disease, sinusitis, and otitis media (Allen et al. 2011; Wilson 2005; Francis et al. 2011; Little et al. 1985; Park et al. 2010; Frye and Vaezi 2008; Tauber et al. 2002; McCoul et al. 2011; Lewin et al. 2003; Maronian et al. 2001; El-Serag et al. 2001; Tasker et al. 2002; Vaezi et al. 2006). Children have a higher rate of GER and a different symptom profile compared with adults. Irritability, "spitting up," and food intolerance in infants are thought to be attributable to GER (Gold 2004). Numerous studies have linked reflux with pharyngeal and even otologic disease (McCoul et al. 2011; Tasker et al. 2002). McCoul et al. (2011) reported improved quality of life in children with otitis media with effusion treated for GERD (76% response rate) due to resolution of effusion and avoidance of tympanostomy tube insertion. The effects of refluxate are wide ranging and difficult to isolate. Diagnostic debate remains and controversy exists over what symptoms and signs may be attributed to GER or extraesophageal reflux. Debate even exists over whether LPR is a subset of GERD rather than a distinct disease entity (Rees and Belafsky 2008; Koufman 1991) (Table 4).

Table 4 Differences between gastroesophageal reflux disease (*GERD*) and laryngopharyngeal reflux disease (*LPR*)

GERD	LPR
Supine reflux	Upright reflux
Postprandial	Throughout the day
Heartburn common	No heartburn in most
Obesity related	Usually normal BMI
Esophagitis more common	Esophagitis uncommon
LES dysfunction	UES dysfunction
Associated with esophageal dysmotility	Less common esophageal dysmotility
Multiple episodes required for symptoms (>50)	Few episodes required for symptoms (1–3)

Physicians reach a diagnosis by pattern recognition. Rarely is a single symptom or finding diagnostic of any condition. Reflux is suggested by a symptom complex, like any other disease. The difficulty is that many of the features considered suggestive of reflux are also associated with other common diseases or risk behaviors. Diagnosis, therefore, is usually made on the basis of several different complementary sources of information.

8.1 Symptom Scores and Self-Reported Instruments

Use of patient-reported symptom scales and outcome scores can be helpful in quantifying disease severity and impact on the patient, as well as following disease progression over time or response to treatment. The sensitivity and specificity of scoring instruments for diagnosis of reflux disease is on par with other diagnostic tests, e.g., trial of PPI, pH-metry, and endoscopy. Given that self-reported questionnaires are noninvasive, simple, and cheap, they may be instituted easily in practice. Broadly speaking, instruments may be symptom severity rating scales or quality of life scales. We will discuss only three scales as a representative sample.

8.1.1 Reflux Disease Questionnaire

Designed to act as a diagnostic tool for GERD, the 12-item Reflux Disease Questionnaire (RDQ) has now been used as both an outcome measure and a diagnostic tool (Shaw et al. 2001, 2008; Nocon et al. 2008; Dent et al. 2010) (see Appendix 1). Developed by Shaw et al. (2008), it is a 12-item scale grouped into three subscales—heartburn, regurgitation, and dyspepsia. It is validated and has been tested for responsiveness. The RDQ has subsequently been translated and validated in Swedish and Norwegian. It has been used as a symptom survey to monitor symptom severity over time in patients enrolled in the ProGERD study in Europe, showing useful stability and reproducibility (Nocon et al. 2008) and in the Diamond study comparing diagnostic tools in reflux disease (Dent et al. 2010). One interesting aspect of this survey instrument is the lack of use of the word "heartburn." Initial development suggested that this word was poorly understood by patients, and that a "word picture" was better in conveying the symptom, i.e., burning rising up from the stomach behind the breastbone (Dent et al. 2010). The primary advantages of this survey are its conciseness, short completion time, adapted patient wording describing symptoms clearly, and cross-cultural validation. The primary limitations are inclusion of more than one disease profile (i.e., GERD and dyspepsia), long recall period, uncontrolled treatment in the patient validation population, a diagnostic accuracy equal to that of physician assessment, and variable scoring system.

8.1.2 Gastro-Oesophageal Reflux Disease Impact Scale

Jones et al. (2007) proposed the Gastro-oesophageal Reflux Disease Impact Scale (GIS) as a management tool for primary care physicians (see Appendix 1). The survey aims to assist patients in conveying GERD severity and impact and to prompt clinicians to enquire about reflux-related symptoms. GIS is a nine-item scale with a 1-week recall period that can be completed in a matter of minutes. It has been validated and tested for responsiveness. Primary care physicians using the scale found it helped direct treatment decisions and assess treatment effectiveness. It has been utilized and reported by Gisbert et al. (2009), as part of the multinational European RANGE (Retrospective Analysis of GERD) study. Louis et al. (2009) reported the GIS correlated well with physician-assessed GERD severity and was sensitive to treatment changes over time. The primary advantages of this survey are the multidimensionality of the survey (symptoms and impact of GERD) and the brevity of the survey. The primary limitations of this survey are the tendency for results clusters and lack of diagnostic precision (GER vs. dyspepsia vs. functional heartburn).

8.1.3 Reflux Symptom Index

The Reflux Symptom Index (RSI) is a nine-item self administered survey that asks patients to rate on a scale of 0–5, with 0 being no problem and 5 being all the time, how much a particular symptom bothered them over the past month (Belafsky

et al. 2002) (see Appendix 1). Total scores range from 0 to 45. In validation studies, the upper limit of 95% confidence intervals in normal controls was 13.6. Scores greater than 13 may suggest LPR playing a significant role in symptom production. Despite conflicting studies in support of and against the use of the RSI, it remains a simple, cheap, and reproducible tool, which most patients can answer in an expeditious fashion. It includes most of the accepted symptoms that are thought to be associated with LPR. Criticisms of the RSI have included the lack of frequency modifiers and missing symptom items such as throat pain and burning, and bundling of more than one symptom together. The review of Musser et al. (2011) of rating scales in extraesophageal reflux, although critical of the predictive value of the RSI, actually demonstrated significant correlation of the RSI with reflux area index at pH 4, a new proposed measure that normalizes frequency, duration, and acidity of reflux episodes for the total time of the study.

The greatest contribution of self-reported scales is their role in reflecting changes over time in the same patient, whether treatment is given or not. Subjectivity of symptom reporting differs hugely between patients, but will be more consistent in the same patient, and reflects the patient's level of disease burden. Reflux is a symptom-driven disease and what matters most is how the patient feels. Use of symptom indices and endoscopic grading systems in treatment outcome studies is necessary to allow comparison of relative disease severity (in selected test and control populations) and response to intervention.

8.2 pH Studies

Currently considered the gold standard for diagnosing both GERD and LPR, the pH study is expensive, relatively hard to perform or at least time-consuming, and not by any means 100% sensitive or specific for reflux disease (Vaezi et al. 2006; Arevalo et al. 2011). Inclusion of impedance studies is now advocated for detection of nonacid reflux and volume reflux that may cause symptoms aside from those due to drop in pH (Arevalo et al. 2011). pH and impedance studies may be more specific but are poorly sensitive in this remitting disease, and the appropriate diagnostic criteria remain unclear. Detection of these conditions in the pharynx is poor, and the study may be poorly tolerated in many patients. Patients may find the probe uncomfortable and unsightly and may alter daily behaviors, which reduces the reliability of the test. One in eight patients will remove the probe before a complete study can be recorded (Kotby et al. 2010). In the performance of the study, placement of the probe remains controversial, and probe-related artifacts from drying can be an issue. In diagnosis of GERD, established normative data suggest that prolonged acid times (more than 4% of 24 h spent at pH < 4) are associated with increasing mucosal injury (Vaezi et al. 2006; Arevalo et al. 2011). However, it is apparent that a group of patients with normal acid contact times still have symptoms related to reflux, and this group has been termed "sensitive esophagus" (Arevalo et al. 2011). Furthermore, abrupt esophageal distension that may occur in liquid or gaseous/liquid reflux may also give rise to symptoms via mechanoreceptors (Arevalo et al. 2011), and without impedance testing these episodes are unlikely to be detected. In a recent metanalysis, Kotby et al. (2010) quoted an overall sensitivity of pH studies in the range of 50–80%. Almost one-third of patients with endoscopically visualized esophagitis will have completely normal findings in a pH study. Are the norms asserted for the esophagus applicable to the pharynx? The increasing body of literature in this area suggests not. It is likely that much higher pHs (i.e., those closer to neutral) are still injurious to the laryngopharynx (Postma 2000; Merati et al. 2005).

8.3 Proton Pump Inhibitor Trial

Empirical trial of PPI medication may appear to be an appealing option. If acid production and its reflux were the cause of symptoms, then a potent inhibitor of gastric acid secretion should produce definitive symptom control. Good quality, randomized controlled trials of PPI in treatment of

pH-documented GER still fail to show an unequivocal benefit in terms of symptoms or objective endoscopic findings. Only 60% of patients with erosive esophagitis treated with PPI show a complete symptomatic response (Arevalo et al. 2011). In patients with nonerosive esophagitis, the response rate is a dismal 40% (Arevalo et al. 2011; Mainie et al. 2006a, b). In a multicenter study using combined multiluminal impedance and pH monitoring, 37% of 168 patients with persisting symptoms despite twice daily PPI treatment had a significant symptom association with nonacid reflux episodes (Mainie et al. 2006a, b). Even more important, 11% of patients demonstrated symptoms with continued acid reflux on combined multiluminal impedance and pH monitoring, suggesting that PPI cannot control gastric acid secretion completely in some individuals (Mainie et al. 2006a, b). Numans et al. (2004) undertook a meta-analysis of studies reporting the "PPI test." This demonstrated that the PPI test showed a low likelihood ratio and specificity of only 54% in diagnosing GERD (Numans et al. 2004). Qadeer et al. (2006) undertook a meta-analysis of randomized controlled trials of PPI in treatment of reflux. They found only a modest nonsignificant improvement in symptoms with PPI therapy (Qadeer et al. 2005, 2006).

Acid is not the only component of refluxate that may cause injury. Other gastric refluxate components, including bile acids and pepsin, and the mere volume itself may result in dysfunction (Johnston et al. 2004, 2007; Galli et al. 2002; Tack 2005; Strugala et al. 2009). PPI will not abrogate the effects of these components. Johnston et al. (2007) have demonstrated endocytosis of pepsin into laryngeal epithelium and activity of pepsin up to pH 6.5. In fact, pepsin is not irreversibly deactivated until it is exposed to pH 8. This may explain some of the negative effects of nonacid or weakly acid reflux. There is ongoing debate about the dose and duration of treatment of PPI medication, and more concerning, new evidence suggesting that PPIs are not as benign as we once thought. Significant decrease in calcium absorption has been documented in women receiving long-term treatment, with increase in osteoporosis and hip fracture risk in those taking PPI for prolonged periods. These medications interact with some drugs, including the platelet inhibitor clopidogrel, and alone they have a side effect profile that includes gastric upset, bloating, rash, myalgia, and depressed mood. They also remain expensive medications, especially newer-generation formulations.

Finally, it has now become clear that use of a PPI can result in reflex acid hypersecretion when treatment is terminated, which then leads to false-positive reinforcement to the patient that he or she is indeed suffering from acid reflux (Reimer et al. 2009). This rebound effect may last as long as 4 weeks and may be induced by only 8 weeks of therapy. Trial of medications (primarily PPI) runs the risk of medication side effects, lack of therapeutic effect in nonacid reflux or with other gastric refluxate components, and inducing rebound hypersecretion.

8.4 Endoscopy and Biopsy

Looking at tissue from the area affected at a microscopic and cellular level would, on the face of it, appear to be a definitive diagnostic process. However, ulceration, inflammation, eosinophilia, fibrosis, metaplasia, and dysplasia may be suggestive of reflux damage but are not pathognomonic or diagnostic of reflux on light microscopy (Wada et al. 2009). Many biopsies from patients with typical reflux symptoms show completely normal findings. Endoscopy has weak correlation with symptoms. It is a good screen for reflux complications but has low diagnostic sensitivity. The site of biopsy—the pharynx, upper esophagus, distal esophagus—may affect findings. Acquiring tissue is mildly uncomfortable, may require sedation, is relatively time intensive and expensive, and requires highly specialized tools and practitioners. Esophageal electron microscopy studies suggest that dilated intercellular spaces are correlated with GER (Park et al. 2010; Fox 2011). Park et al. (2010) have demonstrated characteristic dilated intercellular spaces in esophageal biopsies of patients with laryngeal symptoms only, and with both laryngeal and typical GER symptoms, compared with normal controls. Identification of pepsin in tissue or fluid aspirates (e.g., from middle ear, lung) has been suggested as a surrogate marker for reflux and may well prove to be useful over time (Johnston et al. 2003, 2004; Knight

et al. 2005; Tasker et al. 2002; Fox 2011). A new test kit, the Peptest lateral flow device (RD Biomed, Hull, UK), uses a latex bead monoclonal antibody to identify pepsin in saliva in the manner of a pregnancy test. Results take only 5 min to obtain and it may be more useful in primary practice as a diagnostic tool for reflux (Fox 2011). Further testing is awaited.

A history consistent with GERD or LPR and examination findings of laryngopharyngeal inflammation or complications of reflux disease support a clinical diagnosis of reflux. At this point, clinicians differ in their view as to what is the most appropriate next step.

9 Investigation

The options for investigation include those mentioned earlier—pH-metry, manometry, endoscopy, and VFSS. Peng et al. (2010) reported 469 Chinese patients presenting with typical symptoms of GERD (heartburn or regurgitation). All patients underwent early endoscopic evaluation, with 38.4% demonstrating clinically significant endoscopic findings (esophagitis, Barrett's metaplasia, peptic ulcer, carcinoma). Peng et al. (2010) recommended early endoscopy for both diagnosis and identification of complications. In-office endoscopic screening is well tolerated, safer, and cheaper than a sedated esophagoscopy, and these findings support early TNE in the management of GER and LPR (Postma et al. 2005; Rees 2007; Belafsky and Rees 2009). Contrast imaging studies are widely used in the diagnosis of dysphagia. Videofluoroscopy for diagnosis of GERD, however, is poorly sensitive and its use is not routinely indicated without other symptoms being present. Provocative testing during VFSS may demonstrate active GER but will rarely demonstrate LPR.

10 Management

Therapeutic options for reflux disease begin with lifestyle modifications (Table 5). Avoidance of refluxogenic foods, alcohol, caffeine, and smoking is recommended. Positioning with the head elevated during sleep, ensuring gastric emptying by not lying down for at least 2 h after meals, and regular exercise with weight loss may help symptomatic reflux. As yet there are no randomized controlled trials demonstrating efficacy of lifestyle changes alone.

Table 5 Lifestyle modifications recommended in gastroesophageal and laryngopharyngeal reflux disease

Elevate head of bed (more than 10 cm)	Avoid refluxogenic foods Alcohol Fatty foods Chocolate Spicy food Tomato products Peppermint Citrus fruits
Smoking cessation	
Avoid lying down within 2 h of meal	
Sleep on left side	
Weight loss and regular exercise	
Chew gum (sugar free)	
Small frequent meals	

10.1 Medications

The most potent and effective medications for GERD are PPIs. These reduce stomach intraluminal acid secretions by blocking end-organ function (H^+/K^+ ATPase pumps). No tolerance effect is seen; however, rebound hypersecretion can occur if use of these medications is discontinued abruptly, leading to a flare of symptoms. This may occur after only 8 weeks of therapy (Qadeer et al. 2005). The dose and duration of therapy are debated and different depending on whether the patient is deemed to have GERD or LPR. In GERD, response to therapy is seen at lower doses often with once daily regimens; however, in LPR patients, twice daily administration is usually required, with higher doses at each time point (Park et al. 2005). The rate of response in nonerosive reflux disease may be lower than expected, with one study demonstrating only 40% response to PPI treatment in patients diagnosed with nonerosive reflux disease (Dean et al. 2004). Randomized controlled trials have failed to show unequivocal improvement in LPR patients receiving PPIs however, and debate remains over the appropriate duration of treatment (ranging from 4 to 12 weeks) (Postma et al. 2002; Koufman 2002; Noordzij et al. 2001; Steward et al. 2004). Histamine type 2 receptor antagonists (H2RA) reduce gastrin secretion and

therefore overall acid secretion in the stomach. H2RAs have a short onset of action (less than 1 h) but also reduced effective period (less than 12 h). They are effective in healing esophagitis in approximately 50% of cases, but are less effective than PPIs in the resolution rate of symptoms, ulcer healing, and relapse of both mucosal disease and symptoms (Meneghelli et al. 2002; Caro et al. 2001; Farley et al. 2000). Patients taking these medications develop tachyphylaxis or a drug tolerance effect with long-term usage. Instituting a "drug holiday" such as a week off therapy every 3 weeks may limit this effect.

Although acid suppression with PPI treatment is profound, these medications do not prevent reflux—rather they only make it nonacid. Physical reflux barriers such as magnesium sulfate or aluminium sulfate suspensions, alginates, and sucralfate may provide protection against volume reflux (Strugala et al. 2009; Tang et al. 2005; McGlashan et al. 2009; Dettmar et al. 2006). McGlashan et al. (2009) demonstrated equivalent success in treating symptoms of LPR with liquid alginate alone compared with PPIs. Dettmar et al. (2006) demonstrated faster onset of action with liquid alginate than with either H2RAs or PPI. Alginates are polysaccharide copolymers that form a meshlike gel structure which can act as a biological sieve (Strugala et al. 2009). The properties of the gel can be altered by changing the relative proportions of guluronic acid and mannuronic acid in the mix. This adjusts the cross-linking and changes the pore sizes within the gel mesh, critically changing the permeability of the substance (Strugala et al. 2009; Tang et al. 2005). Tang et al. (2005) demonstrated that adhered alginate gel significantly reduced both proton (acid) diffusion and pepsin diffusion in a dose-dependent fashion. Strugala et al. (2009) showed reduced pepsin diffusion in alginate, by up to 82% compared with controls. Furthermore, the alginate used in their study significantly retarded diffusion of bile acids as well. They simulated repeated reflux events by using multiple 5-mL-aliquot exposures of pepsin and bile acids. Even after ten exposures, alginate gel absorbed 50% of pepsin in the sample (Strugala et al. 2009). Alginate gel will coat mucosal surfaces and can stay adherent for up to 60 min without being washed off by saliva flow (Tang et al. 2005). Thus, alginate gel may act like gastric mucus, forming a physical barrier to diffusion of acid and pepsin, and preventing contact with the cell surface and subsequent damage (Strugala et al. 2009; Tang et al. 2005). Allen et al. (2011), using a hamster model of carcinogenesis, demonstrated a significant reduction in tumor growth and proliferation in hamsters treated with alginate versus controls (Fig. 8).

Fig. 8 Photomicrograph of hamster cheek pouch demonstrating three squamous cell carcinomas induced by pepsin and 7,12-dimethylbenz[*a*]anthracene, a known carcinogen

Use of prokinetics agents or γ-aminobutyric acid B agonists is under investigation. Treatment with baclofen has demonstrated increased lower esophageal sphincter tone and reduced transient lower esophageal sphincter relaxations (Ciccaglione and Marzio 2003; Koek et al. 2003). Side effects include nausea, dizziness, and drowsiness which may improve over time.

10.2 Surgery

In refractory cases of GERD or LPR where medical therapy is unhelpful, or in cases complicated by large herniae, subglottic stenosis, brittle airway disease, or cancer, consideration of surgical intervention is warranted. Fundoplication is successful in reducing symptoms in the vast majority of patients with typical GER symptoms (Mainie

et al. 2006a, b). In those with extraesophageal symptoms, there is debate as to the role of fundoplication. Studies have demonstrated both no effect and a significantly beneficial effect of fundoplication in selected patients presenting with extraesophageal manifestations (Westcott et al. 2004; Lindstrom et al. 2002; Swoger et al. 2006; Luostarinen 1993; Shaw et al. 2010; Catania et al. 2007). Fundoplication may play an increasing role in treatment of nonacid reflux (Arevalo et al. 2011). Novel procedures to reduce GER such as endoscopic suture plication, radiofrequency energy treatment, and injection of the lower esophageal sphincter are under investigation, but there are no long-term data to support their implementation at this time.

11 Globus

Globus is a symptom rather than a diagnosis. Previously considered a hysterical manifestation, it is now recognized as being a symptom generated from largely organic dysfunction. This is reflected by a change in terminology to globus pharyngeus. Globus pharyngeus may be used to describe a "lump in the throat" sensation, throat irritation, fullness in the throat, or even effortful swallowing. The cause of this symptom is likewise varied. There may be an association with esophageal reflux and particularly proximal esophageal refluxate excursion. Both the presence of material in the proximal esophagus and slow distension of the proximal esophagus are known to result in reflex contraction of the UES (Szczesniak et al. 2010; Lang et al. 2001), whereas rapid distension may result in UES relaxation (Szczesniak et al. 2010). This protective contraction acts to prevent refluxate escaping into the pharynx and subsequently threatening the airway, whereas the relaxation of the UES enables eructation. It is suggested that intermittent recurrent reflux episodes result in a state of hypertension or hyperactivity in the UES, particularly the cricopharyngeal component. This mechanism is also proposed as the cause of cricopharyngeal bar. Szczesniak et al. (2010) have demonstrated an enhanced esophago-UES relaxation response in patients with symptoms of reflux laryngitis and suggested that this heightened belch response may contribute to symptoms. The sensation of a lump in the throat may be due to a lump in the throat. Vallecula cysts, lingual tonsillar hypertrophy, long uvula, and lingual thyroid tissue may all cause globus sensation.

12 Investigation

Patients presenting with globus as a symptom require full evaluation to ensure no obstructive lesion is responsible. This may entail endoscopy, contrast imaging studies, e.g., VFSS, or computed tomography, depending on other symptoms. If the findings are normal, consideration of pH/manometry studies to examine the UES region looking for a hypertensive or poorly compliant UES may be helpful. Esophageal disease commonly results in a feeling of discomfort in the cervical region. Smith et al. (1998) demonstrated that 58% of patients with a marshmallow impacted at the distal esophagus complained of cervical dysphagia. One-third of patients with globus, cough, or cervical dysphagia have an esophageal cause (Smith et al. 1998).

13 Treatment

Treatment should be directed at the underlying cause of globus. If there is a mass lesion present, this should be addressed. Patients may benefit from reassurance, behavioral changes such as sipping water, or reflux lifestyle modifications. In many cases, patients require aggressive antireflux therapy with medication. Muscle relaxant medications such as diazepam have been used successfully in some patients, and there are anecdotal reports of empiric balloon dilation of the UES showing promise (C.J. Rees, unpublished data). If investigations suggest a cricopharyngeal bar or hypertensive UES, consideration of balloon dilation, botulinum toxin injection, and rarely cricopharyngeal myotomy may be required.

Conclusion

Swallowing disorders are common and will increase in prevalence in the coming decades. Dysphagia is intimately related to GERD and globus, and investigation and treatment of all conditions is best accomplished by thorough investigation and appropriate multidisciplinary-team-based therapy.

Appendix

Reflux Disease Questionnaire (RDQ) (Shaw et al. 2001).

Three domains (heartburn, regurgitation, dyspepsia).

Acid taste frequency.
Acid taste severity.
Movement of materials severity.
Movement of materials frequency.
Frequency of pain behind the breastbone.
Frequency of burning behind the breastbone.
Severity of burning behind the breastbone.
Severity of pain behind the breastbone.
Upper stomach burning severity.
Upper stomach burning frequency.
Upper stomach pain frequency.
Upper stomach pain severity.

Gastro-oesophageal Reflux Disease Impact Scale (GIS) (Jones et al. 2007).

Subjects make one of four responses—daily, often, sometimes, or never:

1. How often have you had the following symptoms:
   Pain in your chest or behind the breastbone?
   Regurgitation or acid taste in your mouth?
   Pain or burning in your upper stomach?
   Sore throat or hoarseness that is related to your heartburn or acid reflux?

Table A.1 Ten-item Eating Assessment Tool (EAT-10) (Belafsky et al. 2008)

My swallowing problem has caused me to lose weight	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
My swallowing problem interferes with my ability to go out	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
Swallowing liquids takes extra effort	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
Swallowing solids takes extra effort	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
Swallowing pills takes extra effort	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
Swallowing is painful	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
The pleasure of eating is affected by my swallowing	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
When I swallow food sticks in my throat	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
I cough when I eat	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe
Swallowing is stressful	0 = no problem	1 = slight	2 = mild	3 = moderate	4 = severe

Table A.2 Reflux Symptom Index (RSI) (Belafsky et al. 2002)

In the last month how did the following problems affect you? (1 = no problem, 5 = all the time)	
Hoarseness or a problem with your voice?	0–5
Clearing your throat	0–5
Excess throat mucus or postnasal drip	0–5
Difficulty swallowing food, liquids, or pills	0–5
Coughing after you ate or after lying down	0–5
Breathing difficulties or choking episodes	0–5
Troublesome or annoying cough	0–5
Sensation of something sticking in your throat or a lump in your throat	0–5
Heartburn, chest pain, indigestion, or stomach acid coming up	0–5

2. How often have you had difficulty getting a good night's sleep because of your symptoms?
3. How often have your symptoms prevented you from eating or drinking any of the foods you like?
4. How frequently have your symptoms kept you from being fully productive in your job or daily activities?
5. How often do you take additional medication other than what the physician told you to take (such as Tums, Rolaids, Maalox)?

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Irritable Bowel Syndrome and Dysphagia

Bodil Ohlsson

Contents

Abstract

Functional gastrointestinal disorders constitute a set of gastrointestinal disorders with absence of obvious organic and physiological dysfunctions observed in clinical routine examinations. The functional disorders are divided into many subclasses, e.g., functional esophageal disorders and functional bowel disorders. The diagnoses are set when the patients fulfil the Rome IV criteria after a careful anamnestic history and exclusion of organic diseases in appropriate investigations. The disorders have a high prevalence in the population worldwide, but are of a benign nature. The etiology and pathophysiology are unknown, but environmental factors, genetics, and psychosocial factors seem to be of importance. Visceral hypersensitivity and hyperalgesia are found. There is a great comorbidity between different functional gastrointestinal disorders, and between these disorders and other chronic pain syndromes characterized by central hypersensitivity, which are all included in the term somatic symptom disorder. The most common of the functional bowel disorders is irritable bowel syndrome (IBS), characterized by abdominal pain in association with altered bowel habits. Functional esophageal disorders represent functional chest pain, functional heartburn, reflux hypersensitivity, globus, and functional dysphagia. The most important in the treatment of these conditions are confirmation and reassurance

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of the symptoms and their benign nature. Dietary advices and symptomatic drug treatment against specific symptoms are the first line of prescription. If these interventions do not improve symptoms, prescription of antidepressants and psychological and behavioral therapy are recommended.

1 Background

Peripheral stimulation of nociceptors leads to detection of a noxious stimulus. This is called nociception and leads both to a reflex withdrawal from the stimulus and a strategy to avoid further contact with the stimulus. Pain is a physiological response from activation of nociceptive pathways. The experience of pain is a protective mechanism for the body to avoid danger. Stimulation of afferent sensory neurons are transmitted through the dorsal horn and transmitted in afferent nerve trunks to the cortex. From the cortex, efferent pain nerve trunks inhibit or facilitate the afferent transmission of pain sensation. This system may be imbalanced with abnormal pain transmission. Different forms of functional, inflammatory, and chemical factors can sensitize the nociceptive system to produce pain hypersensitivity, which may be persistent. Instead of being protective, pain can be evoked by normal innocuous stimulus (allodynia), be exaggerated and prolonged to noxious stimulus (hyperalgesia), and be spread to other sites distant to the injury (secondary hyperalgesia). Hypersensitivity, i.e., abnormal pain modulation, may be peripheral or central.

Peripheral hypersensitivity may be caused by traumatic neuropathic or myopathic damages, or other peripheral irritants, e.g., inflammation (Gerdle et al. 2014).

Central hypersensitivity reflects abnormal sensitization at the level of the dorsal horn in the spinal cord. Several different mechanisms may be involved, but the general phenomenon is characterized by (1) an increased membrane excitability, (2) a facilitated synaptic strength, or (3) decreased inhibitory influences in dorsal horn neurons. This leads to that subthreshold synaptic inputs generate action potential outputs and stimulus of low intensity (innocuous sensations), and noxious stimulus (pain) are no longer distinct and separate, as it is during physiological conditions (Ossipov et al. 2014). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have visualized augmentation of pain processing also in several cortical and subcortical structures. Central sensitization contributes to an abnormal responsiveness to noxious and innocuous stimuli and a spread of tenderness in several organs, e.g., neuropathic pain, inflammatory pain, migraine, irritable bowel syndrome (IBS), and fibromyalgia (Latremoliere and Woolf 2009).

2 Visceral Hypersensitivity

The enteric nervous system (ENS) is situated in the entire gastrointestinal tract, including the esophagus, and is a part of the autonomic nervous system. ENS consists of two parts: the submucosa plexus situated in the submucosa and the myenteric plexus situated in-between the longitudinal and circular muscle layers. The submucosa plexus mainly regulate the sensory and secretory functions of the gut, whereas the myenteric plexus mainly regulate the motility. Both plexa contain excitatory and inhibitory neurotransmitters. The inhibitory neurons are first affected in diseased conditions. By unknown reasons, the myenteric plexus is more vulnerable to injury, and in patients with dysmotility disorders, changes are visible in myenteric plexus at histopathological examination. The sensory neurons projecting to the visceral organs express a wide range of membrane receptors and synthesize neurotransmitters and regulatory peptides. The substances released from nerve terminals may lead to neurogenic inflammation and an enhanced peripheral excitability. These neural circuits may lead to persistent changes (Bielefeldt et al. 2006).

Several neurotransmitters are involved in the transmission between neurons and between neurons and muscle cells. 5-Hydoxytrytamine (5-HT) exerts its effect on several receptor subtypes, and

can be both pro-nociceptive and anti-nociceptive, depending on the 5-HT receptor subtype activated (Dogrul et al. 2009). Activation of spinal α2-adrenergic receptors has a strong anti-nociceptive effect (Eisenach et al. 1998). Glutamate is essential for development of central sensitization (Soliman et al. 2005). Substance P is co-released with glutamate and is another transmitter involved in the development of central sensitization (Khasabov et al. 2002).

Visceral hypersensitivity means an exaggerated pain sensation related to visceral organs, which includes esophagus. There is a close proximity between visceral organs and the organization of the ENS. Furthermore, there is a convergence of afferent pathways at the level of the spinal cord and higher centers within the central nervous system (CSN). The cross-talk between afferent activation of one visceral structure and efferent output to another is necessary for normal regulation of sexual, bladder, and bowel functions, and are the anatomical and physiological bases for cross sensitization. This means that pain or discomfort in one organ increases the risk of symptoms also in other organs, which is called cross organ sensitization. Therefore, several so-called functional diseases are found in the same patients, e.g., functional esophageal disorders, fibromyalgia, IBS, interstitial cystitis, and posterior laryngitis (Pezzone et al. 2005).

Although the exact mechanism behind the original etiology of chronic pain or discomfort is largely unknown, it is well described how psychosocial factors, emotional factors, and cognitive functions interfere with the pain modulation, and reinforces and perpetuates chronic pain. In the Fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-5), functional esophagogastrointestinal disorders and functional non-gastrointestinal disorders have been included in the term somatic symptom disorder (Barsky 2016). Pharmacological treatment in this disease entity which target CNS is superior to pharmacological treatment which target peripheral structures, and non-pharmacological treatment which demands an active participation of the patient is superior to treatment which do not demand an active role of the patient (Henningsen et al. 2007).

3 Diagnoses of Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is the most common of the functional bowel disorders (FBD) and is characterized by recurrent abdominal pain which is associated with defecation or altered bowel habits, and absence of organic or physiological abnormalities in routine diagnostic examinations. The etiology and pathophysiology is rather unknown, but a combination of genetic, environmental, and psychosocial factors are proposed to contribute to the condition. Visceral hypersensitivity and hyperalgesia is a mandatory feature. Other findings may vary among patients, but altered gastrointestinal motility, gut microbiota, and brain-gut function; autonomic neuropathy; and antibodies against neural tissue have been described.

The diagnosis of functional bowel disorders is set when the symptoms present are fulfilling the ROME IV criteria (Lacy et al. 2016). The diagnosis is based on clinical history and physical examination and a minimal of laboratory and other tests. The symptoms must have been present for at least 3 months with an onset at least 6 months before diagnosis to establish chronicity. IBS can be subdivided into IBS with predominant constipation (IBS-C), predominant diarrhea (IBS-D), or mixed bowel habits (IBS-M). If abdominal pain is absent, the altered bowel habits are classified as functional constipation and functional diarrhea, respectively.

3.1 Irritable Bowel Syndrome

3.1.1 Definition

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria:

1. Related to defecation.
2. Associated with a change in frequency of stool.
3. Associated with a change in form (appearance) of stool.

3.1.2 Clinical Presentation

The worldwide prevalence of IBS is 11% (95% confidence interval: 9.8–12.8%). The prevalence is higher in female than in male gender and in younger compared to older persons. IBS is associated with other functional gastrointestinal disorders and chronic painful syndromes, psychological factors, and unhealthy lifestyle habits.

3.2 Treatment

The most important initial treatment of IBS is confirmation of the symptoms and reassurance of the benign nature. It is also important to stop extensive examinations. Physical activity has been shown to relieve pain and improve the condition. It is important to discuss meal habits, since unregular meal intake is associated with symptoms. An admission to a dietician is important to advise the patients about dietary improvements. A diet with restrictions of FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) has been shown to improve symptoms in many patients. If lifestyle changes do not improve the condition, drug treatment to improve symptoms is prescribed, e.g., laxatives in constipation and antidiarrheal drugs in diarrhea. Antispasmodics and probiotics may be of benefit to treat abdominal pain. The next step to treat pain is to try any antidepressants in a low dosage. When drug treatment fails, psychological and behavioral treatments are used. These treatments include cognitive behavioral therapy, hypnosis, and mindfulness. Both antidepressants and psychological treatments have a strong evidence of beneficial long-term effects (Lacy et al. 2016).

4 Diagnoses of Functional Esophageal Disorders

Functional esophageal disorders are disorders characterized by esophageal symptoms in the form of heartburn, chest pain, dysphagia or globus that are not explained by structural changes, inflammation, dysmotility, or gastroesophageal reflux. Although the etiological and pathophysiological mechanisms are unknown, it is anticipated that visceral hypersensitivity through peripheral and/or central sensitization play an important role in the generation of symptoms. Psychiatric diagnoses, especially anxiety, depression, and somatization disorders, have been shown to be present in many of these patients and are important components of the symptoms.

The diagnosis of functional esophageal disorder is set when the symptoms present are fulfilling the ROME IV criteria (Aziz et al. 2016). These criteria exclude gastroesophageal reflux, eosinophilic esophagitis, and esophageal motor disorders, but borderline motor abnormalities in the form of ineffective motility and fragmented peristalsis are not excluded, since these motor patterns can be seen in asymptomatic controls. The symptoms must have been present for at least 3 months with an onset at least 6 months before diagnosis to establish chronicity. The prevalence of the different disorders is mainly unknown, since the diagnoses are not always defined. Many patients with diffuse symptoms without organic findings are not further diagnosed and PPI is routinely prescribed. For specific symptom criteria of subgroups of functional esophageal disorders, see below.

4.1 Functional Chest Pain

4.1.1 Definition

1. Retrosternal chest pain or discomfort; cardiac causes should be ruled out.
2. Absence of associated esophageal symptoms, such as heartburn and dysphagia.

4.1.2 Clinical Presentation

Functional chest pain is a subgroup within the broad umbrella of noncardiac chest pain (NCCP). The prevalence of NCCP in the population is estimated to be 19–33%, and out of these, 32–35% have true functional chest pain. The prevalence is equal between genders, and more common in younger patients and in less developed countries.

4.2 Functional Heartburn

4.2.1 Definition

1. Burning retrosternal discomfort or pain.
2. No symptom relief despite optimal antisecretory therapy.

4.2.2 Clinical Presentation

The prevalence of functional heartburn is difficult to determine due to its link to reflux tests and response to proton pump inhibitors (PPI). Functional heartburn is found in 50% of patients which do not respond to PPI and in 25% of patients which respond to PPI. The symptoms are persisting for a long time in the majority of patients.

4.3 Reflux Hypersensitivity

4.3.1 Definition

1. Retrosternal symptoms including heartburn and chest pain.
2. Normal endoscopy and absence of evidence that eosinophilic esophagitis is the cause for symptoms.
3. Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH-impedance monitoring (response to antisecretory therapy does not exclude the diagnosis).

4.3.2 Clinical Presentation

The prevalence of this disorder is not known, but can be estimated from the non-erosive reflux disease (NERD) population. It is estimated that 37–60% of the NERD patients have normal pH monitoring.

4.4 Globus

4.4.1 Definition

1. Persistent or intermittent, non-painful, sensation of a lump or foreign body in the throat with no structural lesion identified on physical examination, laryngoscopy, or endoscopy.
   (a) Occurrence of the sensation between meals.
   (b) Absence of dysphagia or odynophagia.
   (c) Absence of a gastric inlet patch in the proximal esophagus.

4.4.2 Clinical Presentation

Globus is a common symptom and occurs in up to 46% of healthy individuals. The prevalence of functional globus is unknown. The disorder has a peak in the middle age and is equally prevalent in both sexes. As for all other functional complaints, women are more prone to seek health care for their symptoms. The symptoms are persistent and 75% of patients have a duration of their complaints for more than 3 years, and 50% have persistent symptoms for 7 years. Gastroesophageal reflux disease (GERD) and esophageal dysmotility can include globus as a symptom, but these mechanisms are thought to be of minor importance in the pathophysiology of globus.

4.5 Functional Dysphagia

4.5.1 Definition

1. Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus.
2. Absence of evidence that esophageal mucosal or structural abnormality is the cause of the symptom.

4.5.2 Clinical Presentation

A population survey estimated the prevalence of dysphagia to 7–8%. Functional dysphagia is the least prevalent of the functional esophageal disorders.

4.6 Clinical Examination and Evaluation of Functional Esophageal Disorders

In patients with chest pain, a careful clinical history and examination to exclude cardiac genesis have to be conducted.

The first step in the investigation in these patients is usually the PPI trial. This consists of a standard dose of PPI for 1 week, with symptomatic evaluation after this time. Patients not responding to PPI is then further referred to an endoscopy. In the majority of cases with esophageal and chest pain symptoms, an endoscopy has to be performed to exclude GERD and mechanic obstruction. Signs of pathologic gastroesophageal reflux are esophagitis and Barrett's esophagus. In the absence of visible mucosal changes, ambulatory reflux monitoring may be performed to exclude NERD. One problem is that the amount of reflux may vary from day to day, with a substantial day-to-day variation. Thus, an examination can show different results on different days. Furthermore, examination of acid reflux should be performed when patients do not use PPI. The common use of the PPI trial to define GERD has been questioned since PPI may have a great placebo effect, the specificity is low, and the predictive value is limited. A correlation between symptoms and physiological reflux events, who respond to PPI, is most logically consistent with visceral hypersensitivity and should be included within the functional paradigm, since the separate entity GERD requires a pathological reflux for diagnosis. Patients are diagnosed with NERD when esophageal acid exposure is increased and symptoms are positively associated with acid reflux; with reflux hypersensitivity when acid exposure is normal but symptoms are positively associated with acid and/or weak acid reflux; and functional heartburn when none of these conditions are present. Some patients do not respond to PPI although an apparent GERD is at hand. Overlap between functional heartburn and GERD, and between reflux hypersensitivity and GERD are seen. Although limitations of the PPI trial, clinical experience support that lack of response to PPI most probably has a high negative predictive value for the diagnosis of GERD.

Depending on symptoms, further examinations are needed. Eosinophil esophagitis is excluded by biopsy sampling during endoscopy, and must be suspected in patients with severe, refractory symptoms. Patients complaining of globus must be evaluated by a clinical inspection in the throat followed by an endoscopy examination of pharynx and larynx. Patients suffering from dysphagia should be examined by radiologic swallowing study to exclude strictures or other obstructive processes. If no obstructive lesions are visible, esophageal manometry may be performed to reveal major motor disorders. New modalities such as endoscopic functional luminal imaging probe and high-frequency ultrasound may show lack of coordination between circular and longitudinal muscle layers, leading to abnormal motility (Jung et al. 2005). These changes have not been able to correlate with dysphagia. However, newer investigative modalities will probably identify additional structural and motility mechanisms not visible at routine evaluation, and the prevalence of functional dysphagia is therefore anticipated to be less common in the future.

4.7 Treatment

The primary goal of the treatment of NERD/functional esophageal disorders/conditions when the diagnosis is obvious is to provide reassurance about the benign course of the disease. It is important to avoid repetitive testing to avoid stigmatization.

After the development and establishment of efficient therapies against acid reflux, the focus in esophageal complaints and chest pain has been to reduce acid reflux. The benefit of other therapies is only rudimentarily studied in relation to functional esophageal disorders. This may be due to the more infrequent prevalence of diagnosed esophageal disorders, compared with other functional bowel disorders. More knowledge about visceral hypersensitivity and its related conditions also in esophagus may lead to an increased prevalence of patients with a clear diagnosis of functional diagnoses, and thereby also to more use of behavioral therapies and antidepressants, also in the therapy of esophageal complaints and chest pain.

Different subtypes of 5-hydroxytrytamine (5-HT), serotonin, can be either pro-nociceptive or anti-nociceptive, and exert an important role for bidirectional pain modulation. This is the physiological basis for the treatment option of selective serotonin reuptake inhibitors (SSRI) in chronic pain conditions. Enhanced spinal noradrenergic effects following injury or inflammation provides the mechanistic basis for the clinical use of serotonin/norepinephrine reuptake inhibitors (SNRI). The dosages of antidepressants are average the half of them used in treatments of psychiatric diseases.

Mindfulness, cognitive behavioral therapy (CBT), and hypnosis are all therapies used and proven efficient in conditions characterized by increased visceral hypersensitivity and central sensitization. The methods are established in clinical treatment of IBS and other functional bowel disorders. Since functional esophageal disorders are not that well evaluated and handled in the daily praxis, the experience of these modalities is rudimentary in this setting. However, there is some experience from these patients groups, and the result so far suggest the psychological treatments as efficient in functional esophageal disorders as in other functional bowel disorders (Aziz et al. 2016).

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ICU-Related Dysphagia

Rainer Dziewas and Tobias Warnecke

Contents

Abstract

In intensive care medicine dysphagia is an extremely frequent symptom which has a significant impact on the patients' overall prognosis. The causes of dysphagia in the critically ill can be differentiated into three etiological categories. Dysphagia may be associated with the main diagnosis leading to ICU treatment, can be due to preexisting comorbidities, and may occur as a consequence of the ICU treatment itself. Diagnostic procedures guiding appropriate nutritional management and decisions focusing on airway safety include clinical testing as well as instrumental assessments, in particular FEES. This chapter describes specific diagnostic workflows applicable to the situation on the ICU.

1 Introduction

In intensive care medicine dysphagia is an extremely frequent symptom which has a significant impact on the patients' overall prognosis. Studies in unselected intensive care unit (ICU) patient collectives showed that 50–70% of all patients on these wards suffered from dysphagia (Malandraki et al. 2016; Brodsky et al. 2017; Macht et al. 2014). Although dysphagia resolves in a number of patients until hospital discharge and during subsequent follow-up, Brodsky and coworkers found persisting dysphagia in 25% of ARDS survivors at 6 months. In a recent study in a neurological intensive care

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unit there even was a dysphagia incidence of over 90%, and dysphagia persisted in half of the patients until the day of discharge (Macht et al. 2013a). Of particular relevance is the finding that dysphagia in intensive care patients is most severe and in 10–20% of the patients accompanied by silent aspirations (Ajemian et al. 2001; Barquist et al. 2001; El Solh et al. 2003). Regardless of the diagnostic spectrum analyzed, dysphagia in critically ill patients is a significant predictor of complications, especially aspiration pneumonia and reintubation, and a key determinant of lengths of stay and patients' outcome (Macht et al. 2011).

2 Etiology and Pathophysiology of ICU-Related Dysphagia

The causes of dysphagia in the critically ill can be differentiated into three etiological categories. Thus, dysphagia

(i) may be associated with the main diagnosis leading to ICU treatment.
(ii) may be due to preexisting comorbidities.
(iii) may be a consequence of the ICU treatment itself.

In most patients, however, more than one etiology will play a role, which is particularly true for the neurologically ill.

Ad (i):

As shown in Fig. 1, various neurological disorders that typically require treatment on the ICU impair the swallowing network or associated downstream nerves and muscles. Depending on their location stroke and inflammatory diseases of the CNS affect the supramedullary or medullary control of the swallowing. Acute immune-mediated neuropathies, in particular the Guillain–Barré syndrome (GBS), and critical illness neuropathy (CIP) cause dysphagia due to an impairment of motor and sensory cranial nerve function. Disorders of swallowing muscles themselves, as they can be observed in myositis or

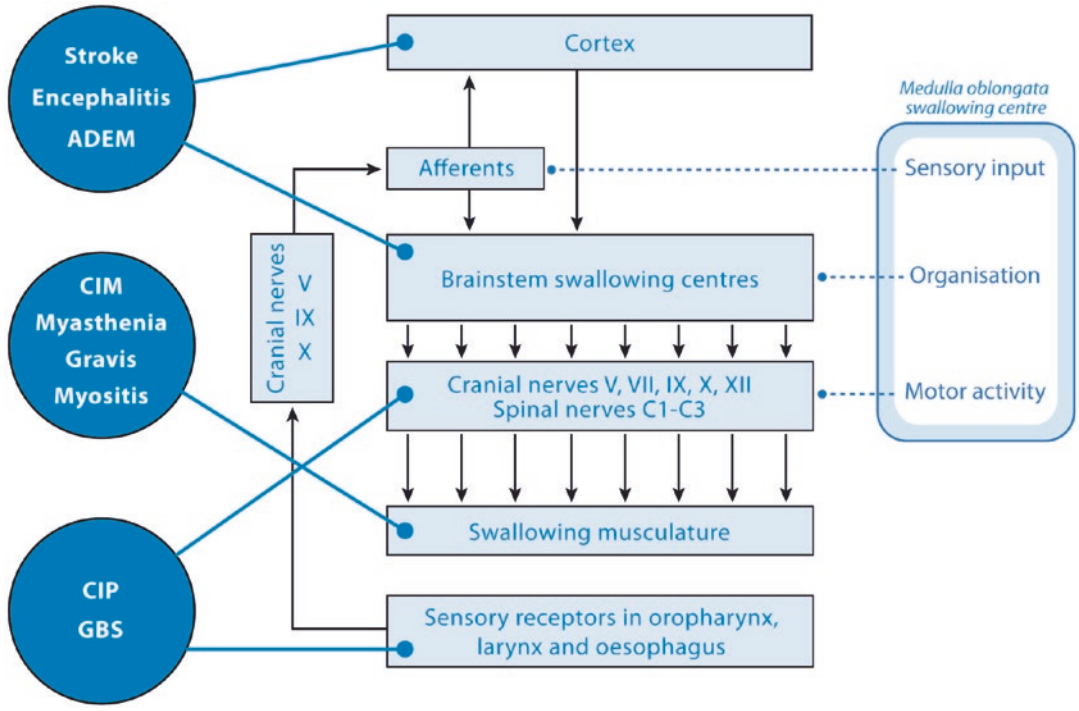

Fig. 1 Neurological disorders that typically require treatment on the ICU and their specific target within the swallowing network (adapted from R. Dziewas, J. Glahn (2015); Schluckstörungen auf der Intensivstation. In: Neurointensiv, Springer, Heidelberg, p. 108-114; copyright H. Blum, Münster)

critical illness myopathy (CIM) as well as disorders involving the neuromuscular junction finally lead to myogenic dysphagia.

Ad (ii):

Apart from the main diagnosis (e.g., acute stroke, GBS, brainstem encephalitis, see (i)), comorbidities also play an important role in this context. A wide range of neurodegenerative (e.g., Parkinson's disease, Alzheimer's disease), neurovascular (Stroke, subcortical arteriosclerosic encephalopathy), or neuromuscular disorders (Polymyositis, ALS) should be mentioned here. These disorders are either associated with preexisting dysphagia or, even if previously asymptomatic with regard to deglutition, increase the likelihood of a deterioration of swallowing function during ICU treatment. Thus, although a given patient may be admitted to the ICU because of urosepsis or myocardial infarction, the further clinical course might deteriorate because decompensation of the swallowing network gives rise to complications.

Ad (iii):

ICU-related dysphagia may also be caused by the treatment itself and/or further environmental conditions. As shown in Fig. 2 there are six pathomechanisms to be differentiated (Macht et al. 2013b).

- The endotracheal tube, the tracheal cannula, laryngeal masks, nasogastric tubes, and tracheal suction probes can lead to various injuries of the pharynx, larynx, or esophagus. Thus, in a recent study, laryngeal edema was found in >90% of patients, more than one-third of patients had vocal cord ulcerations and immobility, and more than 10% had subglottic edema (Scheel et al. 2016).
- Secondly, intensive care patients often develop a weakness of the swallowing muscles due to critical-illness neuropathy and myopathy.
- The third mechanism is the development of oropharyngeal and laryngeal sensory deficits. Among others this condition may be the result of sensory nerve damage due to CIP or because of local mucosal edema followed by a disruption of the sensory feedback.
- Qualitative and quantitative impairment of consciousness either as an effect of sedating medication or as a result of delirium are also involved in the development of dysphagia.
- Gastroesophageal reflux in critically ill patients causes insufficient supply of nutrients and is in particular a main risk factor for aspiration.
- Patients on the ICU often suffer from a dyssynchronization of breathing and swallowing.

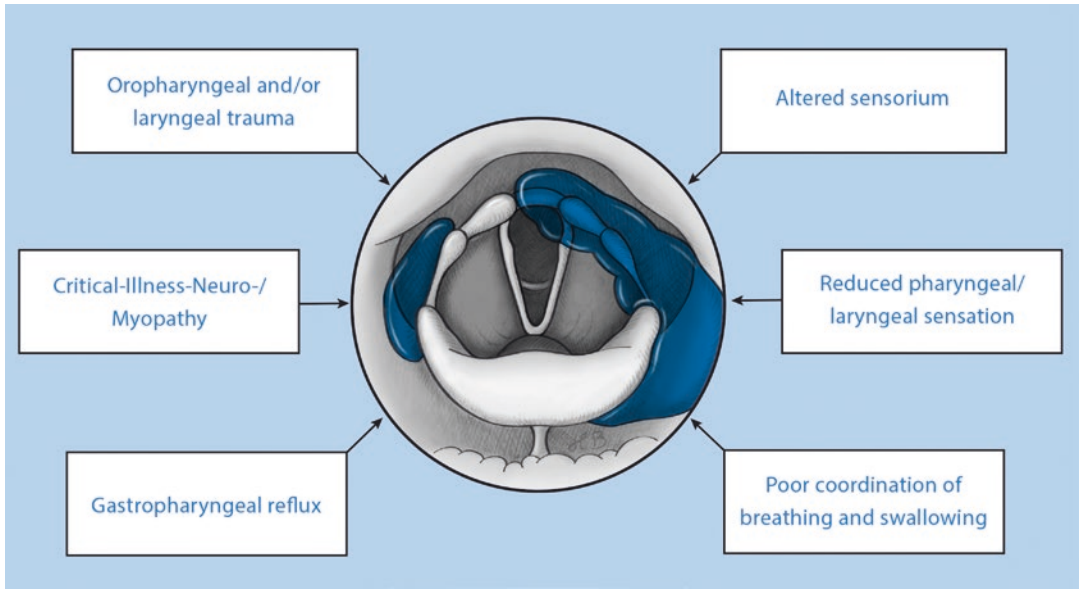

Fig. 2 Pathogenic mechanisms for the development of dysphagia in the ICU (modified from Macht et al. 2013b) (adapted from R. Dziewas, J. Glahn (2015); Schluckstörungen auf der Intensivstation. In: Neurointensiv, Springer, Heidelberg, p. 108-114; copyright H. Blum, Münster)

Both the duration of the swallowing apnea and the coordination of the respiratory cycle and swallowing may be impaired increasing the risk for aspiration (Shaker et al. 1992; Gross et al. 2009).

3 Diagnostic Workup

As shown above, dysphagia plays an important role on the intensive care unit. Adequate diagnostic procedures should help to detect this disorder as precisely and as timely as possible. Based on the results of multilevel swallow assessment appropriate nutritional management and other treatment strategies have to be defined. This section describes a workflow applicable at the ICU.

3.1 Bedside Screening

The aim of clinical examination on the ICU is to identify patients at risk of aspiration and, subsequently, to initiate preventive measures and to plan further diagnostic procedures. To this end, water swallow tests (WST) are usually implemented. As common feature of any WST the patient is asked to swallow a defined amount of water, while the investigator looks for clinical signs of aspiration (voice change, cough, stridor). However, these tests usually do not have a sufficient sensitivity and/or specificity (Kertscher et al. 2014) to be propagated as stand-alone solution. In addition, silent aspiration, which is a key factor in the critically ill, cannot be detected by these tests (Noordally et al. 2011). Finally, it should be noted that in many critically ill patients a water test is not feasible due to their clinical condition, so that in the end both the validity and the feasibility of these water tests in the ICU are significantly limited.

3.2 Clinical Swallow Examination

The clinical swallowing examination (CSE) by an appropriately trained speech and language pathologist (SLP) is certainly the most frequently used diagnostic modality for the evaluation of dysphagia on the ICU (Macht et al. 2012). The CSE typically involves the examination of the oropharyngeal structures as well as swallowing tests with different consistencies. Similar to the WST, the sensitivity, specificity, and reliability of the clinical swallowing examination are also questionable (McCullough et al. 2000, 2001). Thus, Hales et al. found in a prospective study of 25 tracheotomized ICU patients a sensitivity of only 66% for the detection of aspirations with a clinical swallowing examination (Hales et al. 2008). More recently, Lynch and coworkers used both WST and CSE in survivors of acute respiratory failure. Compared to FEES both clinical procedures featured only modest sensitivity and specificity for judging aspiration risk and dysphagia severity (Lynch et al. 2017). In conclusion, the management of dysphagia on the ICU cannot be guided solely by clinical tools.

3.3 Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

During the FEES a flexible naso-pharyngo-laryngoscope is introduced transnasally into the pharynx for direct visualization of the swallowing act. FEES aims at (1) identifying pathological movement patterns, (2) evaluating the effectiveness and safety of the swallow process, and (3) recommending appropriate food consistencies as well as special diets or swallowing techniques on an individual basis. Available data indicate that FEES is a well tolerated and safe examination. In 6000 investigations only 222 (3.7%) had to be stopped on the patient's request (Langmore 2017). The most commonly reported side effect was self-limited nosebleed being present in approximately 1% of cases. More serious events like vasovagal syncope and laryngospasm occurred in 0.03% (Aviv et al. 2000, n.d.; Cohen et al. 2003). These results could be reproduced in a group of acute stroke patients. Although the rate of self-limited nosebleed was with 6% higher than in the other studies, no serious side effects were reported and vegetative symptoms like heart rate and blood pressure fluctuations were mild

(Warnecke et al. 2009a). Meanwhile, numerous studies have shown that FEES is equivalent to the historic gold standard, the videofluoroscopy (VFSS = Videofluoroscopic Swallow Study) in detecting the most important critical findings like aspiration and residues (Wu et al. 1997; Kelly et al. 2006, 2007). Apart from that FEES is also an extremely reliable method, which is underlined by an interrater consensus of over 90% in various studies (Leder et al. 1998; Dziewas et al. 2008).

In particular on the ICU, the essential practical advantages of FEES over VFSS are

- the examination can be done at the bedside and also patients with highly restricted motor functions as well as bedridden or uncooperative patients can be examined.
- repeated follow-up examinations are safely possible without the issue of radiation exposure.
- saliva management can be assessed directly (Langmore 2003).

As has been shown in a large observational study FEES in daily practice on the ICU is indeed helpful to assess airway protection and to steer dysphagia management (Hafner et al. 2008). Altogether 913 endoscopic swallowing evaluations were performed in 553 patients over a period of 45 months at several intensive care units. Based on the result of FEES, 6.3% of the patients were tracheotomized to protect the airway, 49.7% received a feeding tube, and 13.2% a PEG to ensure enteral feeding. In 30.7% of patients oral diet was judged to be feasible.

In addition, two other studies showed that in acute stroke the endoscopic evidence of saliva aspiration is a strong predictor for the need of intubation during the further clinical course (Dziewas et al. 2008; Warnecke et al. 2009b). These results underline the need for early instrumental dysphagia assessment in the critically ill.

4 Diagnostic Algorithms for the Management of Dysphagia on the ICU

In this section algorithms for the assessment of dysphagia both in non-intubated and in tracheotomized ICU patients are presented.

4.1 The Non-intubated Patient

In non-intubated ICU patients dysphagia assessment provides important information for determining the appropriate feeding strategy and is also instrumental in guiding further protective and rehabilitative measures. Although there is currently no standardized algorithm that was evaluated in prospective studies, the one proposed in Fig. 3 is considering the advantages and disadvantages of the various diagnostic modalities described above and is implementing the existing knowledge to give pragmatic recommendations. First, minimum basic requirements for an oral diet such as a sufficient state of consciousness and trunk stability are evaluated. Next, the risk factors for dysphagia are assessed. As mentioned in Sect. 3 apart from the patient's main diagnosis specific comorbidities need to be considered here. Since, as also described above, dysphagia is at least in part a typical side effect of the ICU treatment itself, the duration of intubation and artificial ventilation with a cutoff value of 24 h is introduced as additional criterion. In case there is none of these risk factors present, for example, in a patient with an uncomplicated surgery followed by quick extubation, it is sufficient to carry out a simple bedside aspiration screening. If this test is normal the patient may directly be promoted to an oral diet. If at any of the three steps just described indicators of dysphagia are present, a clinical swallowing examination by a SLP and, ideally, a FEES should be performed. With the help of these diagnostic procedures a decision whether the patient can receive a normal oral diet, requires a special consistency-adapted diet, is in need of tube feeding, or should be considered as a candidate for intubation to secure the airway can be made.

4.2 The Tracheotomized Patient

The tracheostomy, in particular the minimally invasive dilatational approach, is now a standard procedure on most intensive care units. Therefore, today the majority of long-term ventilated patients is ventilated through this artificial airway. After successful weaning from the respirator the question arises, whether the

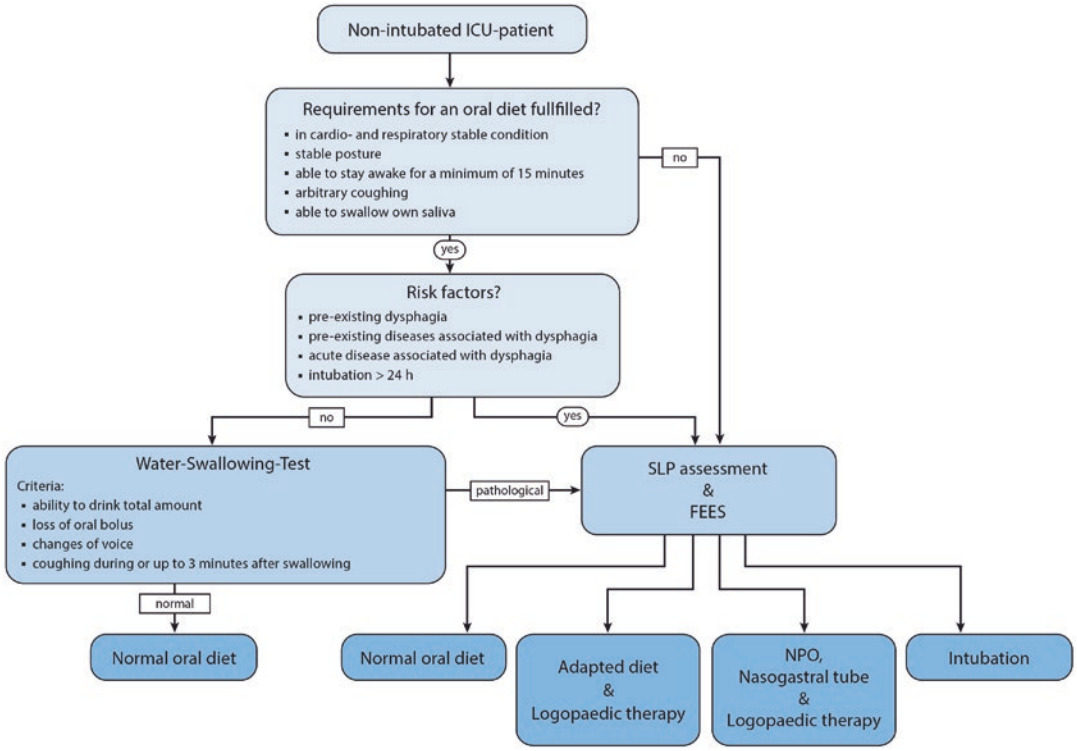

Fig. 3 Diagnostic algorithm for the assessment of dysphagia in non-intubated ICU patients (modified from Macht et al. 2013b; adapted from R. Dziewas, J. Glahn (2015); Schluckstörungen auf der Intensivstation. In: Neurointensiv, Springer, Heidelberg, p. 108-114; copyright H. Blum, Münster)

removal of the tracheal cannula can be achieved. In this context, ICU-related dysphagia is the most important obstacle to a safe decannulation, with up to 70% of patients showing aspirations during the instrumental swallow examination (Ajemian et al. 2001; Romero et al. 2010). Therefore, prior to decannulation, a careful evaluation of the patient's ability to swallow is mandatory. Due to the limitations of the clinical swallow examination assessment of the swallowing function in this context should include FEES (Warnecke et al. 2013). To increase the reliability and reproducibility of the endoscopic examination, a standardized, step-by-step approach might be implemented (see Fig. 4) (Warnecke et al. 2013). After suctioning pharyngeal secretions and deflating the tracheal cuff the extent and localization of salivary retentions are assessed and the spontaneous swallowing frequency is observed. If massive pooling or silent aspiration of saliva is visible (step 1), the investigation is stopped at this point. If not, the number and efficiency of spontaneously occurring swallows is rated for at least 2 min (step 2). If more than one efficient swallow per minute occurs, the investigation proceeds and laryngeal sensibility and cough reflex are tested by gently touching the aryepiglottic region with the tip of the endoscope (step 3). The patients demonstrating an efficient cough are given a teaspoon of puree consistency (step 4). If no aspiration occurs, the patient is given a teaspoon of colored water (step 5). Silent aspiration of the water, without triggering the swallowing reflex, also indicates lack of readiness for decannulation; otherwise, having swallowed successfully, the patient is regarded as being able to sufficiently protect his/her airway and the tracheostomy tube may be removed immediately. After that, the endoscope is briefly inserted through the stoma, flexed upward to visualize the subglottic structures and downward to inspect the lower trachea, in order to ensure that there were no structural abnormalities comprising the

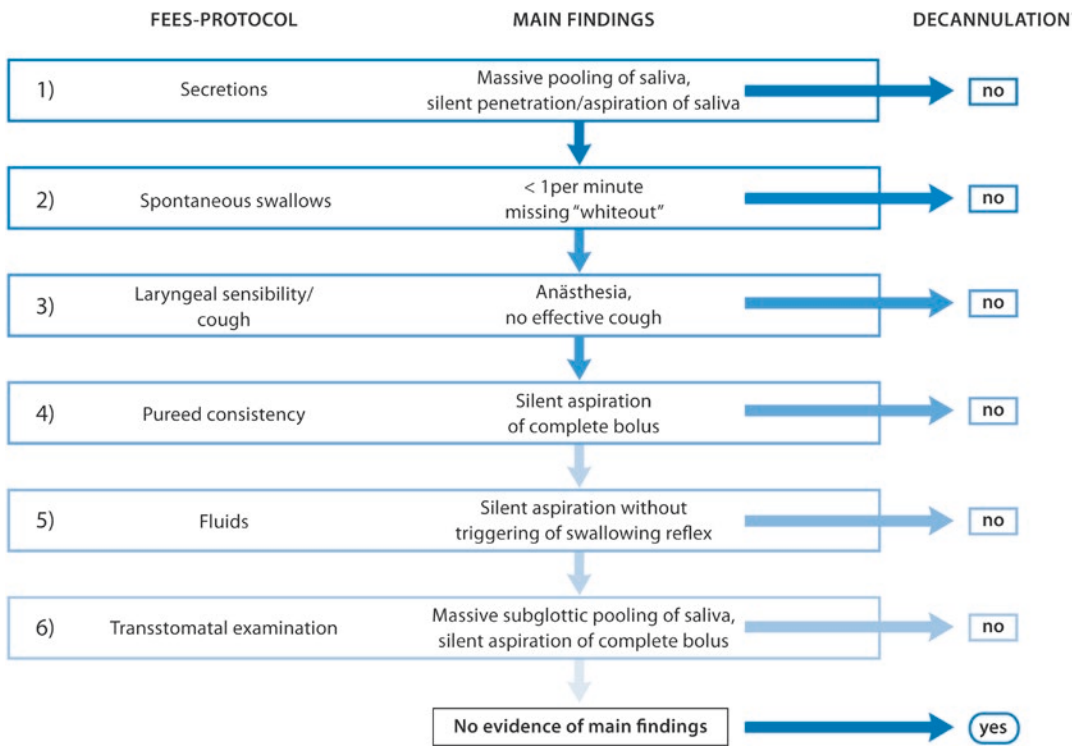

Fig. 4 FEES-based protocol for tracheostomy decannulation. FEES: fiberoptic endoscopic evaluation of swallowing (adapted from R. Dziewas, J. Glahn (2015); Schluckstörungen auf der Intensivstation. In: Neurointensiv, Springer, Heidelberg, p. 108-114; copyright H. Blum, Münster)

airway (Donzelli et al. 2001). The application of this algorithm in 100 tracheotomized patients that were weaned from the ventilator on a neurological ICU allowed a safe decannulation in more than half of the patients (Warnecke et al. 2013). In the further course of treatment, only one patient had to be recannulated. Noteworthy was also that the clinical swallowing examination, which took into account the parameters state of vigilance, cooperation skills, saliva swallowing, coughing, and amount of collected saliva from the tracheal cannula, would have allowed decannulation in only 27 patients.

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Dysphagia in Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis is a rapidly progressive neurodegenerative disease involving degeneration of upper and lower motor neurons leading to muscle spasticity, hyperreflexia, atrophy and weakness. Muscles crucial for normal swallowing and respiratory function are impacted resulting in sensorimotor impairments, specifically dysphagia and dystussia in these individuals. Current interventions consist of symptom management, including feeding tube placement, compensatory swallowing strategies, and dietary modifications. Although exercise has historically been contraindicated, preliminary evidence in animal and human research indicate potential benefits of early intervention, mild-moderate intensity exercise to preserve bulbar function for as long as possible. Additional research is warranted to identify efficacious treatment regimens to maintain and improve swallowing and respiratory function in individuals with ALS.

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1 Introduction

1.1 Pathophysiology of Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is an insidious neurodegenerative disease with a worldwide prevalence of 4.48:100,000 per year, representing the most severe and aggressive form of motor neuron disease (Chiò et al. 2013). A diagnosis of ALS is made using the El-Escorial World Federation of Neurology criterion and confirmed via clinical examination, electromyography, and neuropathic examination (Brooks et al. 2001). Disease onset typically occurs between 55 and 65 years, is slightly more common in men than women (M:F ratio, 1.5:1), and initially involves predilection of either spinal (i.e., lower and upper extremities) or bulbar (i.e., speech, swallowing) musculature (Mehta et al. 2014). Survival rates vary between 2 and 5 years with a more rapid disease progression associated with bulbar onset disease type (Zarei et al. 2015).

1.2 Neuropathologic Underpinnings of Dysphagia and Dystussia in ALS

ALS neuropathology impacts both peripheral and central nervous systems. Neuromuscular degeneration of the upper motor neurons leads to clinical symptoms of muscle spasticity and hyperreflexia, while lower motor neuron involvement results in muscle weakness, atrophy, and flaccid paresis (Fig. 1). Swallowing is a complex sensorimotor behavior requiring precise coordination of oral and upper airway anatomical structures and their neural substrates, while simultaneously reconfiguring the respiratory breathing pattern. Upper and lower motor neuron degeneration leads to a constellation of physiological impairments impacting muscle strength, coordination, and range of motion in muscles crucial for speech, swallowing, and respiration. The neurological underpinnings of dysphagia, dystussia (impaired cough) and respiratory insufficiency occur as a result of deterioration of neurons along the ascending and descending sensorimotor pathways leading to compromised trigeminal,

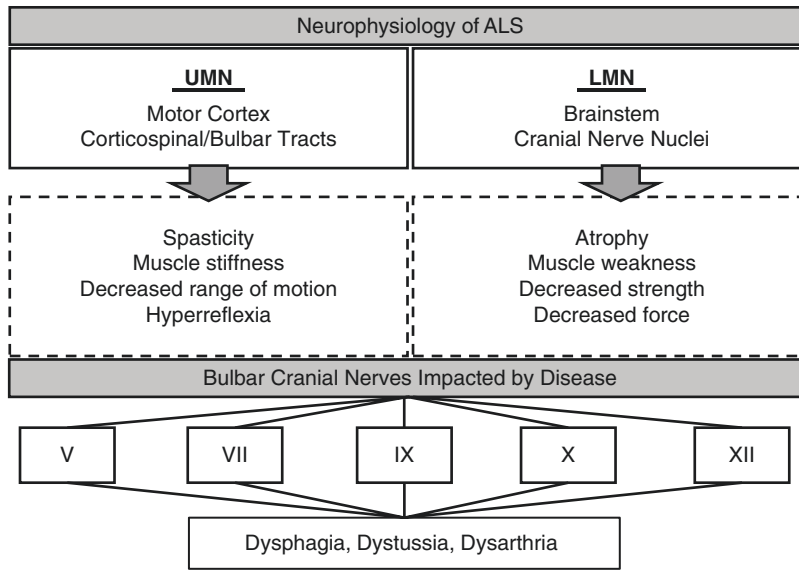

Fig. 1 Flowchart depicting upper motor neuron (UMN) and lower motor neuron (LMN) pathophysiology of Amyotrophic Lateral Sclerosis leading to downstream clinical symptoms and affected cranial nerves leading to dysphagia, dystussia, and dysarthria

facial, glossopharyngeal, vagal, and hypoglossal cranial nerve function necessary for both safe and efficient bolus transport (Kühnlein et al. 2008). Further, individuals with ALS present with compromised pulmonary status resulting from degeneration of phrenic and cervical spinal motor neurons innervating the diaphragm and respiratory musculature (Nichols et al. 2013). Consequently, impaired cough, or dystussia, represents a common but underreported symptom of bulbar dysfunction in ALS and contributes to ineffective cough motor output to effectively clear tracheal aspirate (Plowman et al. 2016a).

1.3 Sensorimotor Impairments in ALS

Historically, ALS has been considered a disease involving primarily motor deficits, attributable to neuromuscular degeneration impacting muscle strength, coordination, and force production (Wijesekera and Leigh 2009). However, recent studies indicate that 50–70% of individuals with ALS report non-motor symptoms, such as odynophagia and bodily pain in the extremities (Luchesi et al. 2014a; Chio et al. 2012). Further, sensory deficits were identified in 12.1% of studies included in a comprehensive descriptive review on dysphagia in motor neuron disease (Waito et al. 2017). Results of a recent study investigating responses to radiographically confirmed episodes of aspiration during swallowing in ALS indicated that 58% of ALS patients demonstrated *no cough response* to tracheal aspirate (Plowman et al. 2016b). These reports are suggestive of multisystem degeneration, including sensory system degradation at some point in the disease process that warrants further investigation. Potential upper airway sensory degeneration, alongside demonstrated impairments in cough motor output, predisposes ALS individuals to fatal pulmonary sequelae. Additional research investigating sensory impairments related to dysphagia and airway protection in ALS would be beneficial to confirm these preliminary findings.

2 Presentation of Dysphagia and Dystussia in ALS

2.1 Assessing Swallow Function in ALS

Weakness and spasticity in bulbar and axial musculature innervated by cranial nerves progressively impair swallowing and respiratory functions throughout the disease course (Chiò et al. 2009). Bulbar dysfunction is the *presenting* symptom in 30% of ALS individuals (Carpenter et al. 1978) and a reported 85% of ALS patients develop swallowing impairment at some point in the disease process (Chen and Garrett 2005). Dysphagia in ALS is characterized by physiological impairments in timing, kinematics, and range of motion of oropharyngeal structures contributing to compromised airway safety and bolus inefficiency leading to pulmonary sequelae, malnutrition, and reduced quality of life (Greenwood 2013; Tabor et al. 2016a; Chio et al. 2008).

Current practice patterns for the management of bulbar dysfunction in individuals with ALS are highly variable (Plowman et al. 2017). The use of validated, objective measures to index swallow function enable timely identification of impairments in swallowing. Objective *instrumental swallowing exam* tools include swallowing timing and kinematics (Molfenter et al. 2014), the Normalized Residue Ratio Scale (Pearson et al. 2013), Penetration Aspiration scale (Rosenbek et al. 1996), and the Dynamic Imaging Grade of Swallowing Toxicity (Hutcheson et al. 2015). Completing these measures following instrumental evaluation yields quantifiable data on pathophysiology that can be tracked over time and provides rationale for management strategies and treatment regimens. Unfortunately, instrumental swallowing evaluations are inconsistently utilized in multidisciplinary ALS clinics, with the majority (73%) of specialized ALS clinics in the United States recommending modified barium swallow studies in less than 50% of their ALS patients (Plowman et al. 2017).

Clinical measures that demonstrate utility for indexing swallowing function in individuals with ALS include the Eating Assessment Tool 10

(EAT-10) (Belafsky et al. 2008), voluntary peak cough flow testing (Plowman et al. 2016a), and the oral motor examination to test strength, range of motion, and integrity of oral motor structures and reflexes (Kuhnlein et al. 2008). Assessing cough motor output using a handheld digital peak cough flow (e.g., Microlife PF100) is valuable in determining concomitant impairments in peak expiratory flow rate and expiratory force generation necessary to clear tracheal aspirate (i.e., airway defense physiologic capacity). Validated patient-reported surveys, including the Eating Assessment Tool-10 (EAT-10, 24] and Swallowing Quality of Life Scale (SWAL-QOL) (McHorney et al. 2000) provide additional information and have been studied in individuals with ALS (Tabor et al. 2016a; Plowman et al. 2016c). The EAT-10 yields high clinical utility, as scores greater than 8 demonstrated excellent sensitivity (86%) and specificity (72%) in identifying aspiration in individuals with ALS (Plowman et al. 2016c). Swallowing-related quality of life is greatly impacted in individuals with ALS and is associated with increased fatigue, eating duration, and fear, which worsen with compromised airway protection (Tabor et al. 2016a).

2.2 Physiology of Airway Compromise

Identified physiologic impairments in swallowing noted to be associated with unsafe swallowing (aspiration) in ALS include increased duration to laryngeal vestibule closure (LVC) and incomplete LVC (Tabor et al. 2017). Physiologic impairments *contributing* to incomplete LVC include: reduced tongue base retraction, incomplete epiglottic inversion, reduced laryngeal elevation, and impaired pharyngeal contraction (Fig. 2) (Tabor et al. 2017; Lo Re et al. 2007; Plowman et al. 2016b). As a result, airway compromise may occur before, during, or after the swallow depending upon the underlying mechanistic impairments. In ALS, aspiration has been shown to occur most frequently with thin liquids *during* the swallow (D'Ottaviano et al. 2013). A study investigating responses to airway invasion in ALS patients demonstrated that among all ALS aspirators, 42% demonstrated an *ineffective* cough response, and 58% *silently* aspirated, or demonstrated no apparent effort to clear tracheal aspirate (Plowman et al. 2016b). Silent aspiration has been reported to frequently occur in individuals with ALS

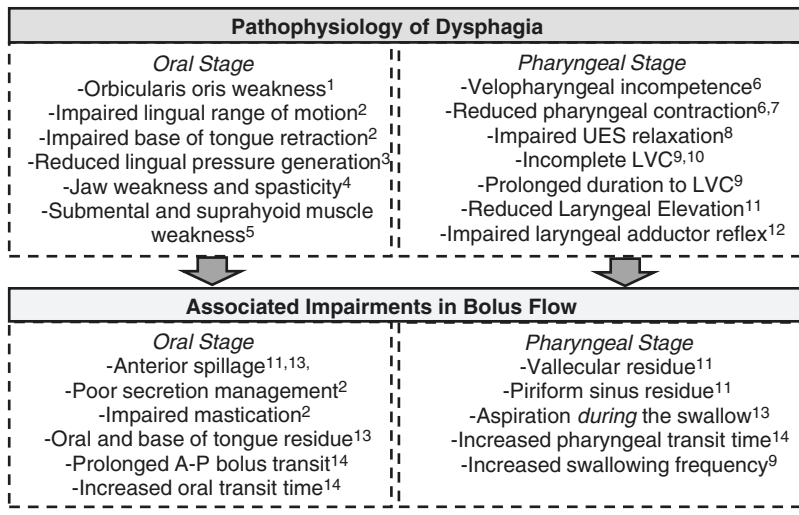

Fig. 2 Pathophysiology of dysphagia and associated impairments in bolus flow parameters in individuals with amyotrophic lateral sclerosis. *UES* upper esophageal sphincter, *LVC* laryngeal vestibule closure, *A-P* anterior-posterior. [1]Hillel and Miller (1989), [2]Ruoppolo (2013), [3]Easterling et al. (2013), [4]Yunosova (2010), [5]Ertekin et al. (2000), [6]Higo et al. (2002), [7]Goeleven (2006), [8]Solazzo (2014), [9]Tabor et al. (unpublished), [10]Lo Re et al. (2007), [11]Higo et al. (2004), [12]Amin et al. (2006), [13]Dejaeger (2006), [14]Fattori et al. (2006)

(Lo Re et al. 2007; Goeleven et al. 2006), further providing a strong rationale for use of an instrumental swallowing evaluations to accurately identify physiological impairments resulting in dysphagia.

2.3 Physiology of Bolus Inefficiency

Swallowing physiology impacting bolus efficiency in individuals with ALS includes: impaired lingual range of motion and pressure generation, pharyngeal contraction, laryngeal elevation, epiglottic inversion, and duration of UES relaxation (Fig. 2) (Ruoppolo et al. 2013; Goeleven et al. 2006; Higo et al. 2002; Solazzo et al. 2014). These physiologic impairments contribute to accumulation of residue along the base of tongue, valleculae, and piriform sinus with liquid, pudding, and solid consistencies during swallowing (D'Ottaviano et al. 2013; Leder et al. 2004; Higo et al. 2004). In individuals with bulbar-onset ALS, Higo and colleagues demonstrated reduced oropharyngeal pressure generation followed by hypopharyngeal pressure generation 1 year later, indicating that oral stage impairments leading to inefficient bolus transport may present prior to pharyngeal stage deficits (Higo et al. 2002). These impairments also contribute to increased oral and pharyngeal transit times and an increase in swallowing frequency (Plowman et al. 2016b; Fattori et al. 2006).

2.4 Dystussia

Impairments in airway safety are compounded by (1) potential upper airway sensory degradation and (2) deficits in cough motor output, compromising the awareness of and ability to expel tracheal aspirate (Plowman et al. 2016a; Ruoppolo et al. 2013). Plowman and colleagues demonstrated that of 26 individuals with ALS who aspirated, none demonstrated an *effective* cough response to tracheal aspirate, supporting the concept of concomitant sensorimotor impairments contributing to airway invasion (Gaziano 2015). Research investigating *voluntary* cough production indicates impaired cough motor output in individuals with ALS. Specifically, unsafe swallowers demonstrated impairments in the expulsive phase of cough that included: (1) reduced cough volume acceleration that was one-third the amount in unsafe swallowers compared to safe ALS swallowers, (2) ~50% lower peak expiratory flow rates, and (3) longer expiratory rise times in unsafe ALS swallowers (Plowman et al. 2016a). These deficits are attributable to disease-related respiratory muscle stiffness, weakness, reduced range of motion and decreased force production from the underlying UMN and LMN degeneration of ALS. Sensory testing using air puff stimulation to the arytenoids revealed reduced laryngeal adductor responses in individuals with ALS, implicating supraglottic sensory deficits (Amin et al. 2006). Progressive degradation of upper airway sensorimotor function impacts the ability for safe and efficient bolus transport, ultimately impacting oral intake and nutrition in individuals with ALS. Although mechanisms underlying impairments in cough motor output have been identified (Plowman et al. 2016a), to date no studies have investigated impairments in upper airway (subglottic) sensory receptors contributing to aberrant responses to airway invasion in individuals with ALS. Determining presence of upper airway sensory degradation in this population would provide rationale for development of novel treatment regimens targeting both sensory and motor planning processes.

3 Research: Evidence-Based Practice and Current State of Affairs

3.1 Palliative Care

Dysphagia in ALS leads to prolonged meal time durations, reduced enjoyment of eating, and malnutrition, a condition that further confounds muscle break down and is noted to increase mortality sevenfold in this patient population (Tabor et al. 2016a; Desport et al. 2000).

Susceptibility to malnutrition in ALS is further confounded by a higher resting metabolism, leading to a hypermetabolic disease state (Plowman 2014). Established ALS practice patterns recommend referral to a speech-language pathologist and dietician following early signs of dysphagia (Miller et al. 2009). Dysphagia management in ALS is currently palliative in nature, comprised of percutaneous endoscopic gastronomy (PEG) tube placement, dietary modifications, compensatory strategies, and patient and caregiver education (Brooks et al. 2001; Pattee et al. 2015; Andersen et al. 2005; Scott and Austin 1994; Katzberg and Benatar 2011; Klor and Milianti 1999; Mazzini et al. 1995). Given the aforementioned high susceptibility to develop malnutrition, early and prophylactic enteral feeding tube placement is noted to have a beneficial impact in ALS patients (Scott and Austin 1994; Katzberg and Benatar 2011; Klor and Milianti 1999; Mazzini et al. 1995). Dysphagia management strategies are primarily compensatory, with a goal of preserving airway safety and bolus efficiency to prolong oral intake and preserve quality of life (Strand et al. 1996). A recent survey completed by nationwide multidisciplinary ALS clinics indicated that 92% of clinics offer speech-language pathology services, but only 27% routinely utilize an instrumental evaluation, indicating high dependence on the bedside clinical swallowing examination (Plowman et al. 2017). Given the multitude of physiological impairments in swallow function, particularly the high incidence of sensorimotor impairments (i.e., silent aspiration) contributing to airway invasion and ineffective airway clearance, instrumental evaluation is crucial to avoid pulmonary sequelae and malnutrition.

3.2 Novel Treatments and Interventions

Traditional exercise-based interventions have historically been discouraged based on the rationale that exercise overburdens muscles already in a constant state of neuroinflammation, thereby accelerating disease progression (Dalbello-Haas et al. 2008). Although there is a lack of comprehensive evidence supporting the use of exercise in individuals with ALS, preliminary studies in animal and clinical models demonstrate benefit following *mild-moderate intensity* exercise to preserve swallowing and respiratory functions (Almeida et al. 2012; Plowman et al. 2015; Bello-Haas et al. 2007; Deforges et al. 2009). Further, exercise induces beneficial cellular adaptations including synaptogenesis, angiogenesis, and astrocyte proliferation, all shown to preserve muscle integrity and function in both health and disease states (Kleim et al. 2004; Kleim and Jones 2008). If implemented early in the disease, and at the appropriate dose and intensity, may reduce further disuse atrophy of muscles in ALS (Plowman 2015).

Rehabilitative treatment regimens incorporate the principles of neuroplasticity in effort to identify interventions that drive functional adaptations in performance. Respiratory muscle training and lingual resistance training represent two novel behavioral interventions targeting neuroplastic principles including use it or lose it, mild-moderate intensity, early intervention, and transference effects. Additionally, respiratory muscle training performed 25 times per day, 5 days per week was demonstrated to be well tolerated and feasible with no adverse effects in a pilot study of 25 individuals with ALS (Plowman et al. 2015). Specifically, respiratory training resulted in improved maximum expiratory pressure generation, inspiratory pressure generation, and hindered disease progression in ALS (Plowman et al. 2015; Pinto et al. 2012). Further, a case study investigating the impact of expiratory muscle training in an individual with ALS demonstrated improvements in respiratory capacity and parameters of cough motor function, which were maintained for 301 training days following baseline evaluation (Tabor et al. 2016b). Additional research is clearly needed to determine the potential role and utility of mild-mod intensity exercise in early affected ALS patients on the swallowing mechanism.

3.3 Dysphagia Management Strategies in ALS

Dysphagia management strategies include postural adjustments and maneuvers utilized during swallowing with a goal of altering physiology to improve bolus flow. To determine the impact of specific postures or maneuvers, instrumental evaluation is imperative to guide targeted recommendations, as many compensatory strategies and postural adjustments exist to improve airway safety and bolus efficiency. Given the physiologic impairments frequently described in ALS, including incomplete laryngeal vestibule closure, the effortful swallow may be an appropriate compensation to trial during instrumental evaluation. The *effortful swallow* has been demonstrated to increase lingual pressure generation (Hind et al. 2001), pharyngeal contraction (Hoffman et al. 2012; Doeltgen et al. 2017), and laryngeal elevation (Jang et al. 2015), which comprise three of the primary mechanisms contributing to laryngeal vestibule closure (Logemann et al. 1992). The *super-supraglottic swallow* facilitates laryngeal closure to prevent airway invasion and is followed by a cough or throat clear regardless of sensation of airway invasion (Ohmae et al. 1996). This may be beneficial to improve timing and extent of laryngeal vestibule closure in individuals with ALS, thereby improving airway protection (Kühnlein et al. 2008). Further, given the high prevalence of silent aspiration in ALS, this is particularly important for management of dysphagia in ALS, as a clinical bedside examination is not sufficient to detect degree of aspiration or cough effectiveness (Watts et al. 2016). Based on the physiological deficits observed during the instrumental swallowing evaluation, other compensatory strategies and postural adjustments may be beneficial including double swallow (Strand et al. 1996; Luchesi et al. 2013), chin tuck(Luchesi et al. 2014b), and modifications to bolus viscosity and volume (Kühnlein et al. 2008; Leder et al. 2004; Luchesi et al. 2013).

3.4 Conclusions

ALS is a rapidly progressive neurodegenerative disease with no currently established practice patterns for bulbar dysfunction resulting in inconsistent care across multidisciplinary clinics (Plowman et al. 2017). Dysphagia management is primarily palliative in nature, and enteral nutrition is most frequently recommended to prevent malnutrition in individuals with ALS (Waito et al. 2017). Knowledge of the neuropathologic underpinnings of the disease, the impact of disease on swallowing and respiratory functions and expected trajectory is crucial to provide the best evidence-based care. Utilizing instrumental evaluation in conjunction with validated clinical screening tools and assessments to determine specific pathology contributing to unsafe and inefficient swallowing will support recommendations based on objective information. Further, proactive patient and caregiver education is of paramount importance in effort to prepare our patients and for the prevention of pulmonary sequelae, malnutrition, and dehydration.

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Dysphagia in Parkinson's Disease

Emilia Michou, Christopher Kobylecki
and Shaheen Hamdy

Contents

Abstract

Dysphagia in Parkinson's can result in impaired safety, aspiration pneumonia, malnutrition and dehydration and consequently to a well-documented decline of quality of life (QOL) in patients diagnosed with Parkinson's (PwPD). The underlying neurodegenerative mechanisms in central and peripheral nervous system affect all phases of swallowing in PwPD, while marked heterogeneity has been observed in symptomatology of swallowing impairments within PwPD and atypical parkinsonian symptoms. Further research is needed to understand how early should we screen and assess for swallowing impairments

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and nutritional status in PwPD, which will in turn have an effect on the optimal therapeutic technique selection and management. This chapter discusses current knowledge on the neurophysiological underpinnings of swallowing impairments in PD, the health outcomes, the relationship of non-motor symptoms with dysphagia and the clinical assessment and management options, among other important issues in PD management.

1 Introduction

Dysphagia in Parkinson's disease (PD) is a common and clinically important symptom in PD, characterised as multifaceted and affecting all phases of deglutition. Dysphagia was recognised by James Parkinson in his original description of the symptoms and signs of PD (Parkinson Parkinson 1817) in Parkinson, 1817.

Dysphagia in Parkinson's can result in impaired safety, aspiration pneumonia, malnutrition and dehydration and consequently to a well-documented decline of quality of life (QOL) in patients diagnosed with Parkinson's (PwPD). The underlying neurodegenerative mechanisms in central and peripheral nervous system affect not only the oral propulsion of the bolus, but also the propagation of the bolus through the pharyngeal stage towards the oesophagus. Given the neurodegenerative nature of the disease, the clinician assessing and managing PwPD is required to be adept in recognising not only the clinical signs of dysphagia but also the underlying pathophysiology and the evolution and variation of symptomatology with disease progression.

Varying estimates of the prevalence of dysphagia in PD have been identified according to the patient population studied and methodology used. An overall estimate prevalence of 11–81% of dysphagia in PwPD was estimated with a recent systematic review (Takizawa et al. 2016). A recent meta-analysis of studies in PD identified a mean dysphagia prevalence of 35% (range 16–55%) based on subjective swallowing outcomes, but this rose to 82% (range 72–87%) in studies using objective measurements (Kalf et al. 2012a). Factors associated with dysphagia in a large cohort study of 6462 PD patients included older age, longer disease duration and dementia; male sex was associated with increased sensitivity to the effects of ageing and disease duration (Cereda et al. 2014).

Here, we review the pathophysiology of dysphagia in Parkinsonism together with an overview of the neurophysiology of swallowing in movement disorders, the dysphagic symptoms and health outcomes, the differences between the most prevalent parkinsonian syndromes with regard to dysphagia and more importantly the clinical profile of patients with dysphagia. Lastly, we review current and proposed assessment and management procedures.

2 Pathophysiology of PD

Parkinson's disease is a neurodegenerative disorder characterised by four core motor features: tremor, rigidity, bradykinesia and postural instability. Parkinson's disease (PD) is the second most frequent neurodegenerative disease with an incidence between 13.4 and 20.5/100,000 (Lo and Tanner 2013). The mean age at diagnosis of PD is 55 and most patients are between 50 and 80 years old (Twelves et al. 2003).

The motor features of PD are predominantly due to degeneration of dopaminergic neurons of the substantia nigra (SNc), pars compacta, which project to the input regions of the basal ganglia and modulate the activity of projection neurons. The loss of dopamine in pars compacta increases the overall inhibitory output of the basal ganglia and affects motor control. Atypical parkinsonian syndromes, characterised by a more aggressive disease course and multisystem involvement, are discussed below.

Accumulation of α-synuclein-positive Lewy bodies in dopaminergic neurons is thought to be responsible for neurodegeneration in PD (Spillantini et al. 1997). Lewy bodies appear as protein-containing inclusion bodies that develop inside nerve cells and displace other components, and are suspected as the pathological bases of PD (Del Tredici and Braak 2012). Alpha-synuclein is a presynaptic neuronal protein which in aberrant conformations mediates toxic disruption of cellular homeostasis and neuronal death. There is also increasing evidence for Lewy body pathology in non-dopaminergic neurons and those

outside the basal ganglia in PwPD, indicating that the pathophysiology of PD is complex and damage to different neuronal systems accounts for the heterogeneity of symptoms.

The Braak hypothesis outlines a conceptual framework for disease evolution in PD. According to this scheme, Lewy body pathology occurs initially in the olfactory nucleus and dorsal motor nucleus of the vagus (stages I–II), before motor symptoms develop with involvement of the substantia nigra pars compacta and thalamus (stage III–IV) (Braak et al. 2004). The later involvement of neocortical regions in stages V–VI is associated with the development of dementia, a common outcome in PD (Hely et al. 2008).

In the hypothetical sequence of the progression of the disease, alongside the motor system, the cognitive and neurophysiological system presents changes (Kwan and Whitehill 2011), with patients showing a decrease in executive cognitive functions. Somatosensory deficits are also evident that account mainly for disrupted tactile, thermal, nociception and proprioceptive sensation in PD (Conte et al. 2013). All the aforementioned provide weight to the evidence that PD is a multisystem degenerative disorder comprising not only dopaminergic but also noradrenergic, serotoninergic, cholinergic and probably other neurotransmitter systems (Wolters and Bosboom 2007).

The medical diagnosis of PD utilises the clinical diagnostic criteria from the UK Parkinson's Disease Society Brain Bank (Spillantini et al. 1997), including the diagnosis of parkinsonism symptoms, such as bradykinesia and at least one of the following: muscular rigidity, 4–6 Hz rest tremor and/or postural instability. Exclusion criteria for the diagnosis of PD include negative response to large doses of levodopa, history of repeated stroke and stepwise progressive parkinsonism, as well as clinical features indicating a diagnosis of atypical parkinsonism.

On the other hand, the clinical progression of PD and the severity can be rated with the Hoehn and Yahr Scale which classifies the stage of PD (Hoehn and Yahr 1967):

1. Unilateral involvement only
2. Bilateral involvement without impairment of balance
3. Mild to moderate disability with impaired postural stability, but still physically independent
4. Severe disease; can still walk or stand unassisted
5. Wheelchair bound or bedridden unless aided

The Unified Parkinson's Disease Rating Scale (UPDRS) (Lang et al. 2013), although time consuming, is a generalised tool to follow up the course of PD in the longer term, including not only motor symptoms, but also mood, behaviour, activities of daily living and treatment complications. Swallowing disorders and drooling are also examined in UPDRS with two questions addressed to the patient.

2.1 Atypical Parkinsonian Syndromes

Conditions including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are collectively termed atypical parkinsonian syndromes. These conditions are usually relatively poorly responsive to dopaminergic medications compared to PD, and show a more aggressive disease course, with average life span of around 7 years in PSP and MSA (O'Sullivan et al. 2008). Each of these conditions displays characteristic multisystem involvement. MSA occurs in both parkinsonian (MSA-P) and cerebellar (MSA-C) subtypes, and is characterised by prominent and early autonomic involvement, with postural hypotension and urinary and bowel symptoms (Stefanova et al. 2009). The underlying pathology is an α-synucleinopathy, but glial cell involvement predominates over neuronal involvement with particular neurodegenerative changes in the basal ganglia and cerebellum (Ozawa et al. 2004). PSP is characterised by early falls, vertical supranuclear gaze palsy and cognitive/behavioural impairment, due to underlying tau pathology (Litvan et al. 1996a).

In a clinico-pathological study of parkinsonian syndromes with post-mortem diagnostic confirmation, significantly longer latency to develop dysphagia was seen in those with PD (130 months) compared to MSA (67 months) and PSP (42 months) (Muller et al. 2001). Latency to dysphagia was significantly correlated with total survival time in all parkinsonian syndromes, and the authors reported that early dysphagia within a year of symptom onset had high specificity for

the diagnosis of atypical parkinsonism (Muller et al. 2001). Litvan and colleagues reported dysphagia in 80% of PSP patients after a mean 2 years of clinic visits (Litvan et al. 1996b). A recent meta-analysis of predictors of survival in atypical parkinsonism identified early dysphagia as an adverse prognostic marker in PSP (Glasmacher et al. 2017).

3 Pathophysiology of Dysphagia in PD

Safe deglutition requires the timely coordination of several muscle groups from the upper aerodigestive system and is controlled by a topographically diverse brain network. In summary, cortical and subcortical areas communicate with motor nuclei in the brainstem for the execution of the swallow. Swallowing patterned response is a result of polysynaptic connections with several neurotransmitters transferring information across and within brain areas, such as the sensorimotor cortex, the supplementary motor areas (SMA), the premotor cortex, basal ganglia, brainstem and cerebellum.

In order to understand how changes in central nervous system (CNS), as well as peripheral system in PD, may result in changes in efficiency and safety of swallowing, we include here Fig. 1 showing the brain and peripheral areas important for the completion of swallowing in health with respect to movement disorders only, while recognising a more detailed map is required to explain neurophysiology of swallowing. The connections within the swallowing network are direct and indirect and specific neurotransmitters control the function of these connections (excitatory, inhibitory). In Fig. 1, the nature of the connections is also shown with different colours displaying the functionality of those, for instance excitatory (i.e. providing glutamatergic input), inhibitory (i.e. GABA) or modulatory (e.g. dopaminergic).

The brain areas activated in deglutition are represented bilaterally but asymmetrically (independent of handedness). This communication between the areas of CNS is important for the sensorimotor integration and subsequent motor execution, the formulation of the motor plan and the initial drive and lastly the modulatory executive function for the swallow. The oral preparatory phase is under voluntary control, while the pharyngeal stage is an automatic, involuntary sequence of neuromuscular events following the elicitation of the swallowing response, but sufficient cortical and subcortical drive can also override this sequence with regard to the trigger of the swallow and the control of the swallow motor response.

Moreover, the oesophageal phase of deglutition is involuntary with different neurological control in the striated and smooth part of the oesophagus. The activation of the motor units in the swallowing centre regulates the peristalsis in the cervical oesophagus mediated by the vagal fibres. On the other hand, the peristalsis of the smooth part of the oesophagus and lower oesophageal sphincter relaxation is controlled by sacral and parasympathetic nuclei in the spinal cord and the enteric nervous system (ENS). Of interest for the oesophageal problems in PwPD, the dorsal motor nucleus of the vagus (DMV) of the medulla, responsible for the extrinsic innervation and the ENS, has shown α-synuclein pathology, even at the early PD stages (Wakabayashi et al. 1993; Braak et al. 2006).

In deglutition, the areas of the basal ganglia and thalamo-cortical connections deliver the information between the higher centre areas and the brainstem allowing the correct execution of voluntary movements. Several hypothetical models are proposed about the functional changes in PD in the basal ganglia circuitry (Blandini et al. 2000), due to the degeneration of dopaminergic neurons and how these changes in neurotransmitters exert functional changes to the activation of the network and therefore to the brain areas interconnected. Dopaminergic denervation in PD leads to imbalances in the activity of striatal projection neurons which regulate motor activity. A relative underactivity of the direct pathway, which facilitates desired movements, and overactivity of the indirect pathway, which suppresses unwanted movement, lead to bradykinesia, the cardinal clinical sign of PD (Albin et al. 1989). Whereas bradykinesia and rigidity have been proposed as

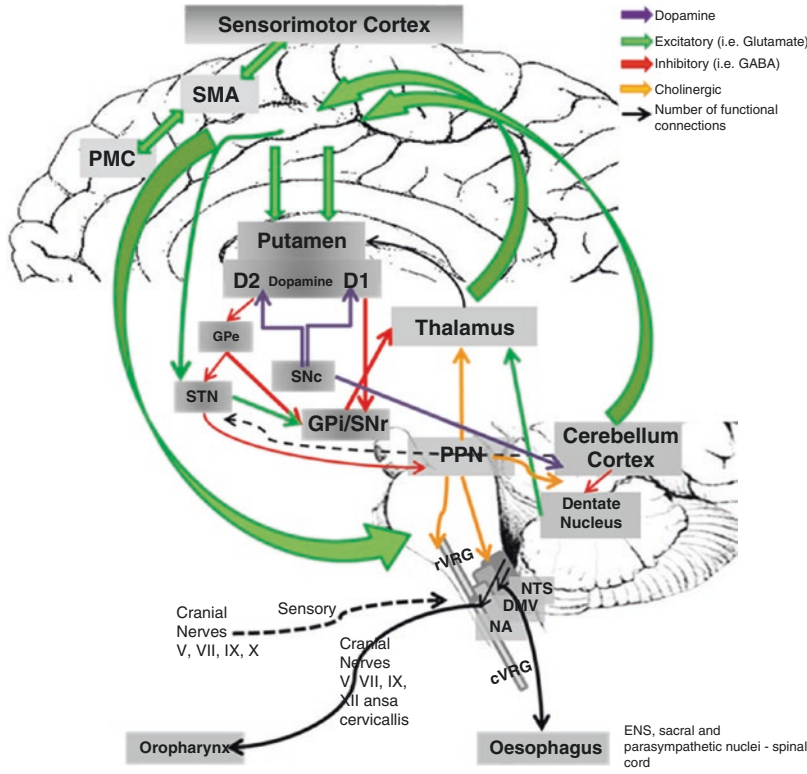

Fig. 1 Simplified diagram of the major functional connections between cortical and subcortical brain areas implicated in voluntary deglutition ***in health***. The nature of the main functional connections is shown with *green* (excitatory) and *red arrows* (inhibitory). Of importance in this context, dopaminergic (*purple*) and cholinergic (*orange*) connections are also shown. In medullary area, connections between motor nuclei are reciprocal and it has been shown that the swallowing patterned response is polysynaptic and several neurotransmitters are involved (i.e. acetylcholine, serotonin, vasopressin and others). Key: *SMA* supplementary motor area, *PMC* premotor cortex, *D1, D2* dopamine receptors suptypes, *GPe* globus pallidus external, *GPi* globus pallidus internal, *STN* subthalamic nucleus, *SNc* substantia nigra pars compacta, *SNr* substantia nigra reticulate, *PPN* pedunculopontine nucleus, *NA* nucleus ambiguus, *NTS* nucleus tractus solitarius, *DNV* dorsal nucleus vagus, *rVRG*, *cVRG* rostral and caudal ventral respiratory group, housing the inspiratory and expiratory neurons, *ENS* enteric nervous system, *GABA* γ-aminobutyric acid

causes for dysphagia in PD, the lack of consistent clinical evidence for reversal of dysphagia by dopaminergic medications (see below) suggests that additional mechanisms for swallowing dysfunction must be involved. The basal ganglia form a critical component of parallel cortico-basal ganglia-thalamo-cortical loops sub-serving different motor, associative and limbic functions (Alexander et al. 1990), which has led to neurophysiological investigation of the role of cortical dysfunction in dysphagia, as described below.

In the brainstem, areas of the nucleus tractus solitarius (NTS), DMV and nucleus ambiguus (NA) involved in the delivery of information to the periphery for the execution of the swallow and their operations depend on information from the periphery for initiation and accommodation of differences in the material ingested (thick vs. thin liquids, etc.). The NTS is involved in relaying visceral afferent sensations from the oesophagus and stomach, but is not pathologically involved in PD. Motor neurons of the NA of the vagus nerve contribute to coordination of muscles in the oropharyngeal phase of swallowing (Jean 2001). Brainstem pathology is observed in the different parkinsonian syndromes and may be hypothesised to contribute to swallowing dysfunction. However, NA is not affected by

α-synuclein pathology in PD, unlike the DMV (Braak et al. 2004), whereas selective loss of ventrolateral NA neurones occurs in MSA (Benarroch et al. 2006).

The relative lack of involvement in PD of brainstem neuronal regions involved with swallowing suggests that other centres which modulate their activity may be crucial to the understanding of dysphagia. Two important areas in movement disorders, the pedunculopontine nucleus (PPN) and the cerebellum, have been shown to play an important part in the swallowing process as well. Located in the midbrain tegmentum, the PPN is reciprocally connected with the basal ganglia, and projects to motor areas of the brainstem (Benarroch 2013). Cholinergic neurons of the PPN undergo neurodegeneration and cell death in PD, MSA and PSP (Schmeichel et al. 2008; Zweig et al. 1989; Zweig et al. 1987), and are increasingly implicated in gait disorders in those conditions. Given its projection to neurons such as those of the NA and NTS, the PPN is also thought to be implicated in impaired regulation of swallowing in parkinsonian syndromes (Cersosimo and Benarroch 2012).

Of importance to dysphagia in PD, due to the close link between breathing, swallowing and apnoea, in the brainstem the nuclei of the rostral and caudal ventral respiratory group (rVRG and cVRG), housing the inspiratory and expiratory neurons, receive input from PPN as well. In PwPD, respiratory impairments and cough impairments have been documented as well as an association with dysphagia and particular aspiration during swallowing (Troche et al. 2011).

Involvement of the peripheral as well as CNS is increasingly recognised in PD (Nolano et al. 2008). Several clinicopathological studies have identified PNS pathology in PD that may be relevant to swallowing. α-Synuclein pathology has been found in both motor and sensory pharyngeal nerves compared to age-matched controls, and is associated with an increased incidence of dysphagia (Mu et al. 2013a, b). More recently, degeneration and α-synucleinopathy have been shown in sensory nerve terminals of the upper aero-digestive tract in PD (Mu et al. 2015). Pharyngeal muscles in patients with PD show evidence of denervation, fibre atrophy and fibre-type grouping which may also contribute to dysphagia (Mu et al. 2012). Type I fibre atrophy could have been a result of hypomobilisation if the PD patients had modifications in oral consumption of food due to dysphagia. Involvement of the peripheral neuromuscular system may therefore play a key role in dysphagia in PwPD.

4 Neurophysiological Studies for Dysphagia in PD

Owing to the advances in neuroimaging, neurostimulation and electrophysiology, the number of neurophysiological studies to describe and delineate the changes in swallowing neural network in PD is increasing (Michou et al. 2013).

Evidence from animal studies and animal PD models in relation to swallowing has been interesting. In animals, PD is induced with the use of a neurotoxin, such as 6-hydroxydopamine, 6-OHDA, infused to areas such as the striatum, substantia nigra and/or medial forebrain and this can serve as a model of PD, although it does not recapitulate non-dopaminergic or extra-nigral aspects (Ungerstedt 1968). Specific testing protocols of orolingual deficiencies have been trialled in animals too (videofluoroscopy (Russell et al. 2013)). Some of the behaviours tested in animals may not be as similar as in humans and could involve reduced force and delayed timing in a complex licking task (Guggenmos et al. 2009; Ciucci et al. 2011, 2013), but it seems that tongue force rehabilitation regime (licking behaviour) on animals to medial forebrain could have an effect on halting deterioration: changes that are centrally mediated rather than peripherally (Ciucci et al. 2013). Different results were observed in rats with a different PD-induced model following lingual resistance training (Plowman et al. 2014).

In a longitudinal and cross-sectional 3-year study (Kikuchi et al. 2013) with PwPD with and without dysphagia, hypometabolism in the SMA as well as anterior cingulate cortex correlated to dysphagia. A strong decrease of the overall task-related cortical activation for completion

of swallowing tasks by PwPD was found with magnetoencephalography (MEG) (Suntrup et al. 2013). Additionally, only the non-dysphagic patients with PD showed a shift of peak activations towards lateral motor, premotor and parietal cortices, whereas activity in the supplementary motor area was markedly reduced. Authors concluded that adaptive cerebral changes apparently compensate for deficient motor pathways, since the non-dysphagic had shown recruitment of better preserved parallel motor loops.

Clinical neurophysiological techniques have been used to evaluate the differences in dysphagia between PD and atypical parkinsonian syndromes. Alfonsi and colleagues evaluated swallowing mechanisms with electromyography in PD, MSA-P and PSP compared to controls (Alfonsi et al. 2007) and found that early in the course of the disease of the atypical parkinsonian syndromes there is a reduction in the duration of the inhibition of the cricopharyngeal muscle activity compared to PwPD.

5 Dysphagia in PD: Clinical Features

Table 1 presents the characteristic clinical features and symptoms of dysphagia in PD across the stages of deglutition. Although dysphagia in Parkinsonism is frequently described as a non-motor symptom (NMS), the patterned response of swallowing has an important motoric component and relies on sensory information and feedback from the periphery—allowing for the modulation of the motor execution of swallowing.

As clearly shown in Table 1, dysphagia manifests a range of different signs and symptoms in PwPD. This symptomatology has been observed with assessment techniques (videofluoroscopy, VFS, fibre-optic endoscopic examination swallowing (FEES) and multichannel impedance and manometric assessments) described below. During the oral phase, bolus manipulation is shown to be one of the main symptoms causing accumulation of residue in the oropharyngeal area and piecemeal deglutition. Impaired preparatory lingual movements and mastication often lead to abnormal bolus formation. Lingual bradykinesia is described mainly in the advanced stages of the disease, while contributing factors to the observed oral motor abnormalities could also be the disease-related tremor, bradykinesia and rigidity. In terms of mastication, PwPD have shown to present impairments due to jaw mobility and oral control. Velocity and stability and coordination of movements in the oral stage of the swallow seem to be reduced and discoordinated, due to rigidity, jaw tremor and incomplete masticatory cycle.

During the pharyngeal phase, there is marked variability amongst patients. Patients have shown prolongation of bolus transfer timings and consequently stasis in the vallecular space and pyriform sinuses. One of the symptoms observed is incomplete cricopharyngeal sphincter relaxation (Ali et al. 1996), which can be either of intrinsic origin (hypertonic sphincter) or a result of the reduced forward and upward movement of the hyolaryngeal complex and even the weak propulsion forces and weak pharyngeal contractions. Reduction in sensation has also been observed in PwPD and it is now recognised that swallowing and airway sensory function change with disease progression (Hammer et al. 2013). Sensory loss of mechanoreceptors at the level of the base of the tongue (Leow et al. 2012) could also account for increased residue in the vallecular spaces. As a result of the pharyngeal dysfunction, penetration in the laryngeal vestibule and tracheobronchial aspirations are common in PwPD. Although further research is required, hypo-pharyngeal intrabolus pressures and reduced peak pharyngeal pressures have also been reported in PwPD (Ali et al. 1996). The presence of Zenker's diverticula, probably as a consequence of the impaired upper oesophageal sphincter function and high hypopharyngeal pressures, has also been reported (Byrne et al. 1994).

Oesophageal phase impairments are very frequent and appear early in the course of the disease (Sung et al. 2010; Bassotti et al. 1998). The nature of oesophageal impairments includes gastro-oesophageal reflux, diffuse oesophageal spasms and fragmented peristalsis. Abnormalities in lower oesophageal sphincter may contribute to reflux.

Table 1 Presents the list of the documented dysphagia signs in PwPD

Phase of deglutition	Findings on formal assessment	References
Oral/preparatory	Oropharyngeal bradykinesia	Bushmann et al. (1989), Umemoto et al. (2011), Nilsson et al. (1996)
	Tongue pumping	Argolo et al. (2015a), Nagaya et al. (1998)
	Smaller tongue movements	Van Lieshout et al. (2011), Leopold and Kagel (1996)
	Piecemeal swallowing	Nagaya et al. (1998), Argolo et al. (2015b)
Pharyngeal	Reduced pharyngeal constriction	Ellerston (2016)
	Premature spillage	Warnecke et al. (2016), Moreau et al. (2016)
	Vallecular residue	Argolo et al. (2015b), Warnecke et al. (2016), Moreau et al. (2016), Kim et al. (2015a), Lim et al. (2008), Fuh et al. (1997), Michou et al. (2014)
	Reduced velopharyngeal pressure	Jones and Ciucci (2016)
	Residue in pyriform sinuses	Argolo et al. (2015a), Fuh et al. (1997), Michou et al. (2014), Kim et al. (2015b)
	Reduced hyoid bone movement	Kim et al. (2015b), Ciucci et al. (2008)
	Decreased epiglottic rotation angle	Kim et al. (2015a)
	Shorter swallowing apnoea	Troche et al. (2011), Gross et al. (2008)
	Prolonged transit times	Nilsson et al. (1996), Argolo et al. (2015b), Kim et al. (2015a), Lin et al. (2012), Sung et al. (2010)
	Altered sensory processing	Pitts et al. (2016)
	Delayed laryngeal closure	Fuh et al. (1997), Leopold and Kagel (1997a)
	Incomplete CP relaxation	Kim et al. (2015a), Sung et al. (2010), Ali et al. (1996)
	Aspiration/penetration	Argolo et al. (2015b), Ellerston (2016), Warnecke et al. (2016), Moreau et al. (2016), Fuh et al. (1997), Hegland et al. (2016), Rajaei et al. (2015), Pitts et al. (2010), Johnston et al. (1995), Hunter et al. (1997), Robbins et al. (2008)
	Silent aspiration	Bushmann et al. (1989), Fuh et al. (1997), Stroudley and Walsh (1991), Nobrega et al. (2008), Monteiro et al. (2014)
	Repetitive swallowing	Sung et al. (2010)

Table 1 (continued)

Phase of deglutition	Findings on formal assessment	References
Oesophageal	Odynophagia	Su et al. (2017)
	Gastro-oesophageal reflux	Su et al. (2017), Bassotti et al. (1998), Park et al. (2015), Leopold and Kagel (1997b)
	Lower oesophageal sphincter obstruction/ aberration	Su et al. (2017), Leopold and Kagel (1997b)
	Diffuse oesophageal spasm	Sung et al. (2010), Su et al. (2017), Bassotti et al. (1998), Eadie and Tyrer (1965)
	Ineffective/fragmented peristalsis	Sung et al. (2010), Su et al. (2017), Bassotti et al. (1998), Leopold and Kagel (1997b)

These signs are observed through formal assessments with the use of FEES, VFS or multichannel impedance and manometric assessments

Abnormal stomach emptying pattern and early satiety affecting in turn pharmacokinetics have been reported and are important to consider when assessing and managing dysphagia in PD. Although there is not enough supporting evidence, PwPD who do not appear to show abnormalities in the oropharyngeal phase of the swallowing in formal imaging assessments may present changes in oesophageal phase even before clinically important dysphagia symptoms (Gibberd et al. 1974). Accumulation of alpha-synuclein in the ENS and DMV has been related to the development of the gastrointestinal tract abnormalities in PD (Cersosimo and Benarroch 2012). It is also unclear whether and to what extent the oropharyngeal problems contribute to the oesophageal dysmotility (Derrey et al. 2015). Disease severity and duration do not seem to correlate to findings of oesophageal dysmotility in PwPD (Castell et al. 2001).

Alongside the dysfunction of the upper gastrointestinal tract, there is increasing evidence for premotor pathological and symptomatic involvement of the lower GI tract in PD, with constipation being the most notable such symptom: a large longitudinal study of 6790 men showed a significantly increased risk of PD in men with <1 bowel movement/day compared to those with more frequent bowel movements (Abbott et al. 2001). Constipation has also been associated with increased density of incidental Lewy body pathology and reduced substantia nigra neuronal density in those without PD (Abbott et al. 2001; Petrovitch et al. 2009). There is emerging evidence for α-synuclein pathology in the colon of PD patients, which is supportive of an extension of the Braak hypothesis that Lewy body pathology may start in the gut and progress rostrally to the brainstem (Braak et al. 2003).

Furthermore, age, gender, disease duration and dementia have been reported to be independent *contributing factors for swallowing impairments in PwPD* (Cereda et al. 2014). Impairments in the oral and pharyngeal phase were associated to bradykinesia as recorded on UPDRS scale (Kim et al. 2015b), but further evidence is required. Importantly, several PwPD may not identify the presence of minimal changes in swallowing process and therefore sensitive clinical formal assessments should take place.

The range of symptoms shown in Table 1 indicates the heterogeneity in the deglutitive profile of PwPD with dysphagia. In addition, differences in symptomatology between the atypical parkinsonian syndromes and PwPD have also been observed (Umemoto et al. 2017). However, further research will allow us to compile a specific profile of differential symptomatology in the future.

Not all patients will experience these symptoms and not at the same period during disease progression. This is another indication for the

clinician who manages PwPD that the clinical assessment needs to be thorough. *Parkinson's disease is a multisystem neurodegeneration and differences in the degree of or rate of degeneration of different levels of CNS system may account for differences in phenotypic features with regard to swallowing function.*

6 Relationship to Other Non-motor Symptoms

Non-motor symptoms are increasingly recognised as a major contributor to symptom burden and impaired QOL in patients with PD. Many of these symptoms are mediated by involvement of non-dopaminergic and extra-nigral sites in the nervous system (Lim et al. 2009). Voice problems and dysphonia (Skodda et al. 2011) seem to be closely related to the presence of swallowing impairments in PD (Muller et al. 2001; van Hooren et al. 2015).

Several of the NMS in PD will have an impact on swallowing function and will have to be closely considered in therapeutic procedures. These NMS include fatigue, cognition, olfaction and taste changes as well as somatosensory changes centrally and from the periphery. Although less frequent than the olfactory problems (Kashihara et al. 2011), taste loss has a direct effect on appetite and is clinically relevant for malnutrition.

In a recent study (Cereda et al. 2014), dysphagia in PwPD with dementia was associated with male gender and disease duration, while in PwPD with no dementia symptoms, dysphagia was associated with male gender, age and disease duration. Cognitive problems have been observed to relate more to the oral phase impairments (Kim et al. 2015b). However, earlier reports mention that the presence of dementia did not influence the age at the time of death in patients with dysphagia (Bine et al. 1995). Cognitive problems, however, might have an immediate effect on the selection of the appropriate assessment and therapeutic approach.

Dysphagia in PwPD was also associated with bradykinesia and axial and postural instability with gait disturbances (Moreau et al. 2016; Park et al. 2015). Of interest, depressive states and dysphagia seem to correlate (Han et al. 2011), but the relationship between depression and dysphagia will be discussed later on.

6.1 Drooling and Xerostomia

Both drooling and xerostomia are NMS reported by PD patients and affect not only the QOL but also their oral health (Barbe et al. 2017) and can result to debilitating conditions in PwPD (Bloem et al. 2009). Pathophysiological underpinning of drooling appears to be the α-synuclein observed in minor salivary glands (Folgoas et al. 2013) and the submandibular glands (Del Tredici et al. 2010).

Drooling is an important NMS that is closely linked to swallowing impairments in PwPD and it is reported more prominently in the 'off'-medication period. Patients, who experienced drooling, showed silent aspiration in formal assessments (Rodrigues et al. 2011) and pharyngeal stage swallowing disorders (Nobrega et al. 2008). Approximately 50% of PwPD experience ptyalism (Martinez-Martin et al. 2007; Kalf et al. 2012b; Verbaan et al. 2007). Drooling correlated to overall patient dyskinesia (Park et al. 2015), while others believe that it does not correlate to disease duration or severity (Ou et al. 2015). It is now accepted that the reduction in the frequency of spontaneous swallowing may be the underlying pathology for the excess of saliva (Bagheri et al. 1999; Proulx et al. 2005) as well as hypomimia (Kalf et al. 2011).

On the other hand, xerostomia, the abnormal dryness due to insufficient secretions, is an important problem for PwPD (Barbe et al. 2017; Cersosimo et al. 2011). Xerostomia is usually related to levodopa dosage with higher doses increasing the xerostomia problem (Clifford and Finnerty 1995) or could be a side effect of the anticholinergic medication and can lead to changes in microflora and reduced oral health (Bakke et al. 2011) and change taste sensation, affecting swallowing function directly.

6.2 Lung Function and Cough

PD patients may present respiratory impairments and complications, including disturbances in ventilation (Gardner et al. 1986) and respiratory dysrhythmias (De Keyser and Vincken 1985), respiratory muscle weakness (de Bruin et al. 1993) and more.

Both inspiratory and expiratory muscles are affected in PD, while reflexive cough is more impaired than voluntary cough (Fontana et al. 1998). In addition, dopaminergic therapy may result in symptomatic respiratory disturbance in rare cases (Rice et al. 2002). In less advanced stages of the disease, it has been suggested that the motor rather than the sensory components of the cough reflex are impaired (Fontana et al. 1998). A recent study with classification of the patients according to their 'swallowing profile' as a response to dopaminergic medication showed that results on pulmonary function test were not as useful in differentiating PwPD with swallowing impairments (Sawan et al. 2016).

Coordination of breathing and swallowing is impaired in PwPD (Gross et al. 2008), with PwPD showing significant more post-swallow inhalation. Association of the reflexive cough (Troche et al. 2016), urge to cough (Troche et al. 2014a) and measurements of the voluntary cough (Ebihara et al. 2003) with penetration of material in the airways in PwPD has already been documented.

Although only small sample studies have been performed, it is a really interesting clinical research avenue because understanding the ineffective cough reflex might help not only in screening but also in choosing therapeutic approach for these patients (Pitts et al. 2009). In a recent study by Troche et al. (2016), sensitivity of cough reflex discriminated between patients who penetrated above the level of the vocal folds and those with more severe penetration/aspiration, but more studies are needed, given that other factors (such as disease duration) may play a role.

7 Medical Therapy of Parkinson's Disease and Effects on Dysphagia

7.1 Pharmacological Therapy

Dopamine replacement therapies have been the mainstay of PD treatment since the demonstration of the therapeutic effects of the dopamine precursor drug levodopa in the 1960s (Cotzias et al. 1967). Subsequent studies have confirmed the efficacy of levodopa in improving motor symptoms and quality of life in PD (Fahn et al. 2004; Group PDMC et al. 2014). Dopamine receptor agonists, which directly stimulate predominantly dopamine D2 receptors in the brain, are also effective at relieving motor symptoms of PD. Monoamine oxidase B inhibitors (MAOB-I) are used to reduce the catabolism of dopamine, and have a modest symptomatic effect as monotherapy as well as adjunctive therapy in PD (Stern et al. 2004). Catechol-*O*-methyltransferase (COMT) inhibitors such as entacapone are used as adjunctive therapies to levodopa, and improve 'on' time in PwPD (Rinne et al. 1998).

Although PwPD typically show a good therapeutic response to levodopa, fluctuations in the motor response complicate treatment in the majority of cases. The most common manifestation is known as 'wearing-off': the re-emergence of parkinsonian motor symptoms, but also non-motor features such as anxiety, pain and cognitive slowing at the end of an inter-dose interval (Jankovic 2005).

Bradykinesia and rigidity have been proposed as causes of dysphagia in PD. However, dopaminergic medications producing a good effect on motor symptoms have little effect on symptomatic dysphagia in PD (Hunter et al. 1997). A study of non-motor fluctuations in 100 patients with PD showed that dysphagia is one of the few NMS not occurring more commonly in the 'off'-medication state, although it is more severe in the 'off' state when measured objectively (Storch et al. 2013). A meta-analysis of five studies, but only two studies with formal assessments, found

no effect of levodopa on any swallowing parameters (Menezes and Melo 2009). These findings suggest that the involvement of extrastriatal and non-dopaminergic systems linked to the basal ganglia may have a critical role in swallowing dysfunction in PD.

Recently, Michou and colleagues (Michou et al. 2014) performed corticobulbar projection mapping with a neurostimulation technique called transcranial magnetic stimulation (TMS mapping) and formal imaging swallowing assessments, videofluoroscopy (VFS), on a group of PwPD with and without swallowing impairments both 'on'- and 'off'-dopaminergic medication. TMS is a safe and non-invasive technique, where a magnetic pulse is delivered through a coil of wire, and when delivered in the form of single pulses over an area of scalp and the cortical areas representing specific musculature from the periphery, information regarding the activation of the cortico-bulbar-muscular tracts can be obtained. Detailed analysis of the swallowing function revealed that there is marked variability in the responses of PwPD, with some patients showing impairments both 'on'- and 'off'-dopaminergic medication and another group experiencing impairments only 'on' medication. Marked differences in cortical maps of the three groups (Fig. 2) were observed. Repletion of dopaminergic medication also had an effect in reflexes from the brainstem in the patients studied. Patients with swallowing impairments only 'on' medication showed a decrease in brainstem reflexes compared to the 'off' state while on medication, implying a similarity to a dyskinetic effect of levodopa to the

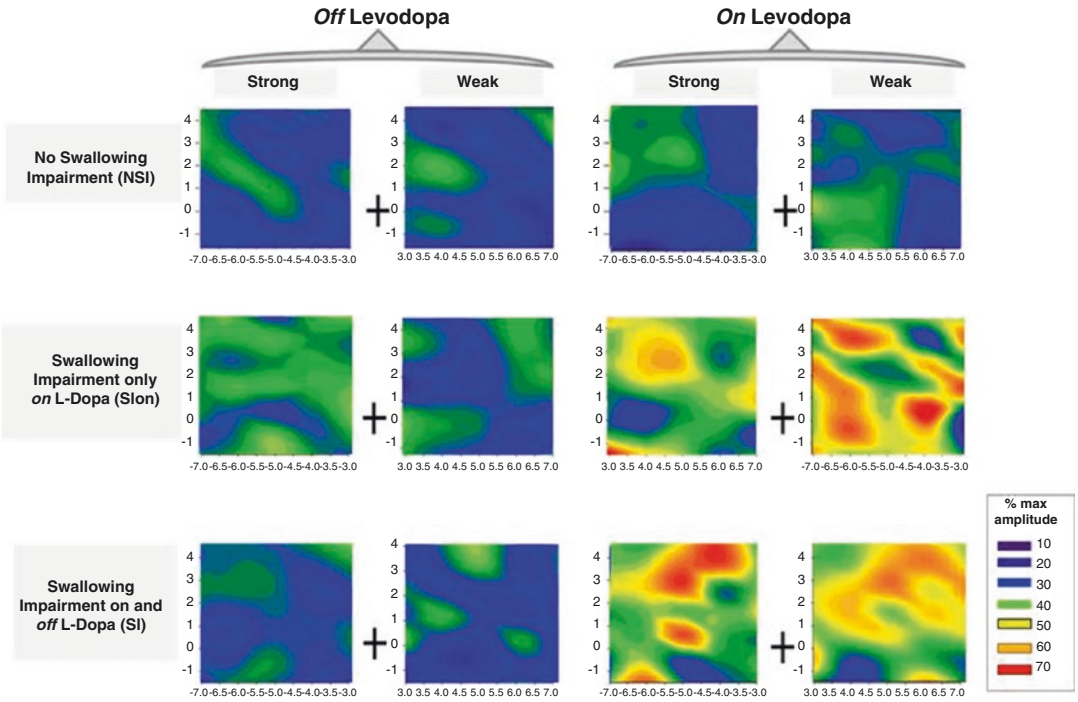

Fig. 2 Topographical maps of cortical representation of the pharynx in the three groups of patients studied with single-pulse TMS when 'off' and 'on' levodopa. The group of patients with no swallowing impairments had a minor reduction in cortical excitability of the stronger cortico-pharyngeal motor map with levodopa and the group with stable swallowing impairment, irrespective of medication (*third row*), had a bilateral increase in cortical excitability with medication. The group with swallowing impairments only on levodopa showed an increase in the stronger representation only. The vertex of each plot is marked by a "+". The intensity scale shown on the right is colour coded as a percentage of the amplitude of the maximum response for each group. With permission Michou et al. (2014)

swallowing pathway or a potential reduction in the ability to compensate for swallowing impairments after dopaminergic repletion.

7.2 Non-oral Medical Therapy

The development of motor complications of PD often triggers the use of non-oral therapies such as apomorphine, levodopa-carbidopa intestinal gel and deep brain stimulation surgery (DBS). Apomorphine is a potent dopamine D1 and D2 receptor agonist which is administered subcutaneously via intermittent injection or continuous infusion, and improves 'on' time and motor fluctuations in PD. A small study using videofluoroscopy showed improvement in some pharyngeal transit time and other aspects of dysfunctional swallowing in PwPD following apomorphine (Tison et al. 1996). The transdermal dopamine receptor agonist rotigotine has also been shown to improve pharyngeal transit time and videofluoroscopy scores in a small open-label study (Hirano et al. 2015).

7.3 Role of Non-oral Dopamine Receptor Agonists in Dysphagia (Acute, Surgery)

Deep brain stimulation surgery involves implantation of stimulating electrodes in basal ganglia nuclei, predominantly the internal globus pallidus (GPi) and subthalamic nucleus (STN). DBS of both nuclei has been shown to improve 'on' time and motor fluctuations in PD, as well as reduce levodopa-induced dyskinesia (Rodriguez-Oroz et al. 2012). A recent clinical trial of GPi versus STN DBS in PwPD showed a rate of dysphagia of up to 15% in those receiving STN-DBS in the first year following surgery, but the long-term rate of dysphagia in both groups after 3-year follow-up was much lower (Odekerken et al. 2016). A systematic review of all studies investigating the effect of DBS on swallowing found no clinically significant effects, although the authors identified that the pharyngeal phase of swallowing appeared sensitive to the effects of STN DBS (Troche et al. 2013).

8 Clinical Assessment of Dysphagia in PD

Swallowing impairments in PwPD should be diagnosed early given the severity of the consequences of dysphagia in PD. Although there is a high risk of aspiration and pneumonia associated with dysphagia in PwPD, swallowing impairments are often overlooked until the patient experiences choking or pneumonia incidences. Amongst the usual symptoms that the patients report are difficulties with swallowing their tablets; therefore a cautionary approach is advisable. Another argument for cautionary approach with dysphagia in PwPD is the fact that the extent and frequency of silent aspiration in PwPD have not been estimated yet.

Screening approaches in the clinical setting sometimes rely on a single question in UPDRS (Movement Disorder Society Task Force on Rating Scales for Parkinson's D 2003) and lately the Non-Motor Symptoms Questionnaire (Chaudhuri et al. 2006) from PD UK has offered a single yes/no question regarding coughing and chocking of PwPD. Swallowing-specific questionnaires designed to be completed by PwPD have been developed (Manor et al. 2007; Simons et al. 2014), but there is not currently a specified screening tool for dysphagia in parkinsonism to be administered in the clinic. However, there is emerging evidence that some dysphagia screening tools (i.e. 100 ml (Belo et al. 2014) or 150 ml timed water test) or wet voice testing (Sampaio et al. 2014) could be potentially useful in screening for PwPD.

Evidence from studies of swallowing–breathing coordination has shown that inspiratory events after a swallow and a shorter apnoeic interval could indicate PwPD who are at risk of swallowing impairments (Troche et al. 2011; Gross et al. 2008). In addition, rigorous research is underway for delineating those indicators for potential risk of aspiration in PD patients based on reflexive cough and other indicators, such as the urge to cough (Hegland et al. 2016).

Thorough clinical assessment is required by the dysphagia specialists, which usually takes into consideration information from the medical notes regarding medication and in particular

dosage concomitant conditions and overall motor symptomatology. Understanding the role that confounding factors such as cognition and fatigue play is also an important part of the assessment. Formal assessments with imaging should be performed and dysphagia specialists can utilise techniques such as fibre-optic endoscopic evaluation of swallowing (FEES), VFS or (video) manometry. FEES is well tolerated and easily repeatable, and attempts have been made to standardise the assessment in parkinsonism (Warnecke et al. 2010). On the one hand FEES and VFS can provide the clinician with information about the occurrence and the cause of aspiration, while multichannel manometric or even more synchronous multichannel intraluminal impedance and manometry assessment, demonstrating the motility patterns of the oesophageal phase, can provide information of bolus propagation and the potential overlapping symptomatology of pharyngeal and oesophageal phase. The use of any formal imaging technique should take place not only for the visualisation of any potential risk of aspiration and further respiratory complications, but also to inform the clinician whether functional swallowing is intact enough so as the patient can remain nourished and hydrated, in addition to informing the treatment and management options (including compensatory manoeuvers). Oral and pharyngeal phase problems, as presented in Table 1, should be carefully evaluated. Post-swallow residue could be multifactorial in nature (reduced sensory and motor functions) (Michou et al. 2014) and it is very important to investigate the severity and the effect on swallowing safety. Also, perhaps of importance in building the most appropriate management plan, there may be loads to learn from supplementing the bedside assessment with lingual strength and reserve, airway somatosensory thresholds and/or cough strength; however more research is needed prior to clinical implementation of these techniques.

In the current clinical practice, the diagnostic examinations (and treatment, below) are conducted during the 'on'-levodopa (medication) phase, which starts roughly 90–120 min after the intake of antiparkinsonian medication. However, given the recent evidence regarding the different responses to dopaminergic therapy from early- to mid-stage PD (Michou et al. 2014) and late-stage PD (Warnecke et al. 2016), there might be important information to be gained from reviewing how efficient is the swallow both 'on' and 'off' pharmacological treatment. More research in this field will provide evidence on the utility of this binary approach.

Lastly, it is important to note that the different forms of clinical assessments are seen to be sensitive enough to investigate subtle and overt differences in dysphagic profiles of PwPD and atypical parkinsonian syndromes. Warnecke and colleagues compared FEES evaluation in 18 patients with PSP to 15 PwPD; despite the much shorter disease duration of 3.4 years in PSP compared to 13.5 years in PD, there were no significant differences in the severity of FEES impairments between groups (Warnecke et al. 2010). All endoscopic variables were affected in PSP, most frequently: bolus leakage, delayed swallow reflex and residues in vallecular spaces and pyriform sinuses. Disease severity and duration correlated with swallow impairment, with only a minority of PSP patients showing any levodopa responsiveness of dysphagia (Warnecke et al. 2010). Higo and colleagues evaluated swallow function in 29 patients with MSA (22 MSA-C, 7 MSA-P, median H&Y stage IV) using VF and manometry: the most common fluoroscopic findings were delayed bolus transport (73%), insufficient tongue movement (55%) and disturbance of intra-oral bolus holding (49%), while aspiration was seen in 21% of patients (Higo et al. 2003). Oropharyngeal and hypopharyngeal pressures were also reduced compared to controls, with frequent incomplete relaxation of the upper oesophageal sphincter in patients with >5 years' disease duration (Higo et al. 2003). A further study by the same group in 21 patients with MSA-C examined progression of VF findings over the disease course: delayed bolus transport was seen in 50% of patients <3 years' disease duration, and 85% of those >7 years' duration, while pharyngeal swallowing disturbance was minimal in early disease but progressed with time (Higo et al. 2005). It seems that further work is

needed, and will increase our knowledge for the profiling of swallowing disorders in different patient groups.

9 Early- vs. Late-Stage Dysphagia in PD

Although dysphagic symptoms are estimated to be experienced around 130 months post-diagnosis (Muller et al. 2001), there is not enough evidence regarding the onset of the symptomatology in the disease progression. As a consequence, there is not enough information regarding the optimal time window for clinical assessments of dysphagia, given that silent aspiration is a common phenomenon. Formally assessing PwPD for dysphagia when this is clinically severe manifested with incidences of choking and pneumonia may not be optimal since the patient may no longer benefit from active treatments.

Early-onset dysphagia in PD is atypical and usually alerts the clinician to an alternate diagnosis such as PSP or MSA. It is clinically important to understand when swallowing impairments appear in the course of the disease and how dysphagia symptomatology develops over the years. Even in early stages of the disease, dysphagia can be observed in a very mild form, while in the advanced stages almost 95% will have dysphagia (Nagaya et al. 1998; Ertekin et al. 2002; Wintzen et al. 1994).

One of the current debates is whether severity of PD is associated with dysphagia. While some clinicians showed that swallowing function is relatively well preserved earlier in the disease, when disease is not as severe, and worsens with disease severity (Umemoto et al. 2011; Leopold 1996; Baijens et al. 2011), others have shown that disease severity does not predict swallowing impairments (Bushmann et al. 1989; Fuh et al. 1997; Ali et al. 1996; Troche et al. 2016; Ertekin et al. 2002). Impaired mastication and orofacial functions are frequent in moderate-advanced PD and there is a trend for progressive difficulties in mastication and orofacial functions with disease progression (Bakke et al. 2011).

From a clinical perspective, disease duration and frequency of swallowing problems, which could be higher in the later stages, may account for the more clinically significant dysphagia problems in PD. Based on the neurophysiological overview provided in this chapter, one can postulate that the changes at the different areas of the CNS of the PwPD could account for the differences in swallowing impairments in PD. Also, it is important to state that there is currently no definition for the swallowing impairments accompanied with changes in swallowing efficiency but no overt risk in swallowing safety as opposed to the clinically significant dysphagia resulting in overt aspiration, which could be the reason behind the differences in clinical opinions.

10 Therapeutic Approaches in PD

Therapeutic approaches in the clinical setting and outpatient clinics are usually prescribed to those who show clinical severe dysphagia problems only. One of the main unanswered question is when should therapy start and longitudinal studies are needed to show that early therapy will have an effect in the long term and will delay the debilitating consequences of dysphagia.

Nevertheless, there are various approaches for dysphagia in PD including surgical interventions, oromotor exercises (Argolo et al. 2013; South et al. 2010), bolus modification for enhanced sensory awareness as well as swallow safety (Robbins et al. 2008; Rofes et al. 2013), biofeedback (Manor et al. 2013), electrical stimulation (Baijens et al. 2013; Heijnen et al. 2012), postural changes and compensatory airway protective manoeuvers, expiratory muscle strength training (EMST) (Pitts et al. 2009; Troche et al. 2010), thermal stimulation applied to the faucial pillars (Regan et al. 2010) as well as pharmacological interventions (for reviews Wood et al. 2010, Baijens and Speyer 2009, Deane et al. 2001, van Hooren et al. 2014).

Most of the clinical studies designed to investigate the effects of the aforementioned treatments on swallowing in PwPD have been performed in a small number of patients. Nevertheless, it seems that improvements in swallowing measurements

(changes in aspiration of material, reduction in residue in the oropharynx) as viewed with formal imaging assessments and changes in QOL have been observed with several of these approaches (Pitts et al. 2009; Argolo et al. 2013; Manor et al. 2013; Heijnen et al. 2012). In addition, as we mentioned previously, therapy is applied during the 'on'-medication state and most of the therapeutic protocols have been applied for about 4–5 weeks (Argolo et al. 2013; Manor et al. 2013; Heijnen et al. 2012; Troche et al. 2014b; Baijens et al. 2012). It is interesting to say that most of the therapeutic approaches have been applied to patients of mild to severe PD severity (H&Y stage II–IV). Further research, however, is needed to allow us to understand whether some of the techniques may have a beneficial effect or not. Some placebo effects have been already observed in the trials with neuromuscular electrical stimulation applied through electrodes on the neck (Baijens et al. 2012). Traditional swallowing therapy seems to be working as good as the recent proposed stimulation techniques (head-to-head comparison: (Baijens et al. 2013, Heijnen et al. 2012); direct application of traditional therapy only (Argolo et al. 2013; Regan et al. 2010), while gum chewing seemed to increase swallowing frequency in a case-control study (South et al. 2010).

The clinicians' toolbox of swallowing therapies includes biofeedback, thermal tactile stimulation (Regan et al. 2010), compensatory head postures, modification of the bolus, etc. Biofeedback with the use of videos of normal swallowing process, videos obtained with FEES showing the individual's swallowing impairments and the effects of compensatory techniques in a paradigm called video-assisted swallowing therapy (VAST) showed that it can reduce the post-swallow residue in PwPD (Manor et al. 2013). Another interesting approach is the EMST, which is received as individual training and can be performed at home. Four weeks of EMST had a direct effect on measurements of cough (increase in cough volume acceleration) (Pitts et al. 2009) and reduced penetration in PwPD (Troche et al. 2010). The sustainability of the effects of this non-specific treatment (Laciuga et al. 2014) has to be examined in details, as a study investigated the 3-month post-training period and showed that maintenance protocols are needed to sustain the effects (Troche et al. 2014b). Especially for drooling, botulinum toxin (BT-A) injection in the parotid gland has been effective for reducing sialorrhea (Truong et al. 2008) but may not have specific beneficial results on swallowing measurements (Nobrega et al. 2009). Evidence also exists that supplementation of the bolus with piperine could speed swallow response and improve safety of swallow (Rofes et al. 2013), but further studies should take place to elucidate the mechanisms and the medium of supplementation.

Importantly, there is missing evidence as to which patients and what type of swallowing impairments can be targeted with which therapeutic approach, given the marked heterogeneity in PwPD.

In the more severe swallowing problems, PwPD are not able to receive adequate oral nutrition due to severe aspiration or reduced oral intake as a result of food modification and oral-stage symptoms for instance. Alternative options should be considered for the PwPD. The decision for percutaneous endoscopic gastroscopy (PEG) insertion is important to be made after careful consideration and discussion between the multidisciplinary team, the patient and carers. The complication rate of PEG insertion in PwPD and atypical parkinsonian syndromes is increased, as is the 30-day mortality rate (Sarkar et al. 2017). In the retrospective study by Sarkar et al. (2017) aspiration pneumonia was the main cause of early mortality in PwPD with PEG feeding tubes, indicating that PEG is not a direct solution to aspiration and dysphagia.

One of the important complications of a PwPD experiencing dysphagia or being nil by mouth is the loss of medication administration, which can lead to neuroleptic malignant-like syndrome when dopamine levels drop dramatically in the brain. Even though specific medications such as carbidopa/levodopa/entacapone among others are not manufactured to be crushed, this is usually the case in the current practice. However, different approaches to medication should be considered at this stage (Alty et al. 2016). Evidence also

shows that a specialist inpatient Parkinson's disease Unit could tackle the multifactorial patients' outcomes when PwPD required hospitalisation (Skelly et al. 2014), but further work might be needed to see how dysphagia and aspiration pneumonia can be readily managed in such units.

11 Health Outcomes of Dysphagia in PD

The health outcomes of dysphagia in PD and atypical syndromes include malnutrition and dehydration, aspiration pneumonia and a reduced overall QOL, as well as depression and anxiety.

Malnutrition and dehydration in PwPD are highly prevalent, yet there is no accurate quantification of prevalence as yet. There are different factors such as dysautonomia, disease severity and dopaminergic repletion medication dosage (Barichella et al. 2013) for malnutrition in PwPD. A systematic review found that the prevalence of malnutrition ranges from 0 to 24% in PwPD, while 3–60% of patients were reported to be at risk of malnutrition (Sheard et al. 2011). Progressive weight loss, and especially fat mass loss (Markus et al. 1993), is a major feature in PD starting 2–4 years prior to diagnosis (Chen et al. 2003) and prevalence of malnutrition and sarcopenia is significantly increased with increasing disease duration, advanced stage and severity of disease (Kashihara 2006; Montaurier et al. 2007; Lorefalt et al. 2004). Additionally, it has also been observed that decreased skeletal muscle mass could be a risk factor for dysphagia in long-term care (Murakami et al. 2015). Dysphagia is one of the main factors contributing to malnutrition in PD along neuropsychiatric symptoms contributing to reduced food intake, increased catabolism and resting energy expenditure—in both untreated and optimal treated PwPD. Therefore, screening for malnutrition should be performed and weight changes should be monitored over time with validated and reliable nutritional risk screening tools.

In PwPD, aspiration pneumonia is the leading cause of death (Fernandez and Lapane 2002; Lo et al. 2009; D'Amelio et al. 2006), with dysphagia being associated with a reduction in survival time. Aspiration pneumonia events in hospitalised PwPD can reach 2.4% (Martinez-Ramirez et al. 2015). Death seems to occur within 15 to 24 months post-confirmed swallowing disorders in PD patients (Muller et al. 2001); however further longitudinal studies are warranted to understand the natural history of dysphagia in PwPD. In the Sydney Multicenter Study (Hely et al. 2005), which investigated the effects of low-dose levodopa compared with low-dose bromocriptine, half of the population followed up was reported to 'choke', indicative of dysphagia that may lead to consequent pneumonia; the latter was the most common cause of death in the study. Impaired resistance to infections and bacterial colonisation could be an additional factor for aspiration pneumonia (Ortega et al. 2014), although significant different oral bacterial load has not been found between PwPD and same-age control group (Pereira et al. 2017).

Quality of life is reduced in PwPD and dysphagia may reduce QOL even further. In studies where QOL questionnaires specifically designed for the effects of swallowing disorders were used, such as SWAL-QOL (McHorney et al. 2000), it is demonstrated that PwPD have clearly reduced QOL (Michou et al. 2014; Carneiro 2014; Leow et al. 2010). There is also a potential link between dysphagia and depression and/or QOL (Carneiro 2014; Leow et al. 2010; Manor et al. 2009; Perez-Lloret et al. 2012; Plowman-Prine et al. 2009; Walker et al. 2011). It is now accepted that depression is commonly experienced NMS by PwPD and that such psychosocial factors have a significant impact on QOL (Maass and Reichmann 2013). Importantly, cognitive impairments could have a significant negative impact on QOL (Chagas et al. 2014). McKinlay et al. (McKinlay et al. 2008) reported that PwPD-related dementia is more likely to have psychosocial illnesses such as anxiety and depression. Nevertheless, most of the studies that described a relationship between reduction in QOL and dysphagia (above) rigorously excluded patients with cognitive problems, which indicates the factual correlation of dysphagia and reduction in QOL. Being able to eat and drink safely is not only of importance to

a person's health, they are also social activities around which society places a lot of emphasis through ritual and custom. Ekberg et al. (Ekberg et al. 2002) argue that dysphagia has a significant impact on an individual's confidence and desire to participate in social activities.

Conclusions

This chapter focused on the current clinical status and research directions on swallowing impairments (dysphagia) in PwPD. The increased incidence of dysphagia in PwPD leads to increased risk of mortality, secondary to aspiration pneumonia. Although studies show that aspiration pneumonia is a common cause of death in this group of patients, therapeutic approaches for dysphagia lack a strong evidence base and there is an increased need for large randomised clinical trials that will allow us to understand how early and what swallowing impairments can be treated as well as the compliance and sustainability of the effects of treatments in this neurodegenerative disease. Importantly, the underlying mechanisms accounting for the progression of dysphagia in PD are still unclear. It is noteworthy to state that investigating changes in physiology alone as an outcome measure for the effects of treatment, without observing the underlying neurophysiological basis for such changes, is likely to give an incomplete picture of the aetiology, the volume of therapy required and how to use even compensatory techniques in the management of dysphagia in PD (Michou and Hamdy 2010). Future research in the field is warranted and may result in improved management of dysphagia in patients with PD.

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Oropharyngeal Dysphagia and Dementia

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Abstract

Dementia is one of the leading causes of dysfunctionality and disability among older people and has a high physical, psychological, social, and economic impact. Oropharyngeal dysphagia (OD) is a frequent condition in patients with dementia of various types, including early stages, showing a delayed and prolonged swallow, and usually self-feeding difficulties and feeding dependency. In addition, OD is associated with several complications and negative outcomes such as malnutrition, respiratory infections, aspiration pneumonia and increased hospital stay, health-resource consumption, and mortality. OD should therefore be systematically screened, managed, and treated in patients with dementia, taking into account their intrinsic characteristics. The aim of this chapter is to present an overview of the prevalence, pathophysiology, diagnosis, complications, and treatment of OD in patients with dementia.

1 Introduction

Dementia is one of the leading causes of dysfunctionality and disability among older people and has a high physical, psychological, social, and economic impact. From the beginning, dementia affects the nutrition of the patient, producing

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several complications such as weight loss leading to anorexia, feeding apraxia, and dysphagia (Gómez-Busto and Andia 2009). Dementia is defined by the World Health Organization (WHO) as "a syndrome in which there is deterioration in cognitive function beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not affected. The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation" (World Health Organization 2017). It is estimated that, globally, there are 47.5 million people with dementia with an incidence of 7.7 million new cases per year. By 2030, the total number of people with dementia is expected to reach 75.6 million and to almost triple by 2050 (135.5 million) (World Health Organization 2017). Prevalence of dementia in adults older than 65 years is estimated between 6 and 14% (Hendrie 1998; Plassman et al. 2007) and increases to more than 30% over 85 years of age (Hendrie 1998), and more than 37% over 90 years (Plassman et al. 2007).

Oropharyngeal dysphagia (OD) is a frequent condition in patients in several types of dementia and is a risk factor for mortality. In addition, it causes serious complications such as malnutrition, dehydration, respiratory infections, and aspiration pneumonia (AP) (Clavé and Shaker 2015). Changes in swallowing and neural control of deglutition depend on the type of dementia and the cortical and/or subcortical lesions that exist (Chouinard 2000). OD is the most common cause of aspiration, and pneumonia, probably caused by aspiration, is the most common cause of death in patients with dementia (Mitchell et al. 2010; Brunnstrom and Englund 2009). The prevalence of OD in patients with dementia increases with age and can reach up to 93% (Affoo et al. 2013), with 28% of them presenting signs of aspiration assessed by videofluoroscopy (VFS) (Horner et al. 1994; Feinberg et al. 1992). The prevalence of OD increases with the severity of the dementia, explaining the variations in the prevalence rates published. The pathophysiology of OD in these patients is explained by the changes in deglutition and in the neural control of swallowing that dementia causes.

2 Prevalence

The type of dementia and its severity have an impact on the prevalence of OD, results varying according to the study and method of evaluation. In general, OD is more prevalent in nursing home residents (Alagiakrishnan et al. 2013) and it can occur either in early stages of dementia with Alzheimer's disease (AD) (Humbert et al. 2010) or in late stages of other types of dementia including frontotemporal dementia (FTD) (Ikeda et al. 2002). Thus, a study by *Ikeda* et al., using a screening questionnaire, found a higher prevalence of OD in patients with FTD (26%) and semantic dementia (20%) compared with those with AD (7%) (Ikeda et al. 2002). A meta-analysis showed a prevalence of OD of between 32 and 45% in AD patients clinically assessed and between 84 and 93% instrumentally assessed (Affoo et al. 2013); and the prevalence of aspiration was found to be 55% using VFS (Logemann et al. 2008). One study showed that 92% of patients with Lewy body dementia (LBD) who acknowledged signs of dysphagia had their swallowing dysfunction verified by VFS (Londos et al. 2013). A cohort study using VFS found a higher prevalence of OD in patients with vascular dementia (VD) (47%) compared with AD (13%) (Suh et al. 2009). Using VFS, *Logemann* et al. found a 39% prevalence of aspiration in patients with Parkinson's disease (PD) (Logemann et al. 2008). Using a swallow speed test, Miller et al. showed that 23% of patients with PD could not finish the test and 80% showed a slower swallowing rate compared to healthy controls (Miller et al. 2009).

Finally, one study found that the probability of developing eating disorders in a group of nursing home residents with advanced dementia was 85.8% over a period of 18 months (Mitchell et al. 2010) and in another the same type of patients showed a prevalence of clinical signs of aspiration of 35.6% (Rosler et al. 2015). More than 45% of institutionalized patients with dementia may present the same problem (Horner et al. 1994).

3 Pathophysiology

In general, patients with dementia have delayed and prolonged swallow (Groher and Crary 2010) and usually present self-feeding difficulties and feeding dependency. These difficulties are associated with motor deficits (apraxia), sensory deficits, cognitive impairment, loss of appetite, and/or food intolerance which may increase mealtimes and so the risk of malnutrition (Alagiakrishnan et al. 2013; Groher and Crary 2010), and, consequently, opportunistic infections such as pneumonia (van der Maarel-Wierink et al. 2011; Rofes et al. 2011; Serra-Prat et al. 2012).

In patients with AD, deficits tend to occur in the sensory aspects of swallowing (Suh et al. 2009). In the early stages of AD, the most common cause of dementia (60–70% of cases), there is a prolonged oral phase, a delayed start of the pharyngeal phase, and decreased lingual movement leading to low propulsion force (Priefer and Robbins 1997). In the moderate phase of AD, there is associated difficulty in the oral preparatory phase, pharyngeal clearance, upper esophageal sphincter opening, and aspiration, as has been demonstrated by VFS (Horner et al. 1994). In early AD, changes in cortical control of swallowing may begin long before dysphagia becomes apparent. There are functional changes in the cortical swallowing network as measured using functional magnetic resonance imaging. Videofluoroscopic measurements have shown that patients with AD have significantly reduced hyolaryngeal elevation over controls (Humbert et al. 2010).

A comparative study between patients with AD and patients with VD showed that those with AD presented over 5 s longer oral transit delay with liquids while patients with VD had more deficits in bolus formation and mastication of semisolid food, hyolaryngeal excursion, epiglottic inversion, and silent aspiration ($P < 0.05$). The swallowing disorders of this group (VD) may be primarily caused by motor impairments due to disruptions in the corticobulbar tract (Suh et al. 2009).

A study investigated the prevalence of OD, and defined the swallowing dysfunction according to VFS in 82 patients with LBD and Parkinson's disease (PDD). Twenty-six patients (32%) reported symptoms of dysphagia such as swallowing difficulties or coughing; 24 (92%) of these had documented swallowing dysfunction with VFS and 88% suffered from pharyngeal dysfunction. Almost all DLB or PDD patients with subjective signs of dysphagia had pathologic results with VFS, the majority of pharyngeal type (Londos et al. 2013).

In FTD there is a tendency to eat rapidly and compulsively while taking large bolus sizes. Patients also have a tendency to leak food into the pharynx, which could be due to lack of awareness of food in the mouth. Incomplete bolus clearance was also seen, due in part to reduced force of contraction of tongue, pharynx, and larynx (Langmore et al. 2007).

Finally, there are several drugs which affect the swallow response with potentially harmful effects (Table 1), particularly sedatives, commonly taken by patients with dementia, that have a depressive effect on the swallow response (Miarons et al. 2016). It is necessary to rule out the presence of associated symptoms, such as depression, constipation, or pain, and to evaluate the use of specific medication, including orexigenic agents, despite their discussed efficacy (Golden et al. 2003; Berenstein and Ortiz 2005).

Table 1 Drugs related to OD

	Drug	Possible mechanism	References
Drugs with potentially beneficial effects on swallowing	*Benzodiazepines*	Inhibit rapid eye movement (REM) and thus preventing bronchial microaspirations associated with this phase of sleep	Gaillard (1989) and Almirall et al. (2008, 2013)
	Antagonist of angiotensin	Improve muscle remodeling and protect against disuse atrophy	Burks et al. (2011)
	Beta-blocker agents	Act on pharyngeal muscles increasing isometric contractile forces. Reduce thickness of oral, nasal, and pulmonary secretions	Miarons et al. (2016); Murphy et al. (1997) and Bradley et al. (1997)
	Angiotensin-converting enzyme	Increase substance P that improves swallow response and cough reflexes	Favorable effect Arai et al. (1998); Ohkubo et al. (2004) and Shimizu et al. (2008); not Miarons et al. (2016) and Lee et al. (2015)
	Dopamine agonist (amantadine, folic acid, L-dopa)	Activate dopaminergic neurons and reduce swallowing abnormalities	Nakagawa et al. (1999); Monte et al. (2005) and Han et al. (2011)
	Rivastigmine	Might improve swallowing function by slowing the degradation of acetylcholine in the cholinergic nervous system	Uwano et al. (2012) and Lai et al. (2015)
Drugs with potentially harmful effects on swallowing	*Antipsychotic* (loxapine, fluphenazine, risperidona, trifluoperazine and haloperidol)	Have adverse effects such as extrapyramidal symptoms and tardive dyskinesia Increase latency for swallowing, which increases the risk for aspiration pneumonia (OR 3.13, 95% CI 1.46–6.69, $p < 0.003$)	Dziewas et al. (2007); Sokoloff and Pavlakovic (1997); Stewart (2001, 2003); Bashford and Bradd (1996); Gonzalez (2008) and Wada et al. (2001)
	Antidepressants with anticholinergic action like tricyclic antidepressants	Potentiate GABA system	Dantas and Nobre (Souza 1997)
		Related to sedative effects, The risk of pneumonia was greatest within the first 30 days of benzodiazepine use (HR 2.09, 95% CI 1.26–3.48)	Taipale et al. (2017)

4 Diagnostic Approaches

According to a systematic review, clinical swallowing evaluation, VFS, and fiber-optic endoscopic evaluation of swallowing (FEES) are the three main methods used to assess OD in patients with dementia (Alagiakrishnan et al. 2013).

Methods to assess OD can be divided into two main categories, clinical and instrumental.

4.1 Clinical Evaluation of Dysphagia

The aim of the clinical screening is to detect the majority of patients at risk of OD early. If positive, these patients should be referred for more comprehensive swallowing assessment to prevent OD complications. Several screening methods exist and can be used (i.e., the Eating

Assessment Tool-EAT-10- or the Sydney Swallowing Questionnaire) (Rofes et al. 2014a; Belafsky et al. 2008; Wallace et al. 2000). In addition, the Edinburgh Feeding Evaluation in Dementia scale is an instrument to assess eating and feeding problems in patients with dementia. It is easy to perform and is composed of 11 items, and although it is not a screening or diagnostic tool, it can define the level of assistance the patient needs (Watson 1994a, b; Stockdell and Amella 2008).

Clinical assessment aims to evaluate the efficacy and safety of swallowing, and some methods are able to detect silent aspirations at the bedside (Baijens et al. 2016). A recent systematic review recommended two bedside clinical methods: the Volume-Viscosity Swallow Test (V-VST) (Clavé et al. 2008) and the Toronto Bedside Swallowing Screening Test (TOR-BSST) (Martino et al. 2009) due to their excellent psychometric properties (Kertscher et al. 2014). However there are no specific clinical assessment methods for patients with dementia.

In addition, a comprehensive geriatric assessment (CGA) should be considered as an important part of the diagnosis of OD in dementia patients. CGA is defined as a "multidisciplinary diagnostic process that identifies medical, psychosocial, and functional limitations in older persons in order to develop a coordinated plan to maximize overall health with aging." CGA is based on the assumption that a systematic evaluation of older persons by a team of health professionals may identify a variety of treatable health problems and lead to better outcome (Devons 2002).

4.2 Instrumental Swallowing Assessment

Instrumental swallowing assessment is recommended to confirm the diagnosis and treatment for patients that were previously clinically assessed for dysphagia. In the case of patients with dementia, it is important to take into account the cognitive-linguistic status of the patients and their health and functional status. The most frequently used instrumental assessment tools are VFS and FEES (Clavé and Shaker 2015; Baijens et al. 2016).

VFS is a dynamic radiological technique that evaluates signs of impaired efficacy and safety of swallowing in order to establish treatment recommendations and avoid complications. In addition, this technique allows the clinician to make quantitative measurements of the oropharyngeal swallow response to assess, for example, the effect of a treatment (Clavé and Shaker 2015; Baijens et al. 2016).

FEES is a technique that uses a flexible fiberoptic endoscope to visualize the pharynx and larynx and their function. It is a technique that can be done at the bedside of the patient, increasing its diagnostic range. However, FEES can be difficult to perform in patients with dementia due to lack of collaboration. The prevalence of dysphagia in AD and other dementias using VFS is higher than that found with other diagnostic tools (Horner et al. 1994; Humbert et al. 2010).

5 Complications

The main complications of OD derive from impaired efficacy of swallow (inefficient ingestion of nutrients and liquids) leading to MN and/or dehydration, and impaired safety of swallow (penetrations and aspirations) causing respiratory infections and AP (Rofes et al. 2011). All these complications lead to hospital readmissions, frailty, and institutionalization, increasing morbimortality in this population (Clavé and Shaker 2015). A prospective study by *Mitchel* et al. showed an association between OD and mortality, considering it a bad prognostic criteria (Mitchell et al. 2010).

Dysphagia is a risk factor for poor outcomes as shown in a large retrospective cohort study from the USA with 234,006 hospitalized patients with dementia. They found that dysphagia was a significant predictor of worse outcomes including a 38% longer hospital stay and a 30% increase in health-care-associated costs in hospitalized patients with dementia (US$10,703 higher). In addition patients with dementia and dysphagia had significantly higher odds ratios of percutaneous endoscopic gastrostomy placement, AP, pneumonia, malnutrition, mechanical ventilation, sepsis, and anorexia and to be discharged at a rehabilitation or long-term facility center

(Paranji et al. 2017). These results showed that if a patient with dementia is admitted to hospital and has dysphagia, there is a higher probability of complications and consequently a greater use of health-care resources.

Weight loss and malnutrition are associated with the progression of dementia and cognitive decline. In general, malnutrition and dementia are part of a vicious circle in which dementia favors the onset of decreased intake and malnutrition and this worsens the functional and cognitive prognosis. In addition, the nutritional problems associated with dementia worsen the overload of the caregiver, and can adversely affect not only the nutritional status of the patient but also that of the caregiver. Caregivers need support and training in the nutritional aspects linked to dementia and OD, such as the use of balanced diets, special requirements in these patients, how to feed a patient with dementia, how to detect problems, and in the case that OD has already appeared, the warning signs, and how to use modified texture diets and fluid adaptation (Volkert et al. 2015). In addition, dementia, malnutrition, dysphagia, and loss of muscle mass are closely related and are part of the vicious circle that impoverishes the overall situation of the patient. *Takagi* et al. hypothesized that loss of muscle mass in patients with dementia was related to disease progression and worsening of swallowing. After studying 232 patients, he found that severe dementia (CDR 3), calf circumference <30.5 cm, BMI <18.5, and dysphagia were associated with loss of muscle mass (Takagi et al. 2017).

6 Treatment

There are several therapeutic approaches in dysphagia management (Table 2) including (a) bolus modification (liquid and solid consistency modification); (b) swallow postures and maneuvers; (c) other interventions (swallow rehabilitation, surgical treatment, and oral hygiene); and (d) new treatments including peripheral and central stimulation techniques (pharmacological treatment, electrical stimulation, repetitive transcranial magnetic stimulation—rTMS—and transcranial direct current stimulation-tDCS).

(a) *Bolus modification*: Bolus rheological adaptation is the main compensatory treatment for patients suffering from OD (Sura et al. 2012) and several studies have found a viscosity-dependent therapeutic effect of thickening agents (Logemann et al. 2008; Newman et al. 2016). In addition, the level of evidence with this therapeutic approach is very high as there are several randomized and non-randomized clinical trials showing this effect (Speyer et al. 2010). On the other hand, enteral nutrition with the use of nasogastric tubes and percutaneous endoscopic gastrostomy (PEG) in advanced dementia does not show any benefit with regard to outcomes and survival (Alagiakrishnan et al. 2013). The ESPEN guidelines recommend avoiding tube feeding in this population (Volkert et al. 2015).

Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) published specific guidelines on nutrition in dementia patients, concluding that "Nutritional care and support should be an integral part of dementia management. In all stages of the disease, the decision for or against nutritional interventions should be made on an individual basis after carefully balancing expected benefit and potential burden, taking the (assumed) patient's will and general prognosis into account" (Volkert et al. 2015). Adaptation of diet in these patients should be based on traditional diet and can be combined with nutritional supplements to improve patient's nutritional status and satisfaction. A review proposed that "assisted oral feeding should be the most natural and appropriate form of feeding patients with dementia, always respecting their previously expressed wishes" (Gómez-Busto and Andia 2009). However, in patients with dementia, there are aspects of feeding that complicate achieving correct nutritional status such as

Table 2 Management of dysphagia in patients with dementia

Study design	Study population	Modified diet	Type of intervention		Study outcomes	References
			Postural modification	Feeding tubes		
RCT	711 AD, PD	Nectar and honey-thickened fluids	Chin-down posture	–	Significant aspiration on thin liquids despite chin-down posture vs. nectar-thickened liquids ($p < 0.001$) or honey-thickened liquids ($p < 0.0001$). Nectar-thickened liquids vs. honey-thickened liquids (OR = 1.63, 95% CI 1.14–2.32; $p < 0.0001$).	Logemann et al. (2008)
RCT	515 AD, PD with or without dementia	Nectar- and honey-thickened fluids.	Chin-down posture	–	3-month cumulative incidence of pneumonia was 0.098 and 0.116 in the chin-down and thickened-liquid groups (HR = 0.84, 95% CI, 0.49–1.45; $p = 0.53$). 3-month cumulative incidence of pneumonia was 0.084 in the nectar group vs. 0.150 in the honey group (HR = 0.5; 95% CI, 0.23–1.09; $p = 0.083$)	Robbins et al. (2008)
RCT crossover design	15 patients with severe dementia	–	Cervical spine mobilization	–	Swallowing capacity improved significantly after cervical spine mobilization from 3 mL (P25-75 = 1–10) to 5 mL (P25-75 = 3–15) after 1 session ($p = 0.01$) and to 10 mL (P25-75=5–20) (+230%) after 1-week treatment ($p = 0.03$) vs. control (no significant changes, difference in evolution after 1 session between treatment and control, p=0.03).	Bautmans et al. (2008)
12-week intervention	Treated group (8 patients) + control group (9 patients)	Minced/pureed foods + thickened beverages	–		Average weight increased, treated group vs. control group (3.90 ± 2.3 kg vs. 0.79 ± 4.18 kg; $p = 0.02$)	Germain et al. (2006)

(continued)

Table 2 (continued)

Study design	Study population	Modified diet	Type of intervention		Study outcomes	References
			Postural modification	Feeding tubes		
Prospective cohort study	30 nursing home residents with AD and OD	Self-control feeding interventions	–	–	Patients' eating/feeding abilities improved overall, including increased food intake ($p < 0.001$), decreased levels on the Kubota water swallow test ($p < 0.001$) and significant differences in skinfold thickness, arm circumference, serum albumin, and hemoglobin ($p < 0.01$), indicating improved nutritional status. No changes were noted in cognition post-intervention. Among 22 patients who initially required feeding, 5 resumed self-feeding after intervention ($p = 0.06$)	Chen et al. (2016)
Prospective case and control study	161 dementia geriatric inpatients and 30 control patients	Water, apple puree, and sliced apple		–	Dementia patients had more signs of aspiration than controls. Signs of aspiration occurred more frequently with water (35.6% vs. 6.7%, $p < 0.01$) than with sliced apple (15.1% vs. 3.3%, $p < 0.06$) or apple puree (6.3% vs. 3.3%, $p < 0.45$)	Rosler et al. (2015)
Retrospective cohort study	361 dementia, stroke, OD malignancies, and miscellaneous	–		PEG	Dementia patients ($n = 22$) had worse prognosis compared to other subgroups. With a 1-month and 1-year mortality of 54% and 90% (log-rank test $p < 0.0001$). This difference remained significant (log rank $p < 0.0001$) after adjusting for age at the time of PEG insertion	Sanders et al. (2000)
Prospective cohort study	97111 nursing home residents (≥65 y) with advanced dementia (91902 PEG, 5209 no PEG)	–		PEG	The majority of feeding tube insertions (68.1%) were performed in acute care hospital with the most common reasons for admission being pneumonia, dehydration, and dysphagia. 1-year post-insertion mortality was 64.1% with median survival of 56 days	Kuo et al. (2009)

PD Parkinson disease, *PEG* percutaneous endoscopic gastrostomy, *AD* Alzheimer's disease, *OD* oropharyngeal dysphagia

refusal to eat, turning the head away, refusing to open the mouth, spitting, allowing food to drop out of the mouth, and not swallowing (Watson 1994a). Patients affected by dementia present these eating disorders, which worsen their nutritional status, leading to malnutrition and increasing the overload of the caregiver (and the professional). *Edahiro* et al. identified in a sample of 150 patients with Alzheimer's dementia that the most frequent causes of decreased independence in eating were the difficulty to start ingestion, the existence of dysphagia, and the severity of dementia (Edahiro et al. 2012). The nutritional approach for patients with dementia should be multifactorial and include an adequate assessment of the patient to identify the needs for support (prepare the cutlery, verbal indications, etc. or be fully supplied in the food) and meet their needs (Lin et al. 2010). *Zanini* et al. launched the *Nutricare* program in older institutionalized patients with dysphagia, who, after careful assessment, are prescribed a personalized diet that adjusts proteins, calories, dietary texture, and viscosity of liquids and does not use oral supplements. With these modifications, 6 months after starting the program, the nutritional parameters (total proteins and albumin) and BMI of the patients were improved (Zanini et al. 2017).

(b) *Swallow postures and maneuvers*: Although the use of postures and manoeuvers is an accessible and commonly used therapy in patients with dysphagia, it is not very useful in patients with dementia due to cognitive impairment and lack of collaboration.

One of the most used is chin-down posture that is easy to perform and helps patients to close the respiratory airway, and it has maximal level of evidence (randomized clinical trials) (Terré and Mearin 2012). In general, the level of evidence for postures and maneuvers is intermediate (non-randomized clinical trials) (Speyer et al. 2010).

(c) *Other interventions*: There are several interventions that reduce the risk of complications, such as oral hygiene or rehabilitation strategies with specific techniques. Poor oral hygiene, common in patients with dementia and OD, is a risk factor for the development of pneumonia (Ortega and Clavé 2013). A systematic review found a preventive effect of oral care (mechanical toothbrushing) on respiratory infections and pneumonia, decreasing the risk of mortality from pneumonia and on nonfatal pneumonia in dependent older individuals (Sjögren et al. 2008). In addition, it is also important to clean mouths of edentulous patients and patients who are fed with enteral nutrition because, although oral feeding is avoided, colonized saliva can be aspirated causing respiratory infections and AP (Van Der Maarel-Wierink et al. 2013). Oral health in patients with dementia can be challenging due to lack of collaboration and cognitive impairment.

Another intervention strategy is the learning and application of swallowing rehabilitation exercises that aim to train specific muscles or muscular groups (tongue exercises, Shaker exercise, etc.). Although there are several studies showing good results using these exercises (Speyer et al. 2010), it is difficult to apply them in patients with dementia due to lack of collaboration and cognitive impairment.

(d) *New treatments*: Nowadays there are treatments based on stimulation of sensorial and motor pathways aiming at improving the swallowing function rather than compensating it. However, there is little or no evidence of the therapeutic effect of these treatments on patients with dementia and many of them need the collaboration of the patient. There are two main kinds of stimulation strategies, depending on the stimulation area: peripheral stimulation techniques that include neuromuscular electrical stimulation (transcutaneous or intrapharyngeal) and pharmacological or chemical stimulation (TRPV1, TRPA1, TRPM8 agonists) (Rofes et al. 2014b), and central stimulation techniques such as rTMS or tDCS (Simons and Hamdy 2017).

7 Dementia and Palliative Care

Dementia is a neurodegenerative disease; it is progressive and leads to death and one in which the complications are well known. It is important to detect problems that could accelerate the progression of the disease as early as possible, such as malnutrition, weight loss, or feeding difficulties to avoid or reduce the development of complications where possible. **S**everal key issues in relation to the person dying with dementia include diagnosis of the dying phase; appropriate timing of referral to specialist palliative care services; ethical decisions in relation to medication and nutrition; the environment; undertreatment especially for pain relief; over- and burdensome treatment interventions; carer involvement; collaborative working; and advance decision making (Lillyman and Bruce 2016). However, there is insufficient evidence to assess the effect of palliative care interventions on advanced dementia (Murphy et al. 2016).

Conclusion

OD is very prevalent in several phenotypes of patients with dementia, including early stages of dementia, with several etiopathogenic mechanisms. OD is associated with the development of negative outcomes such as malnutrition, respiratory infections, aspiration pneumonia, and increased hospital stay and health-resource consumption. Thus, OD should be systematically screened, managed, and treated in patients with dementia, taking into account the intrinsic characteristics of these patients.

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Pediatric Aspect of Dysphagia

Pascale Fichaux Bourin, Michèle Puech, and Virginie Woisard

Contents

Abstract

Pediatric dysphagia is specific because of the different developmental stages from the neonatal period to the infancy. Diagnosis and treatment will be different if it concerns a newborn or a young child having already experienced oral feeding. Furthermore, swallowing and feeding disorders, having a direct impact on the nourishment function of the parents, will have repercussions on the child–parents relationship. Swallowing disorders are frequently multifaceted, and impairments can be morphological, functional or induced. The assessment of these disorders includes anamnesis (reviewing family, medical, developmental, and feeding history), physical examination (searching for nutritional impact, cardiopulmonary state and looking for developmental anomalies or genetic dysmorphism), swallowing evaluation (analyzing oropharyngolaryngeal structure and function by observation, fiber-optic endoscopy, videofluoroscopy, ultrasonography), and feeding evaluation (implicating parents and caregivers). Management of these disorders is a complex task, thus an interdisciplinary team and recurrent assessments are required so as to match the child's development and capacities. Its main aims are to prevent repercussions on developmental milestones and to assure the safety of the child and the psychological balance of child–parents relationship.

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1 Introduction

The child's swallowing evolves; this is one of its principal characteristics. In adults, dysphagia is a loss of the abilities. In children, its evolution is modified, impacting on the morphological development of the organs like on the other functions of the aerodigestive tract such as breathing and speech.

The maturation of swallowing is organized over the first few years of life until 6 years as reported by most authors or 10 years as reported by some authors (Schindler et al. 2011), a date when mastication is fully controlled. This long evolution starts in utero. From 7 weeks' gestational age (GA), the brainstem receives the first sensory information from the pharyngolarynx. The sensory effectors are in place at the end of the embryonic phase. The principal anatomical structures develop as follows: the mandible at 4 weeks, the palate between the 6th and 12th weeks, and the esophagus at 7 weeks' GA. At this time, the fetus starts to swallow the amniotic liquid. From 10 weeks' GA, pharyngeal deglutitions are observable on ultrasonography (Miller et al. 2003). Suction is mature from the 15th week. A sucking–swallowing pattern appears from 18 to 24 weeks' GA. It becomes functional from 34 to 37 weeks' GA. Fetal sucking and swallowing plays a significant role in the morphogenesis of the oropharyngeal cavities. It takes part in the development of the digestive tract, the fetal trophicity, and its fluid balance. It is also the period of the first food experiments, the olfactory particles crossing the placental barrier. The observation of this sucking and swallowing, on ultrasonographic examinations of the second and third quarters of pregnancy, can be used to predict the sucking and swallowing of the baby at birth (Couly et al. 2009; Miller et al. 2003).

All must be in place at birth to ensure good coordination between sucking, swallowing, and breathing. The primary reflexes allow the newborn to ensure its vital needs are met. By rooting, the newborn moves towards the nipple. By grasping it remains attached to its mother. At this stage, the baby is acquiring feeding behavior. The alternation of hunger and satiety gives a rhythm to the baby's days in relation to the alternation of wakefulness and sleep. These various steps are paramount in the psychoemotional structuring of the baby. The progressive contributions of the nutrients must be in agreement with the quantitative and qualitative needs for each age. Food diversification supports the progressive evolution as do textures and tastes, while respecting the organic and neurological evolution of the child and its sensorimotor abilities.

Any modification or obstacle in this long evolution may contribute to significant delays in the emergence of the other oromotor behaviors, including babbling, speech, and language production. The causes of swallowing disorders are multifaceted, and their consequences will depend on the stage of the child's development.

This is why early and suitable evaluation and management are necessary to limit the functional effects of swallowing disorders on the aerodigestive crossroads.

2 The Different Developmental Stages

At birth, the newborn must pass from the liquid atmosphere into the air. The breath goes through the pharyngeal cavities, via the glottis, the trachea, and the bronchi. The alveoli become smooth, and the baby cries for the first time. Then the child starts to suck. The passageway for nutrients from the mouth to the digestive tract depends on the effectiveness and coordination of muscles and on a very precise synchronization (Amaizu et al. 2008).

2.1 The Neonatal Period

At this stage, the baby will coordinate nutritive sucking, swallowing, and breathing.

2.1.1 Sucking

Sucking is an alternation of suction, intraoral negative pressure, and expression/compression,

mouthing, or stripping of the nipple by the tongue against the hard palate. The two basic forms are nonnutritive sucking, on a finger or pacifier, and nutritive sucking, when a nutrient is ingested from a bottle or the maternal breast. The sucking pattern evolves. It is immature in preterm infants, consisting primarily of expression/compression. This is followed by the appearance of suction and the progressive establishment of the rhythmic alternation of suction and expression. The sucking pattern of term infants is characterized by the rhythmic alternation of suction and expression/compression. Lau et al. (2000) have demonstrated that the bottle-feeding performance is positively correlated with the development stage of sucking. They used a five-point scale to characterize the infant's oromotor skills. This scale evaluates the presence or absence of suction and rates the rhythmicity of suction and expression/compression in preterm infants (Table 1).

The sucking efficiency can also be analyzed from the ingested milk flow in the preterm infant. It increases significantly between the 34th and 36th weeks' GA, exceeding 7 mL/min with the 35 weeks (Mizuno and Ueda 2003). The same holds for the pressure of suction and its duration. A functional maturation but also a good coordination of the muscle groups is essential. The coordination of the movement of the oromotor structures controls the changing intraoral pressures that occur during a suck cycle. Successful sucking is dependent on intact brainstem pathways and transmission of impulses through the cranial nerves to healthy musculature in the mouth, tongue, and pharynx.

Table 1 The five-point sucking scale (Lau et al. 2000)

Stage	Description
1a 1b	No suction; arrhythmic expression Arrhythmic alternation of suction and expression
2a 2b	No suction; rhythmic expression
	Arrhythmic alternation of suction and expression; sucking bursts noted
3a 3b	No suction and rhythmic expression Rhythmic suction and expression; suction amplitude increases, wide amplitude ranges, prolonged sucking bursts
4	Rhythmic suction and expression; well-defined suction, amplitude ranges decreased
5	Rhythmic, well-defined suction and expression; increasing suction amplitude; sucking pattern similar to that of a term infant

The pace and alternation of suction and expression will vary during the first month of life in the term infant without a disorder. A 1:1 suck–swallow ratio is most frequent (78.8%), and then there will be bursts of two or three sucks for one swallow as if the child has adapted to be more effective (Qureshi et al. 2002). The normal feeding infant is reflexive without suprabulbar input (Stevenson and Allaire 1991). The maturation of nutritive sucking progresses in a caudocephalad way in the brainstem (Bosma 1985). The baby then becomes able to modify these various paces and acquires new food strategies. The reflex behaviors become automatic functions strengthened by voluntary movements.

2.1.2 Breathing

During nonnutritive sucking, the infant swallows only little saliva, and coordination of sucking and breathing is not important to avoid inhalation. The situation is different during nutritive sucking, the alternations between sucking, swallowing, and breathing being closely dependent. To be effective, the newborn must take milk without aspiration, desaturation, or bradycardia. The patterns most frequently encountered are 1:1:1 and 2:2:1 ratios of sucking, swallowing, and breathing (Lau et al. 2003). According to Lau et al., oral feeding difficulties in a preterm infant are more likely to result from a coordination defect between swallowing and breathing than from sucking–swallowing interaction. During nutritive sucking, the newborn swallows during apnea, preferentially at the beginning of the inspiratory phase or at the end of expiration, at low lung volume. However, during the first oral feeding experiments, it can also swallow at the end of inspiration/beginning of expiration or during the inspiratory phase. After 12 months, a swallowing pattern similar to that of an adult is most frequent: a swallow followed by expiration.

2.1.3 Airway-Protective Reflexes

Protection of the airway during swallow is a reflexive, multilevel function consisting of the apposition of the epiglottis and aryepiglottic folds and the adduction of the false and true vocal folds. The fetus is in an all-aqueous environment and can swallow and inhale amniotic fluid. For the newborn, the challenge is to defend the airways from aspiration of liquid during feeding. Laryngeal chemoreflex includes reflexes such as startle, rapid swallowing, apnea, laryngeal constriction, hypertension, and bradycardia. Water or acidic liquids in contact with the laryngeal epithelium trigger these reflexes. The receptors involved are concentrated in the interarytenoid cleft, at the entrance of the larynx. Laryngeal chemoreflex can cause prolonged apnea in infants. But these responses are functional: swallowing removing fluid from the laryngopharyngeal airway and vocal chord constriction combined with apnea preventing aspiration (Thach 2008). As the infant matures, rapid swallowing and apnea become much less pronounced, whereas cough arousal and possibly laryngeal constriction become more prominent. These changes result from the maturation of the central processing of afferent stimuli rather than reduction of sensitivity.

2.1.4 Central Control

The neuromotor function of the child depends on the stages of motor control maturation. At birth, up to 6 weeks before and 6 weeks after the term of 40 weeks' GA, infant motricity is under brainstem control without suprabulbar input. At this stage feeding is reflexive. The functional development of the central nervous system progresses in an ascending way. The synaptogenesis begins around 6–8 weeks' GA. The development of dendrites and synaptic connections is a dynamic process whose maximum development occurs postnatally. The body structure of the neuronal circuitry is more dependent on the movements themselves than on the genetic program (Lagercrantz and Ringstedt 2001; Hanson and Landmesser 2004).

The wiring of the precise neural circuits seems to be dependent on neuronal activity, which could be stimulated either by sensory input or endogenously driven activity. The fetal swallowing movements will thus play a main role in the organization of specific neural pathways. Conversely sucking–swallowing disorders will have a negative effect on the good development of these circuits. As feeding development progresses, basic brainstem-mediated responses come under voluntary control through the process of encephalization, up to 2 years, going down from the cortex to the spinal cord. The sensory feedback of the gustatory and somatoesthesic stimulations gradually modulates the central patterning of lapping, sucking, swallowing, and chewing.

In summary, the neurophysiological control of feeding and swallowing is complex and involves sensory afferent nerve fibers, motor efferent fibers, paired brainstem swallowing centers, and suprabulbar neural input. Close integration of sensory and motor functions is essential to the development of normal feeding skills. Feeding development, however, depends on structural integrity and neurological maturation. It is a learned progression of behaviors. This learning is heavily influenced by oral sensation, motor development, and experiential opportunities. Finally, the basic physiologic complexity of feeding is compounded by individual temperament, interpersonal relationships, environmental influences, and culture.

2.1.5 The Maturation of the Digestive Tract

The neuromuscular development of the gastrointestinal tract appears relatively early during the gestational period, but the ontogeny of the peristaltic coordination depends on digestive tract segments (Dumont and Rudolph 1994). The three esophageal portions do not have same

maturation. In the median portion of the esophagus, the proximal part of the smooth musculature is acquired well before term. On the other hand, the peristalsis in the two other areas remains variable in half of swallows at full term if there are no disorders (Staiano et al. 2007). Two types of esophageal peristalsis have been described during the neonatal period (Gupta et al. 2009). The first one is initiated during swallowing, transferring the bolus from the pharynx through a relaxed upper esophageal sphincter into the esophageal segments. This primary peristalsis on the level of the striated muscles is under the control of central pattern generators, whereas for the smooth musculature it depends on interactions between central and peripheral neurological control mechanisms. The presence of this primary peristalsis has been observed as early as 32 weeks' GA in the fetus. The secondary peristalsis is described like an adaptation reflex to the esophageal distension. It is under the control of the vagus nerve. This peristalsis has also been described as early as 32 weeks' GA.

2.1.6 Postural Control

The full-term newborn without a disorder is in discreetly asymmetrical flexion. This passive tonicity associated with the primary reflexes (rooting, grasping) permits the newborn to remain fixed at the breast, thus allowing it to have an effective food catch (Radzyminski 2005). The ability to control the head position is also important in the first few days of life. In the study of Radzyminski (2005), letdown was significantly related to active tone. This is interpreted like an active tonicity allowing the baby to comprehend the exterior surroundings and thus to better manage its feeding with the maternal breast.

2.1.7 Neuroendocrine Control

The presence of an effective sucking–swallowing pattern after birth plays a main role in the feeding of the infant. Several hormones have been described as being fundamental in this control: leptin, already known as an orexigenic hormone, and more recently oxytocin. Schaller et al. (2010) showed the effectiveness of oxytocin in the treatment of feeding disorders in the Magel2-defective mouse (animal model of Prader–Willi syndrome). They hypothesized that oxytocin could be used to treat impaired feeding onset in the newborn.

The maintenance of energy homeostasis requires a balance between intake and expenditure. The alternation of hunger and satiety plays an important role in the regulation of food intake. Smith and Ferguson (2008) have well described the neurophysiology of hunger and satiety, which are regulated by complex central nervous system circuitries. Central feeding circuits are localized in hypothalamic nuclei which communicate with each other and project to an area in the brainstem. The regulation is under the control of hormonal and neural feedback. Gastrointestinal and gustatory feedback are the primary controls of ingestive behavior (Smith and Ferguson 2008).

2.2 From 2 Months to 2 Years

The child's swallowing abilities progress with its neuromotor development (Hedberg et al. 2005). This long period of sensorimotor acquisition, named encephalization time, follows the evolution of the corticobulbar tracts. The reflex becomes a voluntary gesture, then automatic motion. Suckling, tongue motions in an anteroposterior direction, corresponds to the abilities of the 6-month-old infant. The bending axial posture evolves gradually from the supine position to the sitting station. The jaw movement is then free, allowing the acquisition of sucking, upright movement of the tongue. Suckling and sucking are combined between 6 and 12 months. They form the bolus control in the oral cavity preceding chewing. The child evolves from a gross to an increasingly fine motricity, alternative pressure preceding malaxation then chewing. At 2 years, the phase of oral preparation starts to be in place (Table 2).

Table 2 Neuromotor development in an infant

Age	Oral sensorimotor function for feeding	Oral structure	Neuromotor skills	Cognitive and communication skills
1st month	Suckling < latching Incomplete lip closure Nasal respiration Unable to release nipple	Tongue fills oral cavity Relatively small mandible No distinct oropharynx Larynx high in neck	Rooting and grasping reflex Hands flexed across chest during feeding Asymmetrical flexion	Facial expression of fear or pain Differentiates vocal voice from other sounds Recognizes parents' voices
2nd month	Suckling with active lip movement > latching Range of movement for jaw Lip closure improved		Letdown Able to control head position VD: Asymmetrical position DD: Lifts head up at	Smile answer Fixes gaze on an object and follows moving ones too Start of labial consonant and [r]
3rd to 4th month	Introduction of spoon, but nipple feeds only Dissociation of movements of lips and tongue Effective and voluntary control of mouth	Chin tuck does not occur until this time	No more grasping reflex Midline orientation VD: Lifts chest and head up DD: Extended and flexed movements of legs	Incites smile Vocal plays and imitates vocalizations and clicks as "fish sound" and tongue clicks Blows bubbles with saliva
5th to 6th month (transition to feeding by spoon)	Sucking, but suckling pattern prominent Start of weaning Gag reflex on new textures Tongue reversal after spoon removal Teething	Growth of neck Larynx goes down in neck Rhinopharynx closed during swallowing	Can likely roll over Bears weight on its leg Able to sit with support Pulls itself up to a sitting position Holds on to a rattle	Perceives itself as different from its mother Smiles to its image in a mirror
7th to 9th month (cup drinking)	Coordinated lip, tongue, and jaw movements Movement of lateral tongue over solids Gag reflex becomes protective		Sits without support Bounces, pulls itself up, and crawls Mouth used to investigate the environment	Afraid of strangers Jabbers and imitates sounds Waves bye-bye Points
10th to 12th month	Self finger feeding Start of chewing, control of sustained bite Closes lips on spoon and uses them to remove food from the spoon	Tongue posteriorization Growth of vocal tract	Stand holding on to things First steps	Intonational jabber and first words Able to understand simple commands
13th to 18th month	All texture taken Well-coordinated swallowing and breathing Lateral tongue motion Straw drinking		Walk acquired Climb up and down the stairs	Well-coordinated phonation Associates words, simple sentences Emotional instability: Impatient, frustrated when it cannot communicate
19th to 24th month	Swallows with lip closure Up–down tongue movements precise Rotary chewing Independent feeding		Runs and jumps Shoots at balloon Climbs more surely Less likely to fall	Marked equilibrium, added maturity, and calm Symbolic plays Stock lexicon of 200 words, first sentences

Adapted from Arvedson and Brodsky (2001)
VD ventral decubitus, *DD* dorsal decubitus, < less than, > more than

3 Etiologies in Children

Any obstacle in the evolution and the development of this set of complex processes can cause swallowing, feeding, and speech disorders. It is necessary to distinguish sucking–swallowing disorders in the neonatal period from feeding behavior disorders in a young child. Neonatal sucking–swallowing disorders, considering them according to the level of trouble, can be classified from the central nervous system to the peripheral nervous system (Fig. 1). The various impairments can be morphological, functional, or induced by enteral feeding, for example.

3.1 Suprabulbar Lesions

Between the basal nuclei and frontal cortex, the causes are classified as encephalopathy, congenital malformations, perinatal stroke, or asphyxia.

3.1.1 Encephalopathy

(a) Neonatal encephalopathy: Risk factors are maternal thyroid disorders, and placental anomalies more than neonatal asphyxia (Badawi et al. 2005; Nelson 2005). Neuroprotective treatments such as hypothermia would appreciably decrease the risks in newborns suffering from moderate neonatal encephalopathy (Gluckman et al. 2005).

(b) Degenerative encephalopathy: Mucopolysaccharidosis, epileptic encephalopathy, and leukodystrophy.

3.1.2 Congenital Malformations

Gyration abnormalities and agenesis of corpus callosum and of vermis cerebellum are congenital malformations.

3.1.3 Perinatal Stroke or Asphyxia

In the case of cerebral palsy, the prognosis depends on the existence of associated neonatal encephalopathy (Badawi et al. 2005). Most perinatal strokes are not diagnosed during the neonatal period. It is necessary to think of stroke and perform neuroradiological investigations when neurological signs or dysphagia arise during the first few months after birth (Wu et al. 2004).

For Armstrong-Wells et al. (2009), neonatal encephalopathy and seizure are the clinical criteria of symptomatic perinatal stroke. In a study done between 1993 and 2003, of 323, 532 births, they found a prevalence of 6.2 per 100,000 infants.

3.2 Bulbar Lesions

Bulbar lesions cause neonatal sucking–swallowing disorders. They can be classified as follows.

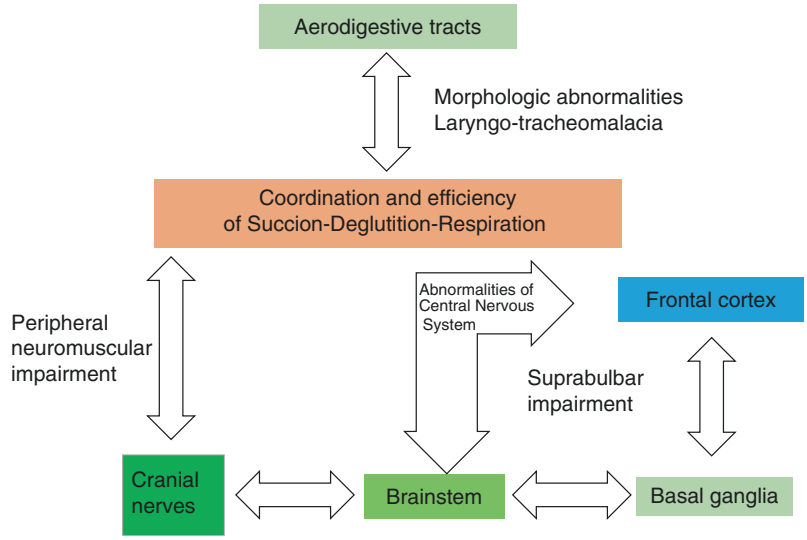

Fig. 1 Summary of various injuries

3.2.1 Neonatal Dysfunctions of the Brainstem

These cause sucking–swallowing–breathing disorders, glossopharyngolaryngoesophageal dysmotricity, and heart rate dysregulation. Neonatal dysfunctions of the brainstem were initially described in children with Pierre Robin syndrome. The metameric organization of the rhombencephalon explains facial malformations associated with failure of cranial nerves (Fig. 2). Moreover, lack of fetal sucking increases the facial dysmorphism observed, such as glossoptosis, microretrognathia, and ogival cleft palate. Other dysfunctions are involved in known genetic syndromes such as Möbius syndrome (agenesis of nerves VI and VII) and Goldenhar syndrome (oculoauricular dysplasia usually affecting one side of the face with microtia and a missing eye).

Sometimes the clinical presentation is not complete "para Robin," with the dysfunction of the brainstem being without palatal anomalies but with typical facial characteristics according to genetic syndromes such as DiGeorge syndrome, microdeletion of chromosome 22 (de Lonlay-Debeney et al. 1997), Kabuki syndrome, and Noonan syndrome, characterized by early eating disorders and a break in the growth curve. Finally, children with CHARGE syndrome (coloboma, heart malformation, atresia of choanae, retarded growth and development, genital hypoplasia, and ear abnormalities or deafness) have durable and complex feeding difficulties. Cranial nerve dysfunction impacts feeding development with weak sucking/chewing, swallowing difficulty, gastroesophageal reflux (GER), and aspiration (Dobbelsteyn et al. 2008).

3.2.2 Clastic

These lesions cause antenatal or perinatal anoxic ischemia of the brainstem.

3.2.3 Malformative

The lesions are visible on MRI and can cause olivopontocerebellar impairments or posterior fossa atrophy. They can cause Arnold–Chiari

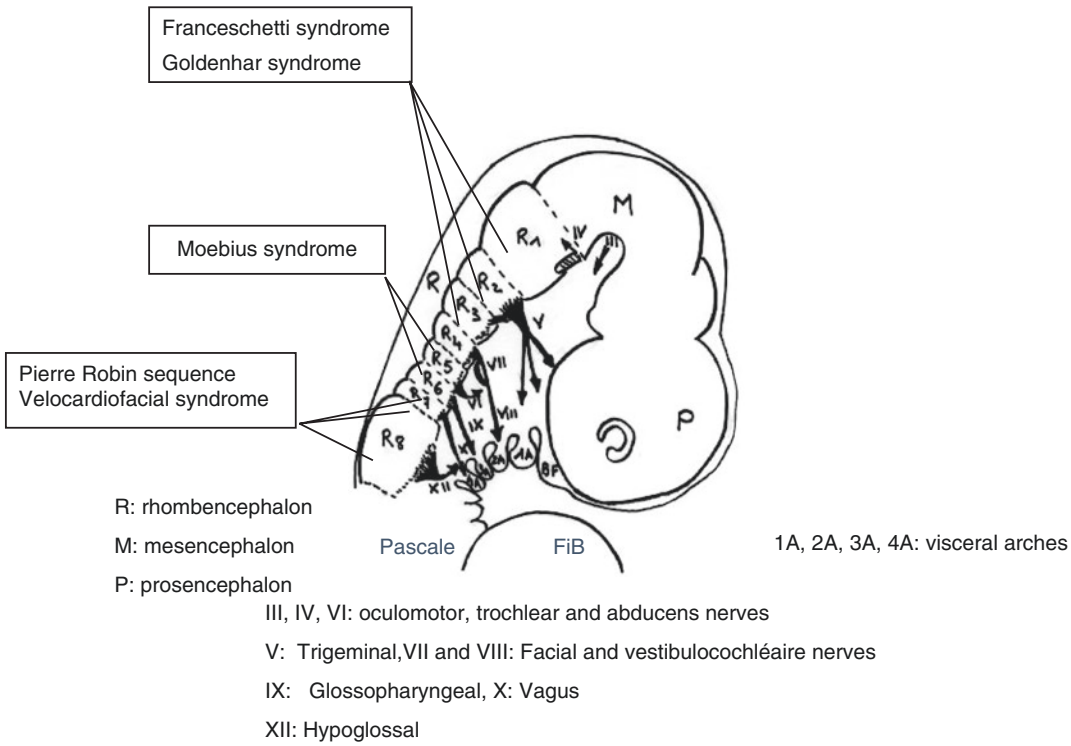

Fig. 2 Rhombomere diagram and cellular emergence of branchial nerves. (From Abadie et al. 1996)

syndrome, occipitocervical malformations (Albert et al. 2010), or Dandy–Walker syndrome, cystic dilatation of the fourth ventricle.

3.3 Peripheral Causes

3.3.1 Neuromuscular Junction or Muscle Impairment

They are often hereditary as in the myotonia of Steinert, or motor and sensory neuropathy.

3.3.2 Upper Respiratory Tract Disease

These diseases contribute to swallowing and breathing disorders. They include laryngotracheomalacia, diastema, and exceptionally laryngeal rhabdomyosarcoma of the larynx (Ferlito et al. 1999). In the case of laryngomalacia, laryngeal tone and sensorimotor integrative function of the larynx are altered (Thompson 2007). Thompson (2007) underlines the worsening role of GER, neurological disorders, and a low Apgar score.

3.3.3 Motility Disorders of the Digestive Tract

(a) GER is often incriminated. An increase of gastric liquid in the esophagus is frequent in healthy children. It is the consequence of anatomical characteristics (reduced length of the diaphragmatic portion and low capacity of the esophagus), diet (exclusively liquid feeding), position (mostly supine position). However, if pharyngitis is associated with inflammation of the esophagus or worse acid aspiration, this GER becomes pathological. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition have published guidelines for evaluation and management of GER (Vandenplas et al. 2009). The reflux is associated with upper airway symptoms in children. But from a review of the literature, the correlation and the risk of upper airway symptoms attributable to GER are difficult to determine (Rosbe et al. 2003). However, the presence of laryngopharyngeal reflux and respiratory symptoms may indicate the need for antireflux therapy (May et al. 2011).

(b) Esophageal transit disorders: A defect of contraction, an esophageal dyskinesia, a faulty upper esophageal sphincter relaxation, or a desynchronization of opening can be the origin of swallowing disorders with aspirations. An esophageal atresia is to be searched for in a systematic way. It is frequently associated with a tracheoesophageal fistula. Esophageal atresia and tracheoesophageal fistula are congenital malformations that occur in one in 3500 births. The association is a multifactorial complex disease that involves genetic and environmental factors (de Jong et al. 2010).

(c) Finally, a delay in gastric emptying can support backward flows and can impact on hunger–satiety balance.

3.3.4 All Morphologic Abnormalities from the Oral Cavity to the Stomach

Oropharyngeal lymphangiomas, cysts of the tongue, and facial clefts can be observed in the upper aerodigestive tract. At the level of the esophagus and stomach, one can encounter tracheoesophageal fistulas, esophageal atresia, and stricture (Castilloux et al. 2010; Till et al. 2008; Prasse and Kikano 2009). Microgastria, which will require exclusively enteral feeding, can also have long-term repercussions for the sensorimotor development of the aerodigestive tract.

3.3.5 Food Allergy and Sucking–Swallowing Disorders

These are encountered in an exceptional way as recalled by Abadie (2008). However, in the older child some can be the origin of eosinophilic esophagitis inducing vomiting and food blocking (Abu-Sultaneh et al. 2010).

3.3.6 Induced Causes

These are multifactorial complex diseases involving environmental factors and consequences of the initial pathology. They follow from the lack of

neonatal oral experimentation, with the traumatizing effect on the aerodigestive tract from suction probes, intubation, and an enteral feeding tube. Moreover, the mode of continuous enteral feeding or exclusive parenteral feeding will have noxious effects on the acquisition of pace by the child and in particular that of hunger–satiety. Finally, major disturbances in the link between the mother and child with an often traumatizing birth, an obligatory more or less long separation, and the impossibility for the mother to play her life-sustaining part are worsening factors. This is why most dysphagic infants had difficult perinatal antecedents, including prematurity (Salinas-Valdebenito et al. 2010).

3.4 The Young Dysphagic Child

All the causes previously mentioned can be encountered as can anorexia and feeding disorders as described in the following sections.

3.4.1 The Common Anorexia of Opposition in the Second Half of the Year

Anorexia arises in the first 3 years of life, most commonly between the ages of 9 and 18 months, as infants become more autonomous and make the transition to spoon feeding and self-feeding. The following are often found to have occurred: a traumatic event, aspiration during a mouthful, an infectious episode, especially as it required hospitalization, and a change in the child's life and its relationship with its mother (e.g., family death). The meal time is then marked by anxiety, the child is opposed to any attempt at spoon feeding, whereas often a feeding bottle is accepted just as drinking from a glass. The lack of interest in food contrasts with strong interest in exploration and interaction with caregivers. The child remains joyful, plays, and stays awake.

3.4.2 Severe Form of Infantile Anorexia

Children with infantile anorexia have an anxious neurosis, depression, or even maternal deprivation. The baby can only express its suffering through its body. Food refusal is accompanied by other signs, such as loss of contact, avoidance, irritability, sleep disorders, vomiting, and ruminations, which will worsen nutritional repercussions (Thouvenin et al. 2005). Failure to thrive is often associated with poorer cognitive development, learning disabilities, and long-term behavioral problems. Chatoor et al. (2004) described the importance of distinguishing between nonorganic forms of growth deficiency related to maternal neglect and growth deficiency that is related to dyadic conflict during feeding. They suggested that the concern for the nutritional needs has to be balanced with the management of feeding difficulties in young children.

3.4.3 Autism Spectrum Disorders

Although not revealing, anorexia or another feeding disorder is very frequently encountered in invading neurobehavioral alterations (Nicholls and Bryant-Waugh 2009).

3.4.4 Feeding Disorders

These involve problems in a range of eating activities that may or may not be accompanied by swallowing difficulties. These disorders may be characterized by disruptive mealtime behavior, rigid food preference, or food refusal:

(a) Pick eating: One can think of this as a child cherry picker who selects and eats only very modest amounts. There is no attachment disorder and the nutritional repercussion remains mild.
(b) Food phobias with behavior disorder: Selection of a color or an exclusive consistency, or the need to sniff at food before putting it in the mouth. They can also be the expression of an infantile neurosis beginner.
(c) Pica: Children who swallow in addition to foodstuffs nonnutritive substances such as stones and paper. This feature can be seen in a specific way between the ages of 9 and 12 months, and is then not pathological. On the other hand, it becomes abnormal if it continues, and is often associated with backwardness or behavior disorders in certain genetic syndromes such as Prader–Willi syndrome and also in autism spectrum disorders.

3.4.5 The Dyspraxia of Feeding

This is encountered in children with specific language impairments, oromotor dyspraxia, and during meals, difficulties in bolus formation.

Tongue movement and chewing are limited. The child is described as a whole-food swallower when given mixed textures.

4 Assessment and Treatment of the Child with Swallowing Disorders

Diagnosis and treatment will be different if it concerns a newborn in a neonatology intensive care unit or a young child having already experienced oral feeding.

In the first case, it is necessary to be able to answer three main questions:

1. When should oral feeding be proposed?
2. What stimulations support a good maturation of oromotor abilities?
3. How can the functional consequences for food and verbal acquirements be avoided?

For the young dysphagic child, there will also be an etiologic diagnosis of the disorder, and an analysis of its consequences for feeding, hydration, and nutrition and the pulmonary repercussions. The evaluation must be able to inform about:

- The symptoms of the disorder and its evolution
- Whether or not there is an association with other dysfunctions and integration in a neurological or syndromic clinical presentation
- The somatic and psychogenic part of the feeding disorder (Abadie 2004).

4.1 The Premature Baby and the Infant in the Neonatology Service

The realization of the noxious effect of unfavorable surroundings on the morbidity of premature babies led to the installation of a newborn individualized developmental care and assessment program (NIDCAP) in most neonatology intensive care units. This program aims at limiting stress by controlling the extraneous auditory, visual, vestibular, and tactile stimulations. It is achieved by putting the child in the fetal position with a soft application, with supporting presence of the two parents (mini isolated rooms). Its positive effects in the short- and long term were objectified by many studies (McAnulty et al. 2009; Symington and Pinelli 2001; Ullenhag et al. 2009).

The premature baby is deprived of sensory stimulations normally tested by the fetus during the third quarter of pregnancy. They are replaced by noxious stimulations in the form of probe introductions such as intubation, suction, or enteral feeding tubes. To propose early positive stimulations of the oral sphere seems to be essential, as mentioned by Lapillonne (2010), but which ones can be proposed? Promoting breastfeeding as soon as it is possible seems to be most suitable for premature babies. It is necessary, however, that the preterm infant has the capacity to manage this. Acquiring a safe and efficient swallow and the capacity for oral feeding of infants in neonatology intensive care units are some of the prerequisites for the reduction of the consequences of the hospitalization. Safe swallowing is conditioned by sucking–swallowing–breathing coordination avoiding aspirations while allowing proper ventilation.

For the preterm infant, the principal difficulty is the integration of breathing in an already delicate sucking–swallowing pattern. Moreover, the respiratory condition is often precarious especially if it is associated with bronchodysplasia. Gewolb and Vice (2006) compared two cohorts of infants born between 26 and 33 weeks' GA. In the group with bronchodysplasia, they found a clear immaturity of acquisition and a greater incoordination of sucking, swallowing, and breathing.

The second difficulty is for the weary baby feed efficiently in a short time (about 20 min and no more than 30 min). Indeed the purpose is to feed so that the infant consumes sufficient volumes to gain weight appropriately. The transition from tube to oral feeding in the preterm infant depends on the teams. For some, any premature baby can manage the transition even for very tiny quantities. This is used in the "Kangaroo Mother Care", a continuous skin to skin contact, which includes thermal care, supports for breastfeeding and for early recognition and response to illness. The ability to make the transition from gavage to oral feeding depends on neurodevelopmental status, which is related to behavioral organization, cardiorespiratory regulation, and the ability to produce a rhythmic

sucking–swallowing–breath pattern (Delaney and Arvedson 2008). The readiness of the infant for oral feeding may differ (Nyqvist et al. 2001; Delaney and Arvedson 2008; Lau et al. 2000).

4.1.1 The Different Means of Evaluation

(a) Morbidity assessment: This involves the awareness of the general state of the child according to the neonatal medical index, which has five stages, stage 1 being a baby without an intercurrent medical problem and stage 5 concerning serious complications. The birth weight and not the term are also part of the score. Delaney and Arvedson (2008) mentioned that it is important to differentiate "premature by date" from "premature by weight," for which the latter already has an important perinatal morbidity.

(b) Behavioral assessment: According to the NIDCAP, the reactions of premature babies can be staged in keeping with five behavioral subsystems: autonomic, motor, state regulation, attention, and self-regulation or regulatory system. Assessment of the infant's current functional competence and state of equilibrium determines if it is possible or not to propose oral feeding or oral stimulations. The infant must be either calm, awake, and in a stable cardiorespiratory state.

(c) Sucking behavior assessment: Some authors have linked oral feeding abilities with an effective nonnutritive sucking (Pinelli and Symington 2001). Others have shown that it is the oral feeding experimentation which improves the sucking capacities (Pickler et al. 2006). During nutritive sucking, two patterns exist, a continuous sucking and an intermittent sucking stopped by breathing. The continuous sucking, which is more common at the beginning of feeding, represents a long single sucking burst. Sucking does not automatically initiate swallowing. The preterm infant which has a respiratory rate from 40 to 60 inspirations per minute cannot have too frequent swallowing under penalty of interference with breathing. In a study of 88 preterm infants, Pickler et al. (2006) noted that experience in oral feeding may result in rapider maturation of sucking characteristics, increasing very quickly the numbers of sucks, sucking bursts, and the sucking rhythm. For them it is especially the infant's level of arousal and the neonatal medical index which will condition the possibilities of oral feeding, more than the capacities for sucking–swallowing–breathing coordination. Other authors prefer proposing oral feeding only when sucking–swallowing and breathing are well coordinated (Delaney and Arvedson 2008; Lau 2007).

For breastfed infants, Nyqvist et al. (1996) proposed an assessment using the preterm infant breastfeeding behavior scale. This scale evaluates the reflex activities (rooting, grasping), sucking, and swallowing. It also considers the number of sucks and sucking bursts. It considers, under the term "behavior," the awakening of the child, the influence of the surroundings, and the maternal behavior. Thoyre et al. (2005) described a method based on the assessment of early feeding ability of preterm infants. The ability is evaluated according to 36 items gathered in three domains: oral feeding readiness, oral feeding skills, and oral feeding recovery. The items require yes/no answers or rankings from 1 to 4 (Table 3).

(d) Surface electromyography. This is a noninvasive objective method for evaluating the muscle activity during oral feeding. Nyqvist (2008) recommends coupling it with observation of mouthing and sucking bursts and the trains of sucks to evaluate the infant's competencies during breastfeeding. The electrodes in this study were placed on orofacial muscles (orbicular, mylohioid, geniohyoid, stylohyoid, and digastric) and on pharyngeal muscles. Gomes et al. (2009) in a review of the literature underlined the significant role of the masseter muscle during breastfeeding. The feeding bottle was not tested in this study.

4.1.2 Management

(a) To support nonnutritive sucking: The observation that babies intubated orally maintained their sucking capacity and even sucked the intubation tube led many neonatology intensive care units to propose in a quasisystematic way the use of a pacifier (Delaney

Table 3 Oral feeding readiness, skill, and recovery—example of items (Thoyre et al. 2005)

Oral feeding readiness				
Able to hold body in a flexed position with arms/hands toward midline	Yes	No		
Demonstrates energy for feeding, maintains muscle tone and body flexion through assessment period	Yes	No		
Oral feeding skill				
Ability to remain engaged in feeding				
Predominant muscle tone	Maintains flexed body position with arms toward midline	Inconsistent tone, variable muscle tone	Some tone consistently felt, but somewhat hypotonic	Little or no tone felt; flaccid, limp most of the time
Ability to organize oral–motor functioning				
Opens mouth promptly when lips are stroked at feeding onsets	All	Most	Some	None
Once feeding is under way, maintains a smooth rhythmic pattern of sucking				
Ability to coordinate swallowing and breathing				
Able to engage in long sucking bursts (7–10 sucks) without behavioral stress signs or an adverse or negative cardiorespiratory response				
Ability to maintain physiologic stability				
In the first 30 s after each feeding onset, oxygen saturation is stable, and behavioral stress cues absent				
Stops to breathe before behavioral stress cues appear				
Clear breath sounds; no grunting breath sounds (prolonging the exhale, partially closing glottis on exhale)				
Oral feeding recovery (during the first 5 min after feeding)				
Predominant state	Quiet alert	Drowsy	Sleep	Fuss/cry

and Arvedson 2008). Nonnutritive sucking is a motor reflex activity which will make it possible to improve the capacity to control and coordinate nutritive sucking. A pacifier is proposed for any premature infant of more than 28 weeks' GA.

(b) To treat the infant by taking account of its level of vigilance of its physiological state of stability or instability according to the NIDCAP: The infant is allowed to regain the quiet state by keeping it in a flexed position during the transfer time and bringing its hands back to the middle of the body near the mouth to help the self-regulation. The infant should be calm before nutritive sucking is attempted. Clinicians and caregivers have to structure and adapt the care and interaction to enhance the infant's own competencies and strengths, to prevent the infant being in pain, stress, or discomfort.

(c) To facilitate oral feeding: Many authors think that the systematic proposal of breastfeeding or bottle feeding is the most effective stimulation and that other sensitive stimulations are not necessary (Thoyre et al. 2005; Pieltain et al. 2007; Nyqvist 2008; Ullenhag et al. 2009). Facilitating means to mitigate the inefficiency of sucking having been proposed such as the feeding cup or using soft or perforated pacifiers. It is then necessary to be wary of too fast a flow, which may incur risks of inhaling and shock. This is why Lau and Schanler (2000) advise the use of a "vacuum-free bottle." For them, self-paced milk flow

seems the technique most suitable for use with preterm infants. Delaney and Arvedson (2008) described the transition between enteral and oral feeding as difficult for the preterm infants of less than 32 weeks' GA because of neurological immaturity and cardiorespiratory instability.

(d) To complement feeding by parenteral feeding: Pieltain et al. (2007) described the importance of early efficient feeding, as in the first few days of life, in low-weight premature infants. This is "aggressive feeding," i.e., rich in protein. The high proteinic contribution makes it possible to preserve the low weight of these infants and to limit their insulin resistance. Lapillonne (2010) prefers the term "optimal feeding." The aims of preterm management are multiple and are to improve the growth and its quality, to preserve the cerebral, neurosensory, and pulmonary development, and to mitigate digestive diseases dominated by ulceronecrotizing enterocolitis and GER disease.

Oral feeding, because of great neuromotor immaturity, often causes stress and increases the state of agitation and suffering of these fragile babies. In all cases, early clinical assessment and management of sucking–swallowing is one of the priorities. In this way, the long-term complications could be decreased as described by Buswell et al. (2009) in a cohort of preterm infants whose food functions were evaluated at 10 months of corrected age.

4.2 The Young Child

Assessment of infants and children with dysphagia and feeding disorders involves an interdisciplinary evaluation (Arvedson 2008). These disorders are multidetermined and need a multiaxial diagnosis. The interdisciplinary feeding/swallowing team approach allows optimal management decisions and understanding of health conditions and specific issues (Arvedson 2008). The parents are imperatively involved and so are the child's caregivers. The anamnesis locates the disorder in the family context and the setting of the meal. Knowledge of the oral history of the child is essential to specify the origin of the disorder in its food and neurophysiological development.

When should a specific evaluation be requested? It will be systematic when personal autonomy during meals is impossible; this is the case for children with cerebral palsy or multiple disabilities. It is also the case for young patients with a disease with a high risk of feeding and swallowing disorders, e.g., in a genetic syndrome and in brainstem or cerebellum impairments.

A specific evaluation is necessary when the duration of feeding is abnormally prolonged, when mealtimes are stressful, and when there is increasing irritability of the child or on the contrary lethargy.

Food refusal might be diagnosed if there is any somatic cause.

Finally, vomiting, nasal food reflux, respiratory signs during or after meals, and frequent bronchopulmonary infections must also alert the physician to the need for a specific evaluation.

One is frequently confronted with a child who either does not chew or does not accept pieces of food during food diversification.

How should the child be approached? From 0 to 2 years, it is necessary for the child to be closest to its usual situation. The friendly evaluation takes place during a meal or in a play context: grimaces resulting from mouth and vocal plays, linguistic situations adapted to its developmental age.

After 2 years, it is then possible to perform a morphological and dynamic evaluation of the child's oral functions and its swallowing, but before an examination of the mouth is undertaken, the child must have confidence in the physician.

4.2.1 Assessment Process

The assessment of infants or children with signs of feeding or swallowing disorders includes first the anamnesis reviewing family, medical, developmental, and feeding history and then physical examination and swallowing evaluation. In some cases other diagnostic tests may be required:

1. The anamnesis: The findings of interviews of parents, medical and educational professionals, and caregivers specify the reason for the evaluation, the complaints, and the repercussions of the disorder. The taking of the anamnesis appreciates the medical and psychological context.
   (a) Grounds for evaluation: The most frequent difficulty for infants is a sucking–swallowing incoordination noticed by parents or caregivers. Bottle feeding or breastfeeding is slow and hard, often interrupted by the child crying. This also applies to weak suction, the baby sucking with difficulty and often stopping. A long period of apnea during feeding can be observed too. This is more alarming if all these signs are associated with hypoxia and bradycardia, implying oral feeding should be stopped. Oral or nasal regurgitations as well as episodes of cough at the time of the meals are often signs of a protective reflex from aspiration. Less specific signs are food refusal and prolonged feeding duration. Slow weight gain or worse weight loss is often one of the signs of the nutritional repercussion of a swallowing disorder. This evaluation may also be required to survey a disease with a risk of swallowing disorders such as a Pierre Robin sequence or cerebral palsy. Finally, the occurrence of repeated bronchopulmonary infections or severe asthma should lead one to suspect the existence of chronic aspiration.
   (b) The feeding history summarizes the main steps and in particular weaning and specifies on which consistencies the disorder depends, its degree of severity, and its constancy with time. It also reflects the parents' difficulties to feed their child.

Assessment of the impact of feeding defines the consistencies given to the child and specifies for liquids if they should be water, milk, and fruit juice and for pasty consistencies if they should be compotes or dairy produce. Does the child take semisolid foods such as blank or rice pudding? Does it accept soft solids (fruit cocktail) or tough solids (cookies and meats)? The symptoms, medical context, and evolution of the disorder are correlated with the oral-food trainings. The functional repercussion on the feeding makes it possible to envisage the upcoming risks. Limme (2011) stressed the importance of food diversification in the development of the masticatory function. This will allow the harmonious growth of the jawbones and the dentoalveolar structures.

It is also important to specify if it is or was necessary to resort to enteral, parenteral, or ancillary feeding

2. Medical and developmental history can yield possible clues to the causes of dysphagia, in particularly prenatal birth, a genetic syndrome, and a neonatal accident.
   (a) Physical examination: As Arvedson (2008) says, this is the prefeeding assessment.
      - Assessment of nutritional impact notes the somatic growth patterns, in particular weight, height, and body mass index curves as well as the occipital frontal circumference and thoracic circumference (Lapillonne et al. 2011; Thibault et al. 2010). So recalled by Amiel-Tison (2005), "Increase in the volume of skull is particularly dramatic in the second part of gestation and the first 6 months of the life." A stagnation or a failure of growth is the unquestionable sign of a repercussion on good cerebral development. The thoracic circumference is a notable marker of the nutritional status of the child.
      - Assessment of cardiopulmonary state: For the infant, bronchopulmonary infections and asthma are often markers of the repercussion of the dysphagia. But sometimes they can also be nasopharyngitis blocking the possibility of feeding. Moreover, one cardiopulmonary dyspnea interferes with the synchronization of breathing and swallowing and can be the cause of aspirations. This assessment is made to note deviations from normal expectations, in particularly respiratory patterns such as breathing rate at rest and

during effort. Can the child breathe by nose and by mouth?

- Observation of developmental anomalies directed toward a genetic diagnosis. The developmental anomalies can be an epicanthus for the eyes, a low implantation of the ears or abnormal lobules, or the characteristic form of the upper lip in Prader–Willi syndrome. In the same way, systematic observation is required for anomalies of the palmar folds, hands, feet, fingers, and toes. "Café au lait spots" will suggest a neurofibromatosis.
- Neurodevelopmental examination: A semiological analysis according to the age and the neuromotor skills is essential. It can follow the scale of Amiel-Tison et al. (2005) or the Gesell stages in the revised test of Brunet-Lézine.

The observer notes the child's behavior and its spontaneous motility in resting posture and during interactions with its parents. The observations include the position, movement patterns, asymmetry or the stiffness of posture, response to sensory stimulation, temperament, and self-regulation abilities.

Then the examination of the child is performed in a dual situation, with the child lying on its back until 6 months of age or sitting on the examination bed or on the knees of a parent if it needs further reassurance. The physical examination appreciates axial and segmentary tonicity, proximal and distal muscle strength, and Babkin and jerk reflexes. Finally, the clinician should focus on cranial pairs V, VII, IX, X, and XII.

(b) Oropharyngolaryngeal structure and function assessment

- The oral examination must analyze the anatomical structures, the muscular functions, and symmetry at rest and in movement of the oral cavity and the face. The aspect of the lips, the jaw, the tongue position, and the shape and height of the palate are significant components that should be observed. In the infant, oral reflexes (rooting, gagging) and nonnutritive sucking have to be noted. In general, laryngeal function is noted by voice quality.
- Instrumental evaluation of swallowing: The visualization of oral, pharyngeal, and upper esophageal phases of swallowing is performed with fiber-optic endoscopic evaluation of swallowing and a videofluorosopic swallow study. Arvedson (2008) advocates the use of ultrasonography too. Although ultrasonography is not used routinely, it provides useful data on the temporal relationships between movement patterns of oral and pharyngeal structures in the fetus, infant, and child during swallowing (Miller et al. 2003; Bosma and Hepburn 1990; Fanucci and Cerro 1994).

Fiber-optic endoscopic evaluation of swallowing makes sure there is no morphologic or dynamic abnormality (Hartnick et al. 2000). The attempt to swallow is not always easy before 2 years of age, being dependent on the anatomical characteristics of the pharyngolarynx and the need to keep the rhinopharynx free. However, according to Sitton et al. (2011), it is practicable very early, as early as 3 days of life.

Sitton et al. (2011) propose collecting in a systematic way the outcomes of this analysis by specifying, according to textures, the level of release, and the existence or not of penetration and aspiration. Temporal relationships of the different events and the efficiency of the mechanisms of expulsion are also noticed. It is a useful examination to visualize with the parents the pharyngolaryngeal structures, as well as to define some aspects of pharyngeal swallowing of secretions and food. The objective aspects of swallowing are noticed together, allowing the best following of oral feeding recommendations.

A *videofluoroscopic swallow study* allows visualization of the oropharyngeal and esophageal transit. It can be realized on very young children by respecting a suitable placement (Figs. 3 and 4). The irradiation must obviously be controlled using reduced fields and short periods of radioscopy. The study provides information on the dynamics and the temporality of the various events of swallowing. It permits one to check the postures and adjustments of texture to avoid aspiration and to facilitate oropharyngeal transit.

Fig. 3 Installation during videofluoroscopy

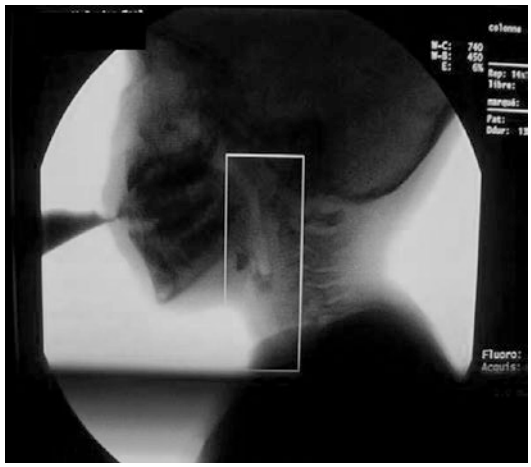

Fig. 4 Installation during videofluoroscopy

In all cases, a functional suction must always be available in case aspiration occurs. In infants, the observer notes the sucking efficiency. The movements of the jaws and the tongue are correlated to the neurodevelopmental level of the child. Pharyngeal time is analyzed as in the adult by considering the synchronization and the efficiency of the protection mechanisms and expulsion in the case of penetration. Arvedson (2008) proposes relating videofluorosopic swallow study findings to various swallowing disorders (Table 4). But it must be remembered that this examination captures only a brief window in time and does not simulate a real meal, and that is why it must be coupled with an observation of a meal.

3. Feeding observation: Observation of the child during meals allows one to collect useful information about eating and drinking (Table 5). Various observation grids can be used, such as the schedule for oral motor assessment (SOMA) (Reilly et al. 1999) and the nursing child assessment feeding scale (ratings of cognitive-growth fostering during meals) (Barnard 1978). The observation of feeding is made with a familiar feeder as typically as would be done with the child at home. The interactions between the parent and the child and positions adopted during feeding are observed. Food consistencies must be varied, starting with those which are usual and best controlled by the child. The child is observed for specific aspects of oral sensorimotor skills and the way of swallowing, in particular if multiple swallows are necessary to clear a single bolus. This feeding observation allows one to adjust the diagnosis and list the necessary adaptations.

(c) Other diagnostic tests are sometimes useful; for example, it is necessary to refer the child to a psychiatrist when the child

Table 4 Videofluorosopic swallow study findings for various swallowing disorders

	Radiographic finding	Possible common swallowing disorder
Bolus formation	Loss of food or liquid from mouth	Loss of lip closure
	Material in anterior sulcus	Loss of lip tension or tone
	Material in lateral sulcus	Loss of buccal tension or tone
	Material pushed out with tongue	Tongue thrust, loss of tongue control
	Limited/immature chewing	Loss of jaw and tongue control
	More than three sucks per swallow	Loss of suck strength or coordination
Oral transit	Searching tongue movements	Apraxia of swallow, loss of oral sensation
	Forward tongue to move bolus	Tongue thrust
	Material remains in anterior sulcus	Loss of lip tone and tongue control
	Material remains in lateral sulcus	Loss of tongue movement or strength
	Material remains on tongue	Loss of tongue movement or strength
	Material remains on hard palate	Loss of tongue strength, or high and narrow palate
	Limited tongue movement	Loss of tongue coordination or disorganized AP movement
	Tongue–palate contact incomplete	Loss of tongue elevation
	Oral transit > 3 s	Delayed oral transit
Pharyngeal phase initiation	Material in valleculae, preinitiation	If brief, no delay in pharyngeal initiation
	Material in piriform sinuses, preinitiation	Delayed pharyngeal initiation
	Material in/on tonsil tissue	Tonsils blocking bolus transit, delayed pharyngeal initiation
	Material on posterior pharyngeal wall	Delayed pharyngeal phase initiation
Pharyngeal phase	Nasopharyngeal backflow/reflux	Loss of velopharyngeal closure or of UES opening
	Penetration to underside of superior part of epiglottis	Incoordination or loss of pharyngeal contraction
	Penetration into airway entrance	Loss of closure of airway entrance
	Residue after swallows in valleculae	Loss of tongue base retraction
	Residue in piriform sinuses	Loss of pharyngeal contractions or of UES opening
	Aspiration before swallow	Delayed pharyngeal swallow initiation
	Aspiration during swallow	Unilateral vocal fold paralysis, incoordination
	Aspiration after swallow	Reduced pharyngeal pressure
	Residue in pharyngeal recesses which may be cleared or not cleared with the next swallow	Loss of tongue base retraction or of pharyngeal contractions or loss of UES opening
Upper esophageal phase	Slow bolus passage through UES	UES prominence, loss of UES opening, reduced pharyngeal pressures may contribute
	Residual on or in UES	Structural abnormality or UES opening
	Retrograde bolus movement from esophagus to pharynx or from the lower to the upper esophagus	Esophageal dysmotility, structural abnormality

Adapted from Arvedson and Lefton-Greif (1998)
AP anteroposterior, *UES* upper esophageal sphincter

Table 5 Examples of observations that may relate to cranial nerve function according to Arvedson and Brodsky (2001)

Cranial nerve	Input	Normal answer	Overdrawn answer
V	Food on the tongue	Chewing	Bolus not formed
VII	Sucking Food on the lower lip Smile	Labial gripping Labial closing Labial retraction	Labial incontinence Limiting or asymmetry of moving Incomplete
IX and X	Bolus into posterior part of the oral chamber	Swallowing reflex initiated in less than 2 s	RDTP or no initiation
XII	Food on the tongue	Refinement of the apex and protrusion	Miss lateral contraction, of rise atrophies

RDTP- Delayed pharyngeal phase initiation

has signs of a feeding disorder more prominent than swallowing disorders. Neurological, cardiopulmonary, and gastrointestinal functions often have to be explored by specialists.

An interdisciplinary approach with professionals across specialities communicating with parents and caregivers is important. This comprehensive assessment has to include the World Health Organization concepts (WHO 2001), involving information related to participation (society level), activities (person level), and impairment (body function level). Management and decisions will be made taking into account:

- Oral sensorimotor and swallowing deficit
- Nutrition status
- Interactions between parents and the child
- Medical and neurodevelopmental status.

4.2.2 Decision Making and Management

At the end of the assessment process, the most important question is: Can this child drink and eat without risk? Then if it can do so, other questions are: What consistencies, what volumes, and what adaptations are possible?

The neurological examination evaluates the central and peripheral tools necessary for oral feeding.

The evaluation of the developmental stage of the child specifies its capacities for training and its oral, feeding, and speech skills.

The oro-facial examination and instrumental swallow examination define the child's physiological swallowing status.

Finally, the examination delineates underlying causes and diagnoses because treatment will differ according to history, current status, and possible evolution.

The different treatment approaches include oral motor exercises, mealtime adaptations, and feeding adaptations:

(a) Oral motor exercises: Active exercises are used to increase strength and endurance and modify muscle tone by inhibiting or eliciting stretch reflex. Slow stretching reduces muscle tone and quick stretching increases it.

Passive exercises are applied to provide sensory input. They may include tapping, vibrations, and massage. They might reduce abnormal oral reflex such as biting reflex or gag reflex.

Sensory applications may be used to enhance a swallow response and to increase closure of the lips.

Arvedson et al. (2010) emphasize that a treatment exercise should closely parallel the desired task and that "age matter" and "time matter" have implications for the timing of intervention. The exercise protocol will depend on the developmental stage and skills of the child.

(b) Mealtime adaptations: The goal is to increase comfort, security, and pleasure. "Successful oral feeding must be measured in quality of meal time experience with best possible skills while not jeopardizing a child functional health status or the parent–child relationship" (Arvedson 2008). The adaptations concern posture and position, adapted equipment (spoons, glass, etc.), and broad adaptations

(quiet conditions, no TV or too much noise, etc.).

(c) Feeding adaptations: These may concern the taste, consistency, texture, and temperature of food and liquid. It is also useful to schedule meals and to respect mealtimes to facilitate hunger. Otherwise, ancillary feeding is sometimes required.

Indications depend on clinical observations: Abadie (2008) proposed the following classification:

- Sucking disorder
- Swallowing disorder
- Velopharyngeal dysfunction
- Ventilation disorder
- Disorder of sucking–swallowing coordination
- Feeding disorder
- Oral dyspraxia.

For the organization of management plans with parents and caregivers, it seems more relevant to us to separate the various disorders encountered into:

- Child who does not know how to; this is like a maturation disorder.
- Child who cannot; this is a secondary disorder.
- Child who does not want to; this is a behavioral disorder.

Specific therapies are as follows:

(a) Child who does not know how to: The child does not know because of a shift of acquisition or impossibility to train the infant in the case of prematurity, dysmaturity, or lack of training. For example, in the case of tracheotomy, the larynx is deprived of sensory stimulation and the coordination of swallowing and respiration can be lost. For enteral feeding, it may be the oral sensorimotor skills that are not trained and the lost of hunger feeling. It is necessary to stimulate the oral sensorimotor skills and psychological maturation. The child has to find again pleasure in suction and the sensation of hunger to avoid refusing food.

(b) Child who cannot: The child cannot do because of a genetic syndrome or malformations. In the foreground are neuromotor disorders, which of are central, peripheral, or muscular origins. According to the lesional level, there might be weak suction or a lack of sucking reflex. Feeding duration is prolonged, often associated with drooling, delayed initiation of pharyngeal swallow, and penetration (Table 5). There can also be craniofacial anomalies with midline defects such as cleft palate or oropharyngeal tumor such as lymphangioblastoma. In this case, the oral phase of swallowing is generally disturbed and may result in airway obstruction, requiring a tracheotomy. Finally, gastrointestinal tract disorders including motility problems may contraindicate oral feeding and sometimes even enteral feeding. Without appropriate stimulations, the child will not be able to perform the necessary experiments for a harmonious oral construction. So it may secondarily have a faulty knowledge skill. The treatment consists in adaptational strategies to counteract the neuromotor dysfunction or anatomical anomalies.

(c) Child who does not want to: The child does not want to eat, or to test other textures or tastes. This is rather a feeding disorder. The child swallows correctly but not for a long time, as if it were very quickly satisfied. The child refuses to continue by clamping its mouth shut and turning its head away when the spoon approaches its mouth. Sometimes it may vomit purposefully. The meal is then stopped. Oral intakes remain insufficient. This may induce fractionation meals which can worsen GER. After 6 months, it is essential in a healthy child to maintain almost 3 h between each meal. In older children, solid food refusal can occur for a variety of reasons, including but not limited to airway or gastrointestinal tract factors, oral sensorimotor deficits, and disordered parent–child interactions. The distinction has to be made between an early feeding problem possibly amenable to education and an entrenched eating disorder requiring systematic diagnosis and treatment. A compartmental therapy is indicated for the child and its parents. Throughout meal sessions, the therapist points out to the parents the behaviors that can reinforce food refusal. As described by Borrero et al. (2010), these can include attention (coaxing, threats, praise, reprimands,

etc.), escape (spoon or drink removal, allowing the child to leave the table), and tangible delivery (switching to a previously consumed food, to a drink following food presentation, etc.). The child trying new textures and tastes during playtime is indicated.

Swallowing and feeding disorders in a child, from sharing the direct impact on the nourishment function of the parents, will have repercussions on the parent–child relationship. A holistic assessment and management of these disorders cannot be done without the collaboration of the parents. This assessment involves considerations of the broad environment, parent–child interactions, and parental concerns. To be interested in dysphagia in children is to consider the child with its difficulties in its family circle and social environment. It is essential to enable the child to progress as well with the eating plan as in its socialization (Fig. 5).

The first support will be psychological support. The part of the interdisciplinary team is very important:

- To explain to the parents the swallowing disorder and the difficulties their child has
- To help them be more confident about their own capacities to manage these difficulties
- To reassure them and to trust in their child's competencies.

Then there will be educational support: they have to learn adaptational strategies, position, and broader-based sensory and motor intervention to facilitate meal and feeding behavior.

5 Summary

To summarize, management of dysphagia in infants is a complex task based on several approaches. Indeed, these disorders affect the safety of children, the psychological balance of parents, and the delay in developmental milestones. Therefore, an interdisciplinary team and recurrent assessments are necessary so as to match the child's development and capacities. The principal aims are to prevent feeding and speech disorders.

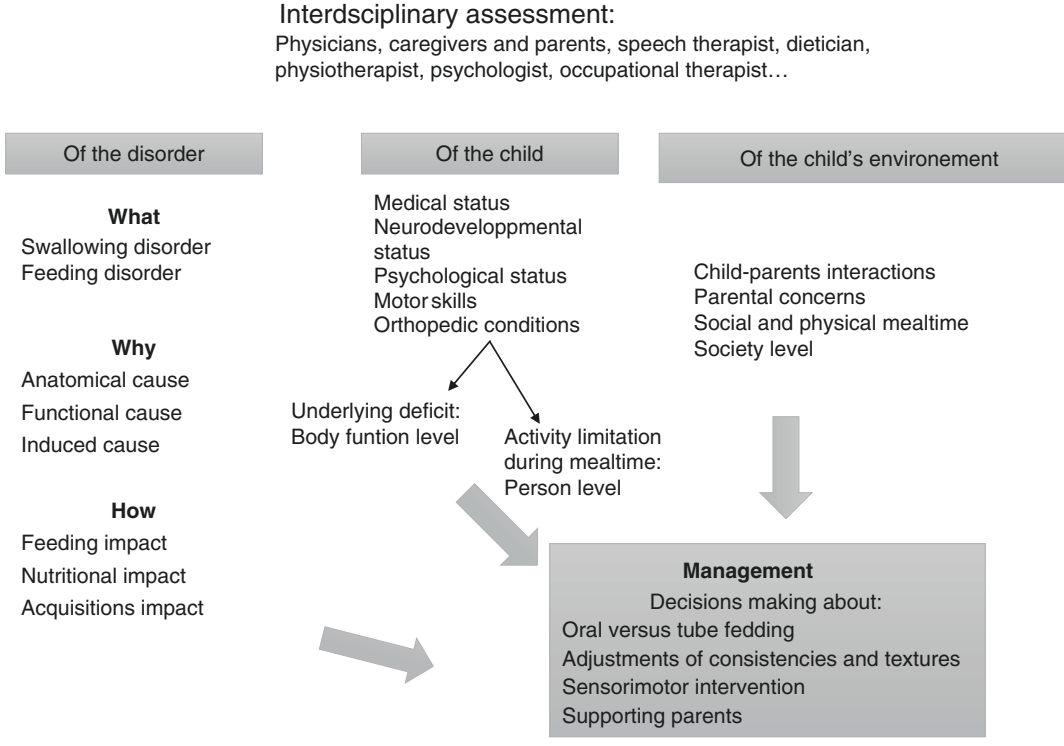

Fig. 5 Decision making

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Dysphagia in Systemic Disease

Thomas Mandl and Olle Ekberg

Contents

Abstract

Systemic disease may result in dysphagia through numerous mechanisms. For example, salivary gland impairment may result in xerostomia, which as well as resulting in painful mucosal blisters and ulcers may impair oral function. Acute or chronic inflammatory processes may result in strictures in the esophagus and/or pharynx. Furthermore, altered biomechanics of oral, pharyngeal, and esophageal musculature may be found in patients with rheumatoid arthritis with cervical spine abnormalities and in patients with scleroderma. Finally, systemic vasculitides involving the central nervous system may result in cortical and brainstem ischemia leading to neurological impairment hampering the swallowing process.

1 Primary Sjögren's Syndrome

Primary Sjögren's syndrome (PSS) is an autoimmune disease, primarily affecting the salivary and lacrimal glands. Impaired salivary and lacrimal secretion and mucosal dryness are the main symptoms. Nonexocrine organs, including the gastrointestinal tract and the nervous system, may also be involved.

PSS has an increased prevalence in patients with certain HLA-DR2 and DR3 genes. Several non-HLA genes may also be involved,

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including genes coding for cytokines and second messengers. An androgen/estrogen imbalance may also be of importance.

PSS is a rheumatic disease with lymphocytic infiltration and hypofunction in the salivary and lacrimal glands, resulting in dryness of the mouth and eyes, without coexisting connective tissue disease, whereas secondary Sjögren's syndrome is when the syndrome is associated with another connective tissue disease, such as scleroderma, systemic lupus erythematosus (SLE), or rheumatoid arthritis. Xerostomia is the most common gastrointestinal symptom in PSS patients (Türk et al. 2005; Kjellen et al. 1986; Anselmino et al. 1997; Rosztóczy et al. 2001; Tsianos et al. 1986; Hradsky et al. 1967). Esophageal dysmotility and esophageal webs have also been reported (Anselmino et al. 1997; Tsianos et al. 1985, 1986; Volter et al. 2004; Palma et al. 1994). Dryness of mucous membranes, due to lack of saliva, impairs swallowing by interfering with the sliding of the bolus on the mucous membranes. Sialometric measurements may be close to 0 mL/min. Esophageal dysmotility including weak contractions, aperistalsis, and tertiary contractions as well as abnormal peristaltic velocity and duration are seen in one third of PSS patients. A decrease in the lower esophageal sphincter pressure has also been reported (Anselmino et al. 1997b). A recent study showed that 65% of PSS patients have dysphagia (Mandl et al. 2007). They presented with solid and/or liquid food dysphagia. Also, a globus feeling was common. Other PSS patients had regurgitation and pyrosis. Some PSS patients had misdirected swallowing leading to coughing after swallowing, and hawking when eating. Others had experienced episodes of obstruction when swallowing. Many dysphagic patients had an increased liquid intake during eating.

In PSS patients a sialometric evaluation is of value (Liquidato and Bussoloti Filho 2005). Evaluation of pharyngeal and esophageal function is best done with barium swallow or fiberendoscopic examination. Manometry of the esophagus can also be of value.

Treatment in PSS patients is in most cases symptomatic and local, aiming at reducing the symptoms and consequences of dryness. However, in some cases treatment may be systemic, including use of pilocarpine and cevimeline. These drugs stimulate the M3 receptors, causing an increased salivary flow. However, side effects of M3R stimulation may be abdominal distress, irritable bladder, and sweating (Thanou-Stavraki and James 2008). The use of biological agents is currently restricted to patients with severe nonexocrine disease, in whom especially B-cell-targeted biologicals, such as rituximab, have shown promising results (Ramos-Casals and Brito-Zerón 2007). The most important treatment is local, including an increased water intake in order to lubricate the dry mucosal surface. Lozenges and chewing gum stimulate the secretory function even in hypofunctioning salivary glands. Good dental hygiene is most important since lack of saliva leads to tooth decay.

2 Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disorder that is characterized by small joint synovitis resulting in swelling, pain, stiffness, and loss of function. Permanent damage to cartilage as well as bones and surrounding tissue may occur. The pathogenesis is multifactorial, and both genetic and environmental factors, especially smoking, are of importance for both the development and the severity of the disease. Lymphocytes activated by cytokines such as TNF invade the synovia and result in a swelling of the synovia and pannus formation. The disease may result in swallowing difficulties through various mechanisms. For example, temporomandibular joint involvement may cause mastication problems. Swelling of synovial membranes in the cricothyroid and cricoarytenoid joints may cause dysphagia (Chen et al. 2005). Medullary compression may result from subluxation of the atlantoaxial joint, causing brainstem compression by the odontoid process. The subluxation of the atlantoaxial joint may also cause altered biomechanics of the swallowing musculature. Pannus located in the anterior cervical spine may cause compression of the cervical esophagus. In addition, xerostomia may also occur

in many patients with rheumatoid arthritis. In patients with juvenile rheumatoid arthritis, dysphagia may be due to micrognathia (Lindqvist et al. 1986; Ekberg et al. 1987). Dysphagia in rheumatoid arthritis may be due to dry mouth, delayed initiation of pharyngeal stage of swallow, and painful swallow (Geterud et al. 1991; Erb et al. 2001; Sun et al. 1974; Ekberg et al. 1987). The clinical evaluation includes imaging and should be done with a broad approach. Early initiation of treatment is important in rheumatoid arthritis patients. Of disease-modifying antirheumatic drugs (DMARDs), methotrexate is the most commonly used. Early initiation of treatment with DMARDs improves the prognosis and stops or delays the joint destruction process that otherwise is a consequence of the disease. In patients where there is an inadequate response to the first-line DMARDs, a combination of older DMARDs may be used or biological DMARDs may be used, of which TNF-α blockers are the most widely used. Corticosteroids and NSAIDs are today mainly used to alleviate symptoms while waiting for DMARDs to start exerting their effect, which may take a couple of weeks after treatment has started. Xerostomia usually causes increased water intake. Chewing gum and lozenges can have a beneficial effect. Other dysfunctions may be treated with direct or indirect therapies according to the underlying cause.

3 Scleroderma (Systemic Sclerosis)

Scleroderma, or systemic sclerosis (SSc), is a disorder resulting in functional and structural abnormalities of small blood vessels as well as leading to fibrosis of the skin and internal organs. The cause is unknown. Affected tissues show varying degrees of inflammation, fibrosis, and atrophy. The cutaneous lesions often appear symmetrically on the distal extremities and sometimes also on the truncal skin. Patients may show early involvement of internal organs. Raynaud's phenomenon is common. Findings of antinuclear antibodies with a centromere pattern as well as anti-ScL-70 antibodies support the diagnosis. Sclerosis of oral mucosa and masticatory muscles and salivary gland involvement may result in impaired mouth function and dysphagia (Ntoumazios et al. 2006; Rout et al. 1996). Microstomia, i.e., fibrosis of the perioral tissue, leads to a small mouth, which is a classic finding of SSc (Pizzo et al. 2003; Menditti et al. 1990). Progressive destruction of smooth muscle in the esophagus leads to abnormal peristalsis or even aperistalsis. Usually, the tonicity in the lower esophageal sphincter is zero, leading to massive gastroesophageal reflux disease (GERD). Therefore, extensive fibrosis and strictures are common findings in these patients (Fig. 1).

Dysphagia is common in SSc patients. Intake of food is difficult owing to microstomia. Dysphagia is also caused by perioral muscle stiffness in the cheeks and tongue. Decreased elasticity is present in masticatory muscle. Decreased salivary production leads to xerostomia, i.e., secondary Sjögren's syndrome. Symptoms from esophageal dysfunction are also common. In patients with esophageal strictures, the characteristic symptom is obstruction of solid foods. The stomach and small bowel may also be involved, resulting in impaired transportation at various levels. Therefore, some of these patients have a very complex set of symptoms. In patients with discrete skin lesions, the diagnosis may be very difficult. In such cases, nail capillary microscopy can be of help in diagnosing the disease. If there are gastrointestinal symptoms, a biopsy can be of value and may show signs of degeneration of smooth muscles and fibrosis. It is important to bear GERD in mind and to do a barium examination of the esophagus and/or gastroscopy.

Current therapies for SSc are still disappointing and mainly consist of symptomatic treatment of the consequences of the disease. Various vasodilatory drugs such as gastrointestinal prokinetics and proton pump inhibitors are used. In addition, cyclophosphamide is used for the treatment of concomitant interstitial lung disease. No specific treatment is available for muscle fibrosis and muscle degeneration. It is very important to keep in mind that patients with GERD should be treated vigorously in order to avoid the development of strictures.

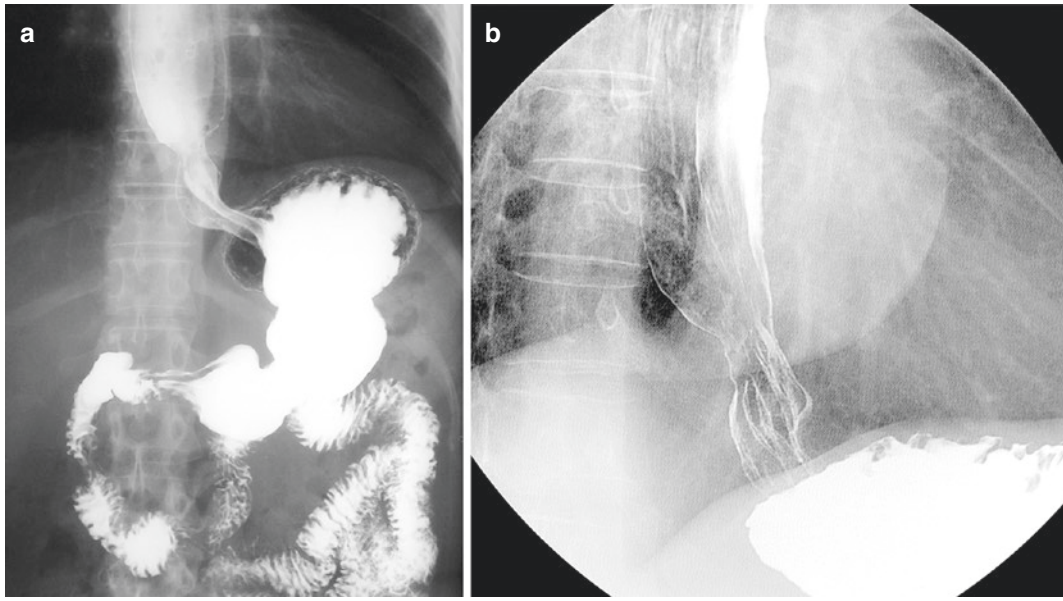

Fig. 1 A patient with scleroderma. The esophagus is dilated owing to insufficiency of the lower esophageal sphincter that causes reflux. Acid reflux has caused a stricture in the distal esophagus seen in the single-contrast esophagram in (**a**) and in the double-contrast esophagram in (**b**) (Courtesy of Francis J. Scholz, Department of Diagnostic Radiology, Lahey Clinic, Burlington, MA, USA)

4 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory, progressive systemic disease of connective tissue with an autoimmune cause and commonly affects the skin and various internal organs (Virella 1993; Goust and Tsokos 1993). Both antinuclear antibodies and the more specific anti-double-stranded DNA antibodies may be found in patients with this systemic disease. Classically, patients present with a butterfly-shaped malar rash and photosensitivity, i.e., skin rash due to exposure to sunlight. Butterfly-shaped malar rashes usually appear on the cheeks and nose bilaterally in patients with SLE. The patients may present with oral and/or pharyngeal ulcers. Ulcers may also appear on the palate. Xerostomia appears when the salivary glands are involved. Dysphagia is present in 10% of patients with SLE (Pope 2005). Erythematous oral ulcers and xerostomia are usually the result of salivary gland involvement. Pharyngeal ulceration may extend into the nasopharynx and even into the larynx. Gastrointestinal dysmotility may include the esophagus but also the stomach and small bowel. This dysmotility may be caused by submucosal fibrosis. Cerebrovascular complications are not uncommon in patients with SLE and may cause motor and sensory impairment. The trigeminal and facial nerves may be involved. Assessment of the swallowing function is done with a thorough clinical examination and may also include barium swallow or fiber-endoscopic examinations. Endoscopy is used for assessment of mucosal lesions.

Treatment of SLE includes antimalarials and corticosteroids as well as various more potent immunomodulating drugs. In the era of biological treatments, B-cell-targeting therapies have shown beneficial effects in SLE patients. Other than the treatments used for specific dysfunctions, there is no specific treatment for swallowing impairment in SLE patients.

5 Pemphigus and Pemphigoid

Bullous pemphigoid is a subepidermal blistering skin disease of chronic character. The disease may also involve mucous membranes. Acantholysis is present in pemphigus but not in pemphigoid disease. Pemphigus and pemphigoid are both autoimmune diseases. Pemphigus has antibodies directed against desmosomes, whereas pemphigoid has antibodies directed against hemidesmosomes. These antibodies bind to their antigens and cause blistering by separation of the dermis and epidermis. The mucosa in the mouth and pharynx may also be affected (Yeh et al. 2003; International Pemphigus and Pemphigoid Foundation 2011). Mucosal abnormalities cause odynophagia, i.e., painful swallowing. Ruptured blisters may be secondarily infected, which aggravates the pain. Submucosal infection may cause fibrosis and strictures. Endoscopy and radiologic swallowing studies are often necessary in order to detect pharyngeal and esophageal involvement in the form of webs and/or strictures. Advanced diseases are treated with corticosteroids and immunosuppressive agents. Good oral hygiene is most important since secondary infections must be prevented. When there is severe mucosal involvement, eating hard and crunchy foods, chips, raw fruits, or vegetables may be very painful. Local steroids can be of value.

6 Epidermolysis Bullosa Dystrophica

Epidermolysis bullosa dystrophica is an inherent autoimmune disease affecting the skin and the mucosa of the oropharynx. The cause is a genetic defect within the human COL-7A-1 that encodes the production of collagen. Collagen VII forms the structural link between the epidermal basement membrane and the collagen fibrils in the upper dermis. Sloughing of the mucosa causes ulcers that are easily infected and painful. Even though the oral mucosa is mostly affected, laryngeal, esophageal, and conjunctival mucosa can be involved. The blisters, erosions, and ulcers may lead to scars, webs, and strictures. It has even been reported that esophageal shortening can be caused by such scarring. This may cause hiatal hernia and GERD (Agah et al. 1983). The patient's symptom is by and large odynophagia.

Topical steroids are often used. Endoscopic dilatation may be necessary if esophageal strictures develop.

7 Lichen Planus

Lichen planus is a chronic mucocutaneous disease that causes papules or rashes involving the skin and mucous membranes but also the nails and genitals. It is likely to be an autoimmune disease that involves CD4+ and CD8+ T lymphocytes. Parakeratosis is present as well as atrophy of the esophageal epithelium. Strictures may have an appearance similar to those in GERD. The strictures are, however, localized in the proximal esophagus. This should raise the suspicion of the cause (Chandan et al. 2008; Madhusudhan and Sharma 2008; Sugerman and Porter 2010; Katzka et al. 2010). Endoscopically elevated lacy white papules, esophageal webs, and pseudomembranes are present. Erosions with and without stenosis may also be present. Strictures are present in advanced cases. Even though the disease is most frequent in the proximal and mid esophagus, the whole esophagus may be involved. The lichenoid lesions may be painful. Odynophagia may occur from lesions in both the oral cavity and the esophagus. Odynophagia is common for solids. Spicy food and liquids may cause pain.

Therapeutic options include systemic corticosteroids, cyclosporine, and azathioprine. Local steroids can be used. Endoscopic dilatation of strictures is usually needed.

8 Behçet Disease

Behçet disease is a vasculitis characterized by aphthous ulcers in the mouth and on the genitals. In addition, various skin lesions, e.g., erythema nodosum and folliculitis, eye lesions, arthritis, venous

thrombosis in various locations, and CNS involvement may be encountered in these patients. The prevalence of the disease is highest in the eastern Mediterranean, the Middle East, and East Asia. In addition, the HLA-B51 gene has been reported to be a strong risk factor for the disease. The vasculitis causes recurrent oral and genital ulcers. Uveitis, erythema nodosum, folliculitis, thrombophlebitis, venous thrombosis, meningitis or CNS vasculitis as well as arthritis may also be present (Brookes 1983; Levack and Hanson 1979; Demetriades et al. 2009; Messadi and Younai 2010). The ulcers are found on lips, tongue, and on the inside of the cheeks. Aphthous ulcers may occur as single lesions or in clusters. They may even be found in the esophagus. Ulcers in the oral cavity and mucosa and esophagus are often painful. These ulcers may be provoked by slight trauma. Treatment of the mucosal ulcers includes colchicine, whereas more systemic disease is treated with steroids and various immunomodulatory drugs. Good oral hygiene is important to prevent secondary infection of the ulcers. Strong-tasting food should be avoided as it may cause pain.

9 Sarcoidosis

Sarcoidosis is a granulomatous disease characterized by noncaseating epithelioid granulomas. The lungs and mediastinum are predominant locations, although virtually most other organs may be affected, including the gastrointestinal tract. An autoimmune cause has been suggested. A reduced delayed-type hypersensitivity response is found in many patients with sarcoidosis. The epithelioid granulomas may occur in the mucosa, where they cause superficial nodules and ulcerations that may be painful. Larger granulomas may cause irregular strictures which cause obstruction. They may be difficult to distinguish from malignant strictures on radiologic examination as well as on endoscopy (Bredenoord et al. 2010). Oral sarcoidosis may cause odynophagia. Also, esophageal involvement may be painful since esophageal strictures may cause obstruction of a solid bolus. Diagnosis is made by fiber endoscopy and/or barium/iodine contrast medium radiologic evaluation. A solid bolus test should usually be included (Levine et al. 1989; Hardy et al. 1967; Cook et al. 1970).

Oral corticosteroids are usually effective. Advanced disease can be treated with various immunomodulatory drugs and in severe refractory cases also with infliximab, a TNF-α blocker. Local steroids can be used in the treatment of oral mucosal involvement. Esophageal strictures can be treated with balloon dilatation or may at times have to be surgically resected.

10 Berylliosis

Berylliosis, or chronic beryllium disease (CBD), is an immunologically mediated granulomatous lung disease due to beryllium sensitization (Flors et al. 2010). CBD is characterized by abnormal formation of inflammatory noncaseating granulomas that causes widespread scarring and most commonly interstitial pulmonary fibrosis. Mediastinal lymph nodes are also involved. A granuloma development may also occur in other organs, including extrapulmonary lymph nodes, skin, subcutaneous tissue, salivary glands, myocardium, liver, and skeletal muscle. Beryllium is a lightweight metal with variable physical and chemical properties that include stiffness, corrosion resistance, and electrical and thermal conductivity. Genetic predispositions seem to have a major role in the development of CBD. A variant of the major histocompatibility complex HLA-DPb1(Glu 69) has been found in many patients (Richeldi et al. 1993).

The symptoms of CBD are dry coughing, fatigue, weight loss, chest pain, increasing shortness of breath, and sometimes also dysphagia due to lymph node impingement on the esophagus. CBD has many similarities with other granulomatous diseases such as tuberculosis, syphilis, and fungal infection. The symptoms are mainly due to extrinsic compression of the esophagus leading to solid bolus dysphagia (Fig. 2).

Exposure to beryllium occurs particularly in miners. Other people are exposed in a variety of industries: aerospace, ceramics, dental supplies. The window in X-ray tubes often contains beryllium.

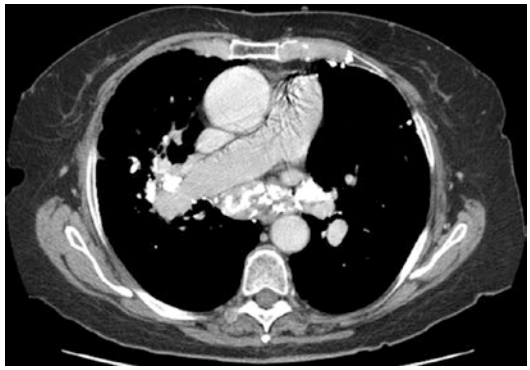

Fig. 2 An 82-year-old patient with berylliosis. CT of the upper thorax shows extensive fibrosis with calcifications in the upper lobes and in the mediastinum. In a patient like this, the esophagus is often encroached by the large lymph nodes (Courtesy of Francis J. Scholz, Department of Diagnostic Radiology, Lahey Clinic, Burlington, MA, USA)

Beryllium exposure occurs primarily by inhalation of beryllium fumes or dust, but even contact through broken skin may occur. Most beryllium is excreted in urine, and the primary half-life ranges from several weeks to 6 months. Relatively insoluble chemical forms of beryllium may be retained for years.

After inhalation of beryllium, large numbers of CD4+ T lymphocytes accumulate in the lungs. These helper T lymphocytes demonstrate a marked proliferation response on exposure to beryllium. Beryllium seems to induce production of proinflammatory cytokines and growth factors that lead to granuloma formation.

Management of CBD includes cessation of beryllium exposure and the use of systemic corticosteroids. However, once pulmonary fibrosis has developed, corticosteroid therapy cannot reverse the scarring of lung tissue (Flors et al. 2010; Sood 2009).

11 Inflammatory Myopathies

Inflammatory myopathies include polymyositis, dermatomyositis, and inclusion body myositis (IBM) (Bella and Chad 1996). These inflammatory myopathies are characterized by mononuclear inflammatory cell infiltrates, myofibrillar necrosis, and regeneration. In polymyositis, T-lymphocyte cells, monocytes, and plasma cells are located in fascicles within the endomysial connective tissue. Dermatomyositis is characterized by the presence of atrophic fibers in the periphery of the fascicles. Unlike in polymyositis, the inflammatory cells are localized in the perivascular area and in the perimysial connective tissue and not in the endomysium. Microvascular changes are also common. Similarly to polymyositis, in IBM inflammatory cells are located in the endomysium. Patients with polymyositis, dermatomyositis, and IBM develop symmetric proximal muscle weakness. Muscle biopsy shows myositis. Patients also have elevated levels of serum creatine phosphokinase. Atypical EMG findings are also seen. In patients with dermatomyositis, there is also a characteristic skin involvement in the form of heliotrope exanthema or Gottron's papules on the knuckles.

Patients with polymyositis, dermatomyositis, and IBM may have abnormal oropharyngeal and/or esophageal stages of swallowing (Darrow et al. 1992; Shapiro et al. 1996). Striated and smooth musculature is affected, leading to weakness of muscle strength but also fibrosis in the musculature. When the oral and pharyngeal stages are affected, this leads to retention with pooling in the vallecula and piriform sinuses. This may then lead to overflow aspiration (Selva-O'Callaghan et al. 2000). However, there is also usually laryngeal muscle involvement leading to defective closure of the airways as well (Fig. 3).

Abnormal upper esophageal sphincter opening is common in polymyositis, dermatomyositis, and IBM (Sonies 1997). Inflammation and edema in the cricopharyngeal muscle has been observed. Muscle fibrosis is often present. This has usually been treated by cricopharyngeal myotomy (Berg et al. 1985). Esophageal involvement leads to abnormal peristaltic transportation. This is similar to that seen in scleroderma. Injection of botulinum toxin into the cricopharyngeal muscle has also been recommended. Early treatment is important in order to avoid muscle atrophy. Treatment generally includes corticosteroids and immunosuppressive agents.

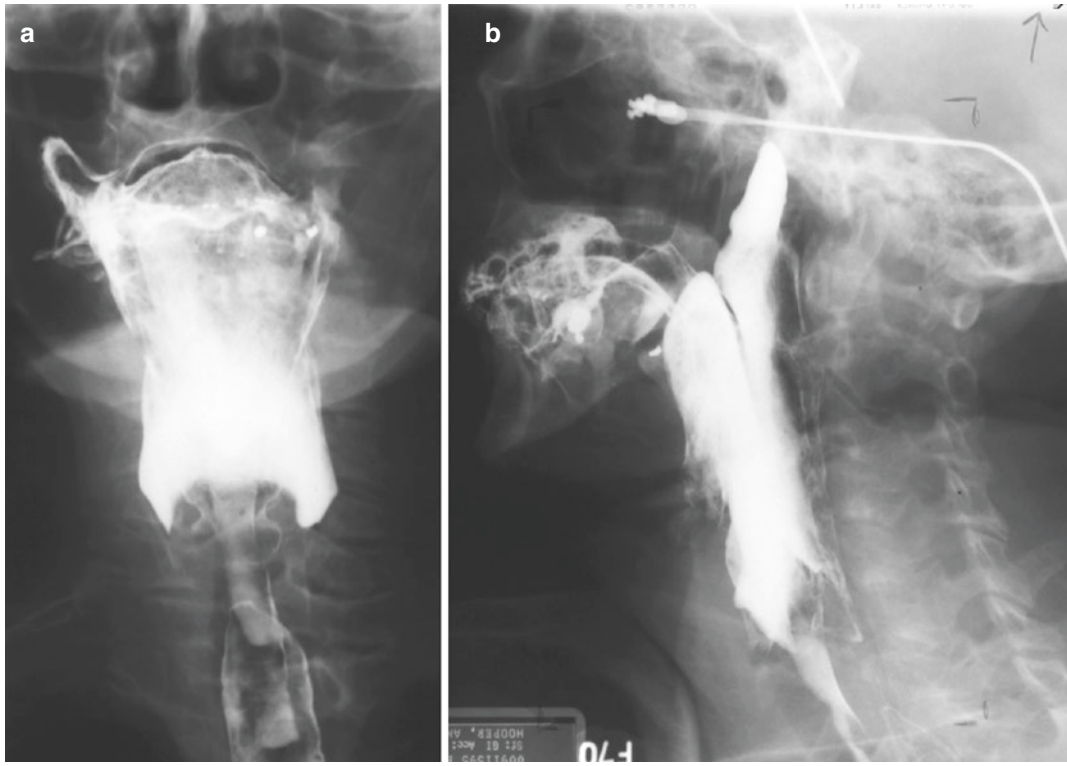

Fig. 3 A 64-year-old woman with dermatomyositis and dysphagia. (**a**) Barium examination of the pharynx shows retention in the piriform sinuses. There is misdirected swallowing that reaches into the laryngeal vestibule. (**b**) Contrast medium also reaches up into the nasopharynx. There was very little contraction and movement of the pharyngeal wall

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The Geriatric Pharynx and Esophagus

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Contents

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Abstract

Dysphagia is common in the elderly. This is mainly due to neurodegenerative abnormalities in the central nervous system. The elderly may be able to compensate, to a certain degree, for deterioration of function but the reserve capacity is much less than in younger. Understanding of the normal ageing process as well as disease processes common in the elderly is important for diagnosis and treatment of dysphagia in the elderly.

1 Introduction

There are several age-related alterations in oral, pharyngeal, and esophageal morphology and function. These variations in the healthy elderly (primary ageing) must be taken into account during clinical and radiological evaluation. In fact, these changes do not normally impair the swallowing process and are thereby not symptomatic. However, when disease processes (secondary ageing) add to primary ageing, they may result in significant impairment.

Deglutition disorders are common and costly in the elderly. The actual prevalence and natural history of such dysphagia are not very well known. Dysphagia is more commonly detected in the hospitalized and institutionalized elderly than in individuals who live in their own homes. In hospitals and nursing homes with predominantly an elderly population, the prevalence of

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dysphagia is up to 50% of the population (Groher and Bukatman 1986). Dysphagia is also much more common in the very old (over the age of 85) than in any other group. Neurologic diseases such as stroke, dementia, and Parkinson's disease are common in these populations. The central nervous system regulates oropharyngeal function in an integrated complex sensory and motor activity pattern. Especially the coordination between the oral and pharyngeal stage, i.e., between a voluntary and an automatic function, is vulnerable. In the elderly this coordination is frequently impaired.

Many elderly people with dysphagia seem to be in reasonably good health, and are not frail or bedridden. They do not seem to suffer from clinically apparent neurologic disease. Oropharyngeal impairment is usually insidious and chronic in these individuals, although acute, transient cases do occur. A rational approach to understanding deglutition in the elderly requires that we differentiate expected, if not clearly predictable, senescent changes (primary ageing) from those caused by disease (secondary ageing). Unfortunately, subclinical disease, especially cerebral vascular disease, makes this distinction difficult.

From other organ systems we know that there is roughly a 1% yearly decline in function beginning at 30 years of age. Overall ageing is a progressive generalized impairment of function resulting in a loss of adaptive response to stress and in a growing risk of age-associated disease (Kirkwood 2000).

The morphodynamics of deglutition can be measured in terms of timing, movement of anatomical structures, pressure generation, and bolus movements (Tracy et al. 1989; Sonies et al. 1988; Shaw et al. 1990; Shaker et al. 1990). Senescent changes in oropharyngeal function can be characterized as "less efficient." However, the relationship between symptoms and morphodynamic abnormalities, especially in the context of compensation/decompensation, is very complex (Jones and Donner 1991).

One important feature of ageing is an inability to adapt to stress, and the videofluorographic examination is certainly a stressful situation. Abnormalities, or differences from younger, presumably normal individuals, may induce alterations that reflect senescent decline in function. Similarly, the examination itself may induce decompensation in those with existing dysfunction due to known disease and minor abnormalities may become major ones.

1.1 The Ageing Brain

In the central nervous system various alterations of the cytoarchitecture occur in ageing. For example, motor neuron counts in the spinal cord show that the number of cells declines by approximately 200 neurons per segment per decade (Schoenen 1991). A study that counted the pigmented neurons in the locus ceruleus in the brain stem found a decline averaging 2000 cells per decade after the age of 60 years (Vijayashankar and Brody 1979). Cell counts in various glossopharyngeal and vagus nuclei within the brain stem are not available in humans, but a similar decline is likely.

1.2 Primary Ageing

The oral cavity undergoes important changes with age. Such changes include an increase in the amount of connective tissue in the tongue, loss of dentition, and reduced masticatory strength (Logemann 1990). In the pharynx it has been shown that the anterior elevation of the larynx is less pronounced in the elderly and that the pharyngeal swallowing phase is significantly slowed down (Sonies et al. 1988). The pharyngeal peristaltic motion has been shown to be slowed down above the age of 60 years (Tracy et al. 1989). However, another study showed that this is not the case but that there is instead a wider intrapersonal variability in the elderly (Borgström and Ekberg 1988a). However, there is no significant change in pharyngeal peak pressure, duration, or in the rate of propagation of contraction (Robbins et al. 1992). Healthy elderly subjects therefore do not have any residual accumulation in the pharynx after swallowing.

2 The Oral Stage

It has been shown that pressure that is generated during swallowing by the tongue does not change in the elderly compared with young individuals. However, when individuals are asked to apply maximal strength, the pressure recording increases considerably in the young, whereas in the elderly such reserve capacity does not seem to exist. Others have shown that lingual peristaltic pressure decreases with age (Shaker et al. 1988).

3 The Pharyngeal Stage

3.1 Misdirected Swallowing

Bolus misdirection into the airways is the most significant event observed during videofluoroscopy. The timing and level of bolus misdirection are important observations, but again may be extremely variable (Dodds et al. 1990; Logemann 1983; Groher 1983). In the elderly, it is not uncommon to see ingestion of too large a bolus volume or a rapid ingestion rate during uncontrolled administrations. This results in disruption of sequencing between bolus ingestion, delivery, propulsion, and laryngeal closure. Some patients aspirate only on the first liquid barium administration; others appear relatively normal until a small amount penetrates and then grossly deteriorate and aspirate before, during, and after some of the subsequent swallows. Particularly in the elderly bolus misdirection most often results from oral stage dysfunction even when it occurs during the pharyngeal stage.

Another common finding in the elderly is failure of containment during ingestion, oral processing of bolus holding. In these individuals the glossopalatal seal is inadequate. Lingual movements may be dyskinetic or disorganized and disrupt the glossopalatal seal. Alternatively, there may be no oromotor activity attempting to contain the bolus once it has been ingested. The third oral stage cause of misdirection is transitional dissociation. This means that the bolus is positioned at the wrong place at the wrong time.

In young individuals the hyoid bone starts to move anteriorly (from its posterior position) before the apex of the bolus passes the level of the faucial isthmus as it can be seen in a true lateral projection during swallowing. With increasing age, the start of this anterior hyoid bone movement is delayed. It is common in the elderly (over 75 years of age) to observe a delay of the anterior movement of the hyoid bone for more than 0.5 s after the apex of the bolus has passed the faucial isthmus (Feinberg and Ekberg 1991). In that study using the previously outlined pattern analysis, it was found that aspiration was due to oral stage dysfunction in 50% of patients, pharyngeal dysfunction in 30% of patients, and combined dysfunction in 20% of patients. The most common oral stage abnormality was failure of containment. Transitional dissociation was seen in many patients. Almost as common was large bolus ingestion or rapid ingestion rate. The most common pharyngeal stage abnormality was incomplete transportation, i.e., retention. A mere defective laryngeal closure was seen less frequently (Feinberg and Ekberg 1991). There is, however, no significant relationship between a patient's specific disease and the pattern of abnormalities during barium swallow. This means that the observed dysfunctions are nonspecific in terms of their cause. The high frequency of oral dysfunction indicates that oral stage abnormalities must be routinely looked for during videofluoroscopy.

The presence of anterior osteophytes larger than 10 mm that impinge on the pharynx may explain aspiration in dysphagic patients (Strasser et al. 2000). Coexisting clinical conditions and diseases such as stroke and partial laryngeal resection increase the risk of aspiration in patients with smaller osteophytes of the cervical spine.

Pneumonia is common in the elderly and it may be due to defective closure of the airways during swallowing, i.e., penetration/aspiration. However, the cause and effect relationship is complex and few studies have addressed this accordingly (Doggett et al. 2001; Feinberg et al. 1996). The most plausible explanation is that infected saliva reaches the lower airways by means of the larynx and causes the infection (Langmore et al. 1998).

3.2 Pharyngeal Constrictors

There are conflicting opinions concerning the effect of ageing on deglutitive pharyngeal pressures. Whereas one study showed that there was no pressure difference (Robbins et al. 1992), other studies have shown differences (Tracy et al. 1989; Perlman et al. 1993; Shaker et al. 1993). However, there are a multitude of methodological differences that makes comparison difficult. In fact, one of the studies (Shaker et al. 1990) showed that the amplitude and duration of the peristaltic pressure wave were significantly greater in the elderly than in the young. Such alterations with age, alterations that actually could be seen as improvements, may actually be regarded as compensatory responses to, for instance, reduced cross-sectional area of the deglutitive pharyngoesophageal segment (PES) opening in the elderly (Shaw et al. 1990). A study supporting this theory was presented by Shaker (1993). In this study he found that intrabolus pressure in the pharynx was significantly higher in the elderly than in young patients, on swallowing in both upright and supine positions and with both liquid and mashed potatoes. This again may indicate that there is lack of distension of the PES in the elderly.

3.3 The Pharyngoesophageal Segment

The PES pressure has also been studied in the elderly and has been compared with that in younger subjects. Cook et al. (1989) did not find significant age-related changes in resting PES pressure measured with a sleeve device; however, they only studied individuals under 55 years of age. Wilson et al. (1989) made the same observation in healthy subjects under 62 years of age. On the other hand, Fulp et al. (1990) showed that normal elderly subjects over 62 years of age have lower resting PES pressure than younger controls. Shaker et al. (1993) studied the effect of ageing (70 years and over) on the resting PES pressure and its response to esophageal air and balloon distension. The results of this study indicate that ageing significantly reduces the resting PES pressure. However, this latter study (Shaker et al. 1990, 1993) also showed that there were normal PES pressure responses to swallowing and esophageal distension by air and balloon in the elderly. Therefore, the protective role of the PES against pharyngeal reflux of gastric acid is preserved in the elderly.

Kendall and Leonard (2001) showed that there is pharyngeal weakness in the elderly dysphagic patient. They also concluded that poor pharyngeal constrictions suggestive of pharyngeal weakness contributed to 75% of cases of aspiration in their study. Feeding and respiratory pattern was studied in normal elderly people (Hirst et al. 2002). Hirst et al. found a fairly stable pattern. It has been shown that particularly in the elderly incoordination commonly leads to aspiration (Nilsson et al. 1997). Solid aspirators also have a lower oxygen saturation level compared with normal individuals (Colodny 2001).

4 Examination Techniques

The examination technique in the elderly does not differ from that in young individuals. However, many elderly people are severely impaired and cannot cooperate. The examination should be custom-tailored to the patient's symptoms, and in a very impaired elderly patient there are very few relevant clinical questions that should be addressed. Therefore, such an examination is usually very easy to perform.

5 The Nondysphagic Elderly

An important aspect is, of course, the prevalence of videofluorographic abnormalities in nondysphagic elderly patients. Ekberg and Feinberg (1991) found that only 16% of the elderly population (mean age 83) were normal. Oral and pharyngeal dysfunction was very prevalent in their study (63 and 25%, respectively) (Fig. 1). Combined dysfunction was present in 60% of patients. Sixty-five percent of patients showed bolus misdirection into the airways (20% showed penetration into the vestibule, 45% showed minor aspiration to the trachea).

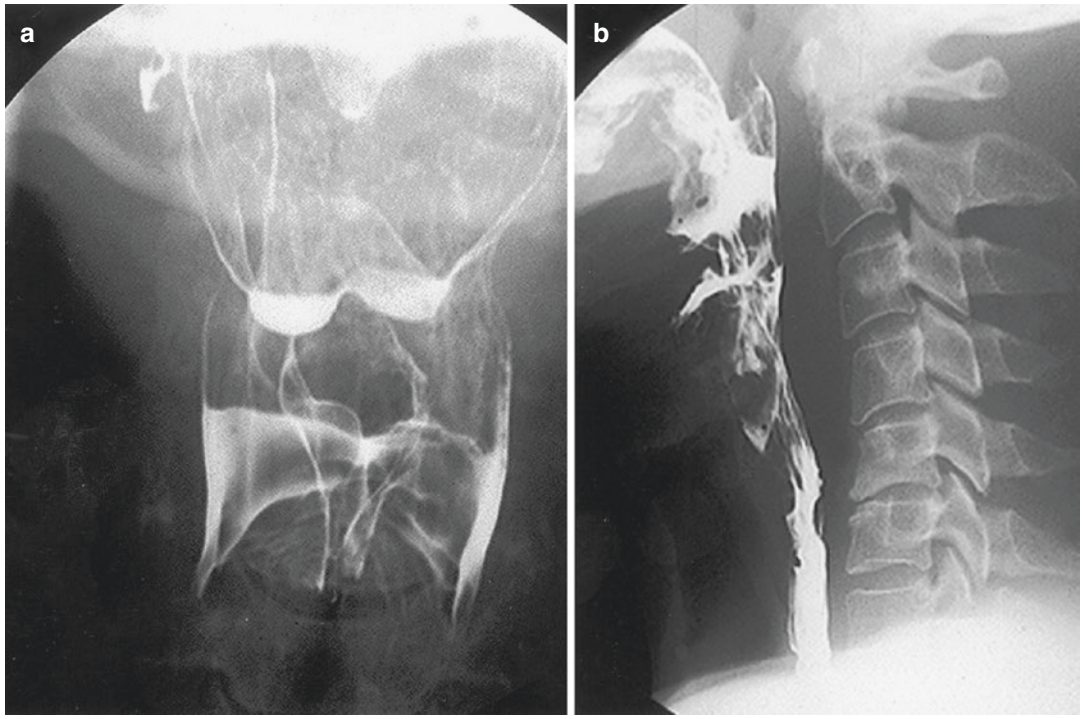

Fig. 1 Pharyngeal dysfunction is common in the elderly. Weak musculature leads to impaired clearance of the pharynx. This is mostly related to defective elevation of the pharynx. In this patient there is pooling of contrast medium in the vallecula and piriform sinus bilaterally. Contrast medium has reached into the laryngeal vestibule and is also seen between the arytenoids

No major aspiration was observed. Misdirection was due to oral dysfunction 4 times as often as pharyngeal dysfunction and twice as often as combined oral and pharyngeal dysfunction. In that study 36% of patients had dissociation between the oral and pharyngeal stage. This was the pathophysiological process of oral dysfunction leading to misdirected swallowing. However, in that study, half of the patients had a history of neurologic disease such as dementia, Parkinson's disease, and stroke, although none had a history of dysphagia or swallowing impairment. Pharyngeal constrictor paresis and lingual dysfunction was much more common in those patients with neurologic disease. The high frequency of abnormalities that was observed in that study may have a number of explanations. Many elderly individuals do not admit to being dysphagic even when it is obvious that they are. Caregivers are relatively poor at detecting dysphagia unless they have been specifically trained (Ekberg et al. 2002).

Altered oropharyngeal function has been documented in asymptomatic elderly volunteers (Pontoppidan and Beecher 1960; Baum and Bodner 1983; Sonies et al. 1984; Borgström and Ekberg 1988b; Tracy et al. 1989; Ekberg and Feinberg 1991; Robbins et al. 1992). Such changes may be due to normal age-related changes in tissues, muscles, and neuromorphodynamics. It is not clear what is "normal decline" in oropharyngeal function among the elderly and what is really the result of disease processes which definitely are more common in the elderly, particularly in the central nervous system (Levine et al. 1992; Buchholz 1992). Again, it is very important to try to compare symptoms with morphodynamic findings (Sheth and Diner 1988; Donner and Jones 1991). There is a confusing overlap of clinical, videofluoroscopic, and magnetic resonance imaging findings in elderly individuals with and without oropharyngeal dysphagia/dysfunction (Figs. 2, 3, and 4).

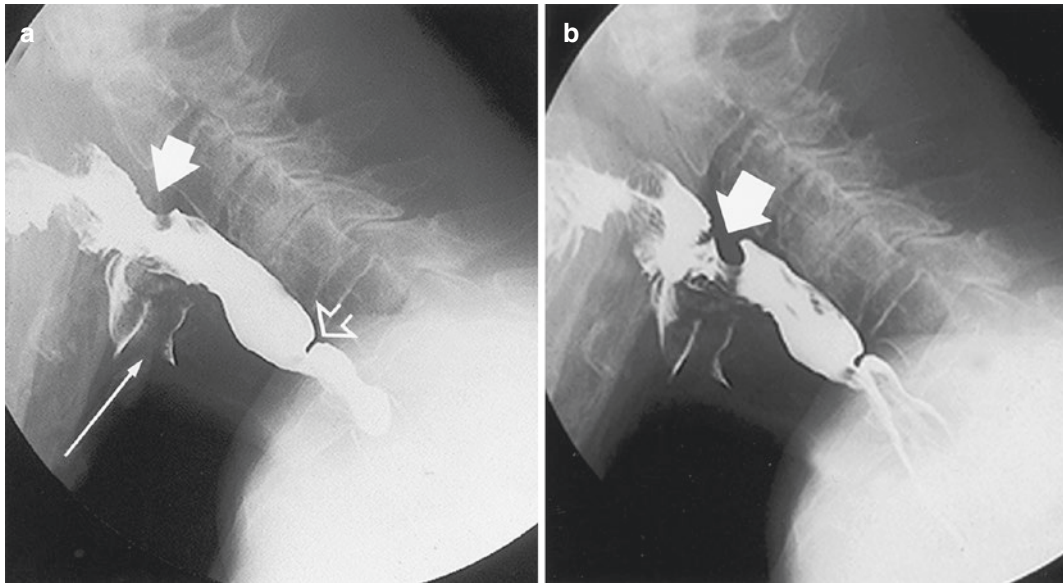

Fig. 2 Barium swallow in a 79-year-old woman with dysphagia. She coughs during eating. Compensation is often difficult to detect on barium swallow. This patient has increased activity in the middle pharyngeal constrictor (*broad arrow*). This is likely to be due to a weak tongue base pressure. In this patient there is also misdirected swallowing. Barium has passed through the vocal cords (*arrow*) into the subglottic area. There is also an incoordination of the opening of the pharyngoesophageal segment seen as an indentation of the cricopharyngeal muscle (*open arrow*). (**a**) Midpharyngeal stage of swallow. (**b**) One quarter of a second after (**a**)

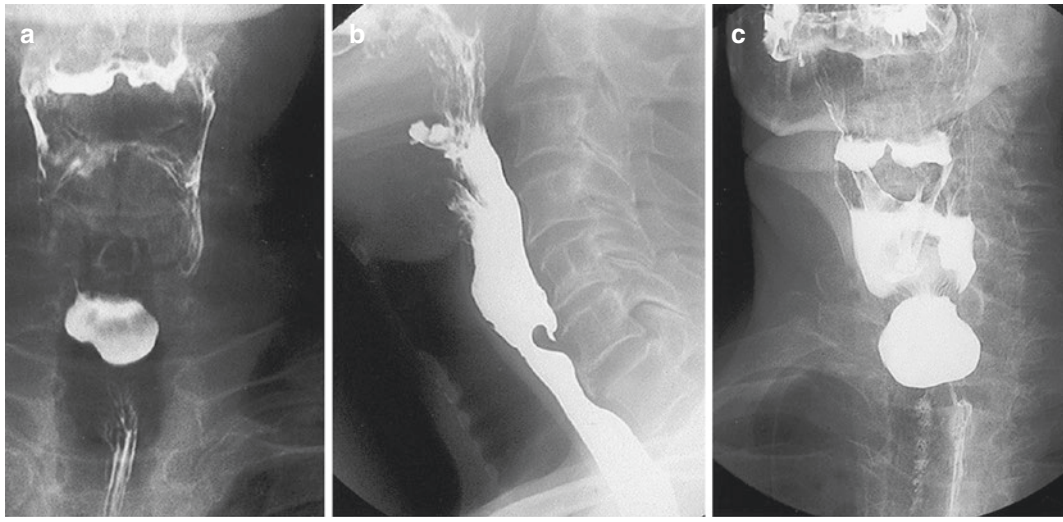

Fig. 3 Zenker's diverticula. These are usually asymptomatic in younger persons (as in **a**, **b**). In a young person, Zenker's diverticulum is usually the only abnormality found. This is in contrast to the situation in the elderly (as in **c**, **d**). In this patient there is concomitant dysfunction with pooling of contrast medium in the vallecula and in the piriform sinuses. There is also misdirected swallowing. Although the diverticulum is bigger in the young patient in (**a**), it is likely that most of the symptoms are due to concomitant pharyngeal dysmotility. However, in elderly patients the diverticulum might be huge as in (**d**). The diverticulum dislocates the cervical esophagus anteriorly, and it was obvious during the examination that there was an obstruction for bolus passage

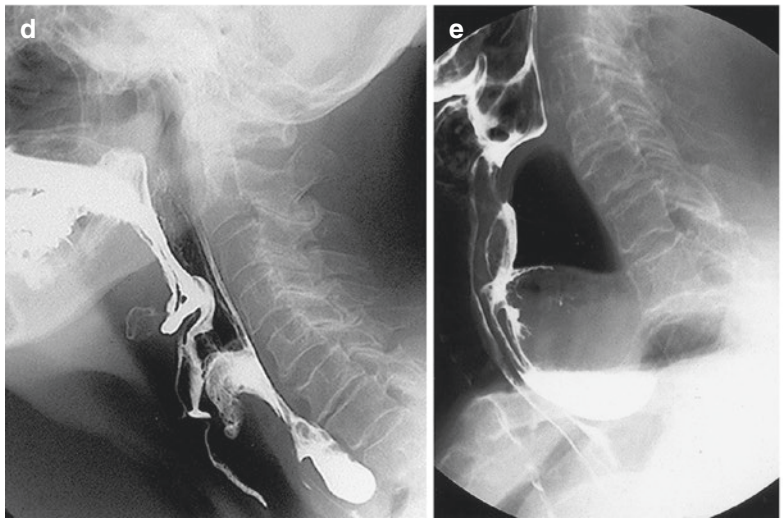

Fig. 3 (continued)

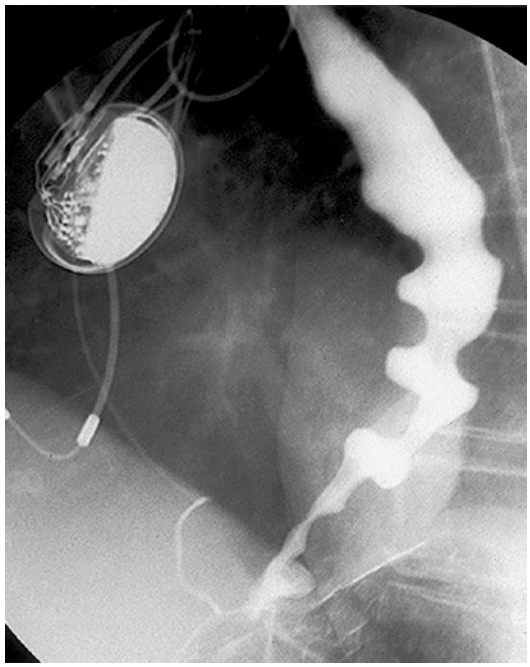

Fig. 4 Esophageal dysmotility is common in the elderly. This patient shows multiple nonpropulsive contractions of the distal esophagus. This may, as in this patient, be very symptomatic. This 81-year-old woman vomited halfway through every meal. The barium study shows retention due to the motor dysmotility. Other patients might show similar esophageal dysfunction but do not vomit and are not otherwise symptomatic either

6 Dementia

Because dementia is the most common neurologic disease associated with misdirected swallowing, it is of interest to study such a population more closely (Feinberg et al. 1992). In the study of Feinberg et al., only 7% of patients were found to be normal during videofluoroscopy. Oral stage dysfunction was found in 73% of patients, pharyngeal dysfunction was found in 43% of patients, pharyngoesophageal abnormalities were found in 33% of patients, and combined dysfunction was found in 42% of patients. When only one stage was abnormal, again oral dysfunction (36%) was much more common than pharyngeal dysfunction (14%). Common neuropsychiatric features of dementia can explain the oral stage dysfunction that was observed in that study. Patients frequently seem to be displaying agnosia (inability to recognize familiar stimuli or situations), dyspraxia (inability to perform coordinated movements), and abulia (psychomotor retardation). Inappropriate ingestion behavior appears to be secondary to faulty judgment and lack of impulse control. Transitional phase dissociation was the most common oral abnormality, seen in 44% of patients. Volicer et al. (1989) have suggested that

Alzheimer's disease patients "simply have forgotten how to initiate the swallowing reflex," and a high frequency of dissociation in the aforementioned study may reflect such a deficit.

A recent study found a correlation between the impairment of the oropharyngeal swallowing phase and the presence of unidentified objects observed incidentally on head magnetic resonance imaging performed on elderly subjects (Levine et al. 1992). Two other studies found alterations of pharyngeal clearance and swallowing pressure in patients with prominent cervical osteophytic formations (Ohmae et al. 1993; Strasser et al. 2000).

7 The Ageing Esophagus

The term "presbyesophagus" has been used to describe esophageal motility abnormalities in the elderly. However, studies have shown that dysmotility does not occur secondarily to ageing as such. However, esophageal diseases are common in all age groups, including the elderly. Some diseases have a relative frequency that increases with age, such as adenocarcinoma. One must also take into account that an elderly patient with suspected achalasia is much more likely than a younger one to have a distal esophageal malignancy. Moreover, long-standing achalasia that occurs in an elderly patient may develop a secondary malignancy.

Symptoms of well-known diseases usually have a more complex presentation in the elderly; therefore, chest pain due to esophageal dysmotility or gastroesophageal reflux disease may be much more difficult to distinguish from coronary artery disease. Moreover, chronic disorders present for a long time in the elderly are more likely to cause complications. This may be true for Barrett's esophagus and adenocarcinoma of the esophagus. Esophageal dysmotility is a major problem in the elderly. The symptoms are characteristically related to abnormal transportation of ingested material through the esophagus. Cardinal symptoms are chest pain and vomiting. The major differential diagnostic problem is to detect any underlying mechanical obstruction such as reflux (or other) stricture and malignancies. Characteristically strictures are symptomatic for solid foods but not for liquids. Dysmotility is usually equally symptomatic for liquids and solids. It is always important to consider endoscopy in this age group. If it is contraindicated or not available, the radiologic study must include morphologic evaluation.

The effect of ageing on the esophageal motor function has been studied by several authors. Nonpropulsive, often repetitive contractions are numerous in the elderly (Soergel et al. 1964; Zboralske et al. 1964). Tertiary contractions and delay of the esophageal emptying, as well as dilatation of the esophagus, are also commonly seen. It has also been shown that the distal esophageal peristaltic amplitude is significantly higher in the elderly than in the young (Richter et al. 1987). Interestingly, however, the proximal esophageal contractile amplitude did not increase with age. Others have shown that the lower esophageal sphincter resting pressure does not differ between the young and the elderly (Shaker 1993).

Esophageal dysmotility is one of the major reasons for drug-induced esophagitis. Commonly reported drugs are NSAIDs, tetracycline derivates, potassium chloride, and now also alendronate. Esophageal injury may be related to acidic pH with some of these drugs. However, potassium chloride causes injury by acting on smooth muscles, particularly on the small arteriole in the mucosa and submucosa, thereby causing an ischemic lesion which may lead to fibrosis and stricture. Such drug-induced esophagitis may be overcome if the patient takes precautions in terms of drinking before and after ingestion, and also to ingest in an upright position.

One common observation in the elderly is so-called corkscrew esophagus. It has a very impressive radiologic appearance. It may or may not be symptomatic. Control of motor activity in peristalsis in the esophagus is a complex interaction of excitatory and inhibitory stimuli. It should be remembered that denervation of smooth musculature leads to contraction. It may well be that these patients have lost contact between the dorsal motor nucleus of the vagus nerve and the smooth muscle of the esophagus and that we are

observing the activity of the enteric nervous system. Such corkscrew esophagus is not the same as nutcracker esophagus seen in young patients. Nutcracker esophagus has normal transportation but an increased contraction pressure. Diffuse esophageal spasm (DES) and corkscrew contractions differ in such a way that it is considered that in the DES the peristaltic contraction obliterates the lumen, whereas in the corkscrew esophagus contraction does not obliterate the lumen. However, DES and curling or corkscrew dysfunction may be closely related. They both fall into the category of spastic esophageal dysfunction.

8 Gastroesophageal Reflux

It is important to realize that gastroesophageal reflux disease may cause strictures in the esophagus as frequently in the elderly as in younger patients. Key to the diagnosis here is, of course, endoscopy, and also double contrast examination. The history taking in these patients must focus on other classic symptoms or gastroesophageal reflux (Castell 1990; Fulp et al. 1990; Hey et al. 1982; Kikendall et al. 1983; McCord and Clouse 1990; Semble et al. 1989; Siebens et al. 1986; Tucker et al. 1978).

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Voice and Dysphagia

Daniele Farneti

Contents

Abstract

The anatomical interaction between the upper respiratory and digestive tracts conditions the smooth running of their functions: breathing, swallowing, and voice articulation. The phylogenetic evolution of our species has rendered possible the optimum integration of these functions, creating the conditions for an extremely refined timing. This functional optimization has facilitated the phono-articulatory function with the possibility of highly skilled aesthetic results, as in artistic voice production.

This anatomical integrity is essential for a proper and optimal functioning. Anatomical alteration may change a function, just as a functional alteration may facilitate, in the presence of comorbidity, anatomical changes. In singing, for example, the physiological adjustments required to produce a more resonant voice can alter, over time, the physiology of structures involved in swallowing. The lowering of the laryngotracheal axis, which facilitates the mechanisms of articulation and vocal projection, may affect the timing of swallowing. The pressures usually required in singing can modify the functioning of the valves between the chest and abdominal cavities.

The chapter reviews the main changes in the physiology and physiopathology of the upper respiratory and digestive tracts and the impact that artistic vocal performances

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have on swallowing. Similar considerations are made for other voice users. The chapter concludes with a review of the literature on the topic.

1 Introduction

Under an anatomical and functional profile the assessment of interactions between upper respiratory and digestive tracts represents a field of great interest (Laitman and Reindenberg 1993). According to the natural indications derived from phylogenesis and ontogenesis, the interaction between the respiratory and digestive systems, in the head and neck, can actually be evaluated almost completely and at the various stages of life, including the intrauterine stage (Wolfson and Laitman 1990). Upper airways can be examined from the nostrils down to the cervicothoracic trachea and digestive pathways can be examined from the oral cavity down to the duodenum. The nasal-buccal-pharyngeal-laryngeal "apparatus" has thus become the site of functions that can be clearly identified: many actions and interactions can now be viewed, even though they are still not completely understood.

In the head and neck there are anatomically and functionally integrated activities responsible for performing vital functions, such as breathing and swallowing, and other equally important nonvital functions, such as phono-articulation. The phylogenetic evolution of the head and neck has favored phonation, which is essential for the human species (differentiating it from others, equally developed but nonverbal), but has penalized the other functions. So, if at birth the newborn can be fed and breathe at the same time, after the first months of life, the maturation of the larynx separates the two functions.

In the course of millennia the possibility of verbal communication has significantly fostered the evolution of our species with an increasingly important role of verbal production (Purves and Litchman 1985). Only over the last few decades has the introduction of different communication modalities and systems (i.e., the Internet) reduced or at least modified the interest of such expression, typical of human beings. The use of voice as an expression mode is however indispensable for various categories of operators, either as an essential part of their everyday working activity or due to its unique and powerful expressive connotations. This is the case in those professional categories that use their voice while carrying out their usual job duties (i.e., teachers, call center operators, telephonists, shop assistants, lawyers) or those who use it according to "athletic" expressive modalities (i.e., professional classical singers, actors).

As regards the intimate anatomical-functional correlation between the head and neck, as mentioned above, it is quite evident that the unusual employment of the common effectors of breathing, swallowing, and phono-articulation may cause disjoint or joint alterations of the functions they carry out. The alteration of such functions may, in the case of existing comorbidity conditions, results in openly pathological events, in the same way as pathological events modify functions (Fig. 1). A vicious cycle is started that may involve both the effectors and the functions according to subsequent and progressive levels of involvement. The alteration of the fine balances of vocal athletic exercises performed by vocal professionals may, for instance, on the one hand, enhance the amplification and capacity of sound, but, on the other, modify their swallowing patterns. The alterations of these events are such as to involve the artists' emotional sphere, making it more difficult for them to recover preexisting or modified balanced conditions.

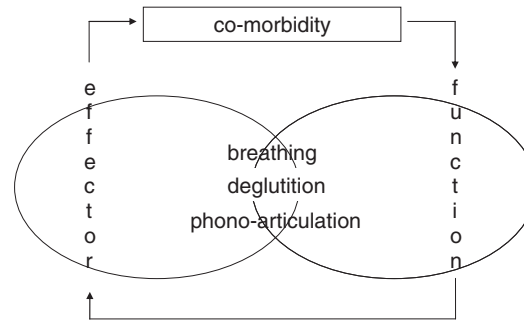

Fig. 1 Interaction among function, structure, and comorbidity

2 Phylogenetic Development

A key element in the balance between respiration, deglutition, and phono-articulation is the position of the larynx inside the visceral space of the neck. In mammals, the cervical rachis consists of seven vertebrae: the larynx is usually placed between the first and the third cervical vertebra with the epiglottis behind the velum of the palate allowing for a sort of airway continuity (Soulié and Bardier 1907). In this way the animal can breathe and at the same time ingest food of various thicknesses. This high location of the larynx, that is also found in human newborns, as said above, strongly limits phono-articulatory capabilities: the pharyngeal cavity is extremely reduced and consequently the tongue movements inside a relatively less wide cavity are limited. The oral cavity, widened by the lip movements, acts indeed as a resonator for the laryngeal sound (Duchin 1990).

What happens in mammals occurs in the human species in the first months of life. After the sixth month, the larynx starts a descent that brings it to the level of the fourth and seventh cervical vertebra (Kirchner 1993). This descent is accompanied by a progressive decrease in cranial base angle that in phylogenesis is found only in *Homo sapiens* (Negus 1949) and, in the development of our species, only after the second year of life. When the epiglottis leaves its narinal location, the child must be predisposed to swallowing in such a way as to protect the lower airways during the passage of the bolus into the pharynx. The laryngeal cavity opens up inside the pharyngeal cavity, thereby imposing the need for a sequential reconfiguration of the organ in relation to what passes through it (breathing configuration, swallowing configuration) (Cook and Kahrilas 1999). In order to facilitate the pharyngeal phase of swallowing and further protect the lower airways, the cervical region has increased its length so as to allow for a sufficiently safe deglutition timing and has widened up to enable the easy movement of structures (Arensburg et al. 1989). With respect to the phono-articulatory capacity, these various changes have certainly represented a significant advantage. The sounds produced in the larynx are amplified in a series of wide and tortuous cavities (vocal tract) with several varieties of harmonic filtering, whereas the transit through the oral cavity allows for a very fine articulation thereof (Houghton 1993).

In the aerodigestive crossroads, the hyoid bone plays an important role, since it acts as a kind of balance arm suspended from the skull base, providing insertion to the muscles of the tongue and subhyoid muscles, the suspensors of the laryngeal-tracheal axis. The hyoid bone anchors the oral floor to the cranial base, thereby optimizing the synchronization of the tongue movements with the jaw and palate. Such movements are in any case important in breathing and phono-articulation (Lieberman 1979).

2.1 Subglottic Pressure and Breathing

Verbal production is a complex anatomo-functional event that involves in parallel and in sequence several organs and systems (Sataloff 1992). The central impulse activates a series of cortical and subcortical areas that act as regulators of muscle effectors distributed in the organs involved to a different extent in the phono-articulatory function (Jurgens 1974; Lotze et al. 2000).

The respiratory tract structures allow for the movement of egressive airflow masses coming from the lungs, after gas exchanges (hematosis) (Jaeger and Matthys 1968). When the diaphragm, which is the main inspiratory muscle, contracts, it increases the size of the thoracic cavity. At the end of inspiration, the diaphragm relaxes, and the elastic structures of the chest return to a balanced state, thereby forcing out the previously inhaled air volume and supplying energy: under these circumstances the volumes (400–500 cm^3) and times of the two acts are equivalent. However, the dynamics of structures involved in breathing for the purpose of phonation change.

During phonation, inspiration is shorter and expiration is substantially longer with some interruptions normally occurring during prosodic breaks within the utterance. The air volumes mobilized are greater. The inspiratory pressure but especially expiratory pressure against the closed glottis is much higher and always requires

muscle activation. Fine adjustments are necessary to ensure the maintenance of adequate pressure levels according to the acoustic characteristics of the articulated vocal emission (Baken 1997).

2.2 Subglottic Pressure and Phono-Articulation

The subglottic pressure ranges from 2 to 5 cm water in normal talking to 10–20 cm water in projected voice up to 50–60 cm water in singing. In thoracoabdominal breathing, the rib movements and the lowering of the diaphragm provide adequate air supply for any vocal need. In the diaphragm-abdominal muscle antagonism (the abdominal muscles push and the diaphragm remains in a state of tonic contraction) a precise amount of expiratory flow and pressure generated immediately below the vocal folds (subglottic pressure) is obtained, according to the specific vocal emission requirements (Fig. 2).

2.2.1 Laryngeal Sound

Sound is produced from the exhaled air at the level of the vocal folds. Current theories and models presently suggested to explain such activity derive from Ewald's myoelastic theory (1898). The contributions by Perello (1962), Hirano (1977), Dejonckère (1987), and Van den Berg (1954) have led to the formulation of the current myoelastic aerodynamic theory of the vocal fold vibration. According to this theory the vibration of vocal folds corresponds to the resolution of the elastic conflict between the air pressure and the closure force of vocal folds.

When the pressure of the subglottic air exceeds the glottis resistance threshold, the vocal folds separate, the air flows out through the glottis, and the subglottic pressure decreases. The vocal folds close back as a result of elastic recoil and mechanical suction ("Bernoulli effect"): a mucous wave is generated that propagates from the inferior aspect of the vocal fold down to the

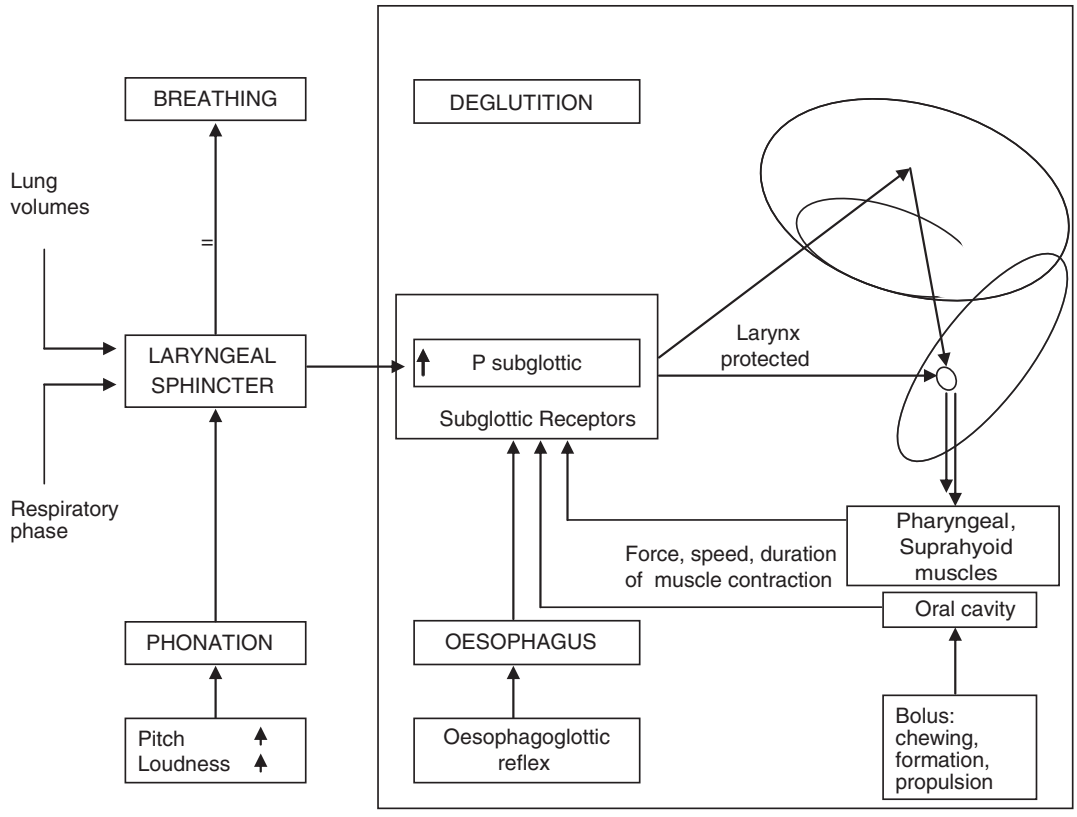

Fig. 2 Interaction of subglottic pressure among respiration, deglutition, and phonation

ventricle, reestablishing first glottis resistance and then subglottic pressure. Cyclic repetition of this mechanism takes place as long as energy is available, resulting in the formation of air condensation and rarefaction areas in the glottis (vibratory mechanical wave). The recurrence of the event, in second, coincides with the fundamental frequency (F0) of the subject's voice.

The respiratory muscles may affect F0, by regulating the subglottic pressure. The hyoid bone regulates the sagittal movements of the larynx: usually larynx lowering is observed during the production of low frequencies, whereas larynx raising occurs for higher frequencies. Larynx lowering is associated with a backward tilting of the thyroid cartilage with shortening, decrease in tension, and increase in the thickness of the vocal folds, antagonizing the action of the cricothyroid muscle. Larynx lowering (controlled by subhyoid muscles) enhances low tones and lengthens the vocal tract.

The volume of the emitted sound is determined by the amplitude of the "airflow variation" during oscillation of the glottis. This variation is related both to the subglottic pressure and to the amplitude of the glottis movement. The "airflow" is the product of the duct section (glottic surface) by the velocity of the air outflow: the laryngeal muscles influence the quality of the fold closure whereas the respiratory muscles regulate the subglottic pressure.

2.2.2 Articular Adaptation

The acoustic signal produced at glottic level is a complex, quasiperiodic sound, characterized by an F0, responsible for pitch perception, and by a series of harmonics at frequencies that are multiples of F0 (Titze 1994). By passing through the supraglottic cavities (vocal tract) the laryngeal sound undergoes changes. The first change concerns the spectrum and refers to the energy reinforcement of groups of harmonics during their transit in a chamber, the resonance frequency of which is closer to their harmonic frequency. This energy reinforcement generates the formants that are at the basis of acoustic and perceptive recognition of the sound produced by the speaker. Such modification takes place in a passive way. The laryngeal sound can also undergo active changes by passing inside the vocal tract (Fant 1983). This occurs through the production of aperiodic signals (noise) that replace or are added to the glottic sound (periodic). Such activity as a whole is referred to as *articulation* and generates voiceless and voiced consonants, respectively: as a result thereof consonants always have an oral (noise) and a laryngeal (sound) source. The sound of vowels, instead, has a laryngeal source, since they are articulated in the oral cavity from a mutual relationship of the tongue with the palate and posterior (pharynx wall) and anterior (lips) limiting structures.

2.3 Subglottic Pressure and Deglutition

Air under pressure, which is important in phono-articulation-related mechanisms, plays an equally important role in swallowing (Fig. 2). This occurs by stimulating mechanoreceptors localized in the subglottic region of the larynx (Ardzakus and Wyke 1979). This type of receptors has been identified, although their function is not clearly known yet (Widdicombe 1986). Patients with tracheotomy, for examples, adequately ventilate; therefore the role of said receptors in breathing can be considered as secondary. In addition to their function in breathing and voice production, these receptors are involved in swallowing. The stimulation of subglottic receptors may possibly act as a signal for the central nervous system (CNS) that the larynx is "ready" (that is protected) for the bolus passage into the pharynx and this signal may, at the same time, influence the low motoneurons of the brainstem innervating the pharynx.

The precise coordination of the respiratory and digestive systems is crucial in safe swallowing and this reflects onto the closed topographic organization of respiratory, deglutitory, and branchial motor neurons (Larson et al. 1994). The localization, function, and interaction of these neurons support the theory of an "online" processing of peripheral afferences both at a cortical and low brainstem level

(Maddock and Gilbert 1993). As a result of the neuroanatomical connection between subglottic receptors and branchial motor neurons for pharynx and larynx, the feedback from subglottic receptors may presumably affect the recruitment of motor neurons in the brainstem capable of activating the pharyngeal muscles during swallowing so that the force, speed, and duration of the muscular contraction are regulated (normalized) by the closing of the larynx. The stimulation of this reflex arc increases the number of pharyngeal motoneurons that, in turn, mediate a higher speed of the bolus transit, decreased time of pharyngeal contraction (resulting in a quicker pharyngeal clearing), and a stronger muscular contraction.

This feed-forward system may detect that a sensory input (subglottic P) has not been received and control a function (swallowing) by increasing the cortical processing, thereby ensuring a safe passage of the bolus into the esophagus. Cortical processing would thus account for a prolonged muscular contraction (Diez Gross et al. 2003).

Another possibility is that the segmental reflex is involved in bolus propulsion and therefore without said reflex the bolus is propelled more slowly. In this way, the pharyngeal muscles may increase the time of their contraction as a result of the increased latency of the bolus transit. This would partly explain the reason why swallowing is located in the later part of expiration. Swallowing during expiration helps the lungs fill with air before swallowing and it might be necessary to maximize the subglottic P and subsequent swallowing. In this way air is removed from the pharynx (thereby reducing air ingestion) and the exit of the bolus from airways into the esophagus is facilitated (Nishino et al. 1985).

3 Professional Voice Users

All those who use their voice within their professional activity may be deemed as voice professionals. This term makes us initially think of singers, actors, or broadcast personalities that are professionals who rely or have relied on their voice for their popularity or career. As a matter of fact a wide variety of professional operators use their voice in their occupations: teachers, ecclesiastics, lawyers, telemarketers, receptionists, and servicemen are just a few of the people for whom oral communication is an essential part of their job. Then there are of course doctors, managers, call center operators, and many others. Although we live in the Internet and e-mail era, we can hardly imagine these professionals without an adequate voice for their professional tasks. In daily clinical phoniatric practice, however, voice disorders are observed also in housewives (Baitha et al. 2002).

Voice professionals can be divided into three main categories: top performers, such as opera singers, for whom any minimal voice alteration may sometimes have disastrous consequences; vocalists, including most other singers and actors; and finally all the other professionals mentioned above.

Workers who rely on their voice as an essential part of their occupation range from 25% to 35% of employees in the USA (Titze et al. 1997) and in other industrialized countries (Vilkman 2000). The professionals who are mostly affected by voice problems are teachers, with an incidence ranging from 38% (Smith et al. 1998) to 80% (Sapir et al. 1993) followed by telemarketers (68%) (Jones et al. 2002), aerobics instructors (44%) (Long et al. 1998), and salesmen for about 4% (Coyle et al. 2001).

Among the 2286 dysphonic patients reported by Brodnitz in 1971, in 80%, dysphonia was due to vocal abuse or psychogenic factors causing dysfunction. Of these patients 20% presented organic lesions that in women were caused in 15% of cases by endocrine alterations. Other frequent causes were infectious laryngitis and reflux laryngitis (Brodnitz 1971).

Professional voice users complain of several problems, including hoarseness, vocal breaks, voice loss, hypophonia, and vocal fatigue. Correlated symptoms may be phonatory dyspnea, dry throat or sore throat, constricted sensation, or pain. Chronic voice problems may be due to laryngitis and edemas, benign cordal lesions,

nodules, hemorrhage, and cysts (Wingate et al. 2007; Behlau et al. 2014; Côrtes Gama et al. 2015; D'haeseleer et al. 2016; Mozzanica et al. 2016).

4 Common Physiopathological Events

From the considerations illustrated above it appears evident that the respiratory, deglutitory, and phono-articulatory functions are closely integrated and such integration resides in the integrity of the structures carrying out these functions.

4.1 Physical Adaptations in Artistic Voice Production

In singing, especially without amplification (classical or lyrical singing), the professional singer needs to exert greater pressures and maintain them for longer periods as compared to those used in normal speech production. The need to obtain a product with a richer timbre (amplification) and carrying greater energy requires mutual adjustments of both the breathing dynamics and the vocal tract (Titze 1994). There is actually the need to realize a wider filtering resonating chamber while keeping the pressures at the lowest possible levels. This is obtained by lowering the larynx and the tongue and through a wider opening of the mouth. The forced and persistent lowering and anchoring of the larynx imply the downward movement of all related structures: hyoid bone, and tongue root, with a strongly arched and raised soft palate. In romantic vocal productions all this goes to the benefit of the volume but to the detriment of articulatory capabilities and voice coloring that were so much appreciated in the previous musical period (Baroque).

As already said, in costal diaphragmatic breathing, during inspiration, the diaphragm contracts and the thoracic cavity gets wider in its vertical and transverse diameters. During expiration, the breathing phase during which speech production and singing occur, the diaphragm is totally inactive and its rising is regulated only by other respiratory muscles (abdominal, intercostals, etc.). According to the need of producing low- or high-intensity tones, high-pitched or low-pitched tones, or *filatura,* the behavior of the respiratory muscles will affect the breathing dynamics. When full volume is reached, the elastic retraction forces of the lungs would spontaneously tend to empty them (as happens during quiet breathing). For most singing requirements, such retraction forces produce a subglottic air pressure that needs to be adjusted to the intensity of the sound to be emitted. A force capable of contrasting the elastic forces and reducing the subcordal pressure is therefore needed upon the attack of the sound with an excessive impact on vocal folds (brusque attack). This is what the singers call "appoggio": the thorax is held in position by the action of external intercostal muscles, whereas the abdominal wall supports this activity. During a musical phrase, in order to keep the desired air pressure, the diaphragm starts rising accompanied by a contraction of the abdominal muscles that provide the "support," which is constantly sought by the singer (Fussi 2003).

4.1.1 Valvular Activities

In these dynamics, diaphragm behavior should be considered as an antireflux mechanism. Nowadays, it is clear that both the smooth muscle of the distal esophagus (lower esophageal sphincter) and the pillars of the diaphragm (crural diaphragm) represent the distal protection mechanisms of the esophagus (Mittal and Balaban 1997). Changes in distal esophageal pressures are correlated to contractions of the esophagus and stomach (Dent et al. 1983), whereas crural contractions are related to the amount of inspiration or to the carrying out of activities increasing intra-abdominal pressure (i.e., Valsalva, cough, defecation, delivery) (Mittal et al. 1990): this mechanism is much more dynamic, powerful, and effective in guaranteeing containment to the lower esophageal sphincter. Furthermore, when the intra-abdominal pressure increases, a reflex is generated that causes crural contraction and an increase in the lower esophageal sphincter pressure (Shafik et al. 2004).

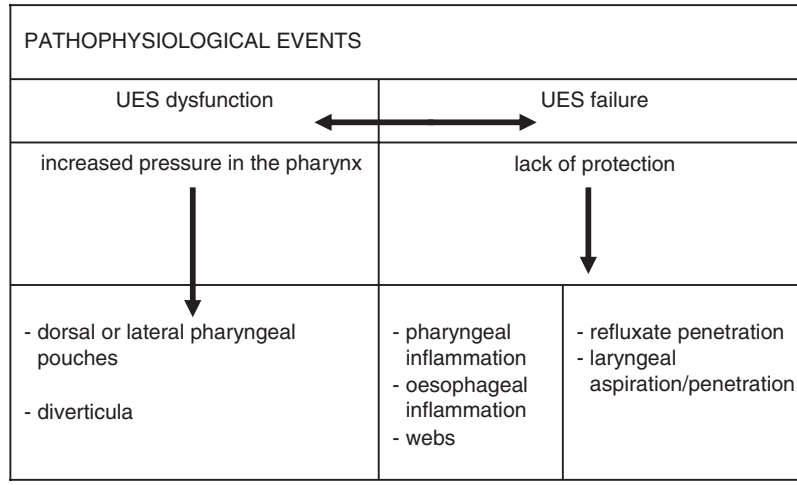

Fig. 3 Direct contact of refluxate with laryngeal structures

The crura, however, consist of easily fatigable striated muscle fibers that are therefore inadequate for prolonged or too fast performances, which are quite often required in singing, for instance in supporting prolonged and sustained musical phrases or vocal exercises at extreme pitches. The air compression generated in the rib cage by the push action of the abdominal muscles and by the lowering of the sternum increases the expiratory push but compresses the stomach, antagonizing the lower esophageal sphincter. These dynamics may also account for the increase in high-reflux episodes up into the pharynx during physical activity (Emerenziani et al. 2005) or with increased intra-abdominal pressure. Under these conditions there might be a direct contact of the refluxate with the laryngeal structures (direct mechanism) (Fig. 3), which can also occur by means of an indirect mechanism (Fig. 4).

Distal reflux through the lower esophageal sphincter causes, through a neural or neurohumoral transmission route, a dysfunction in the upper esophageal sphincter which may result in a reduced opening or early closure thereof (hypercompetence or hyperfunction). The insertion of the cricopharyngeal muscle into the cricoid cartilage determines, in the case of hypercontraction, an antagonism to the closing mechanisms of the laryngeal cavity, by reducing or preventing adequate facing of the arytenoids with respect to the epiglottis, thereby creating a predisposition to penetration episodes in the place of free inhalation. In 1370 dysphonic patients, a high incidence of pene-

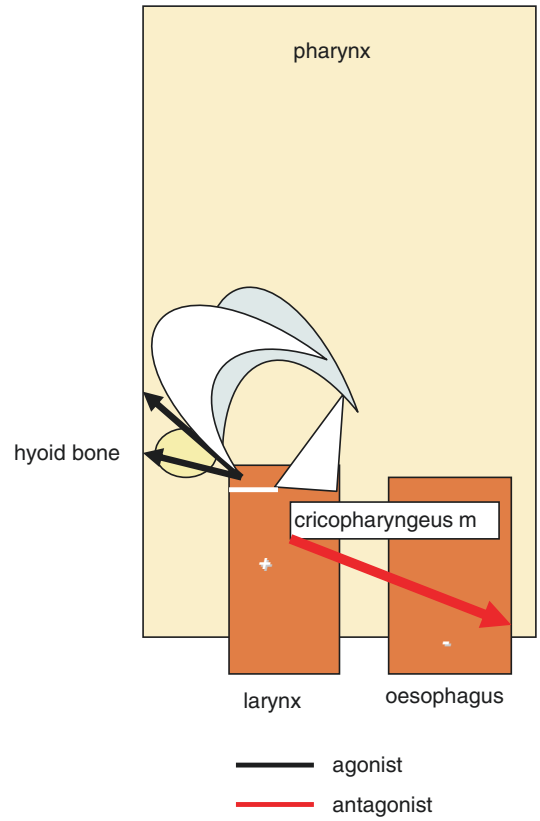

Fig. 4 Indirect involvement of laryngeal structure

tration (1100 patients) was observed by Wuttge-Hannig and Hannig and explained by the authors as a result of such an indirect mechanism (Wuttge-Hannig and Hannig 2009). Also posture can differentiate patients with laryngopharyngeal reflux (LPR, see below): in the standing position, and therefore while awake, the patients may experience reflux episodes during the day (Kouffman et al. 2000).

Some patients with LPR report reflux episodes only when they sing. In relation to what was stated above, we can add that patients with LPR also complain about motility disorders resulting in a delayed acid clearance or affecting the upper esophageal sphincter with an increase in the basal pressure (Fouad et al. 1998). The experimental instillation of acid in the distal esophagus of patients with LPR and in controls determines an increase in the tone of the UES (Gerhardt et al. 1978).

4.1.2 Physiological Influences

In addition to the above, singers often have dietary habits that promote reflux, with late dinners after evening performances and going to bed immediately after eating. Furthermore, the stress that is often part of the singer's career should also be taken into consideration. Esophageal motility disorders or other reflux-related conditions (increased acid secretion, transient reduction in lower esophageal sphincter pressure directly elicited by pharyngeal acid stimulation, decreased threshold of reflex gastric distension) have been described in psychophysical stress conditions (Castell 1999). The need to maintain their voices at optimal performance levels pushes these vocal professionals to take drugs or self-medication that may even worsen subjective or perceptive voice symptoms. Also the impact of an incorrect or inadequate diet on the genesis or maintenance of the reflux disease should not be neglected.

The most evident anatomical alterations of the laryngeal structures are caused by a direct contact with acid or alkaline juices and by the action of enzymes contained therein. In addition to erythema or edema, a hacking cough can cause bleeding or mucosal tears responsible for obliteration of the *lamina propria* and the formation of adherences of mucosa to the vocal ligament. The inefficiency of the laryngeal vibrator associated with the decreased respiratory performance (potentially mediated by the aspiration of the refluxate into the lower airways) triggers vocal abuse and effort circuits that may lead to the onset of nodules or other lesions of the epithelial lining of vocal folds (Sataloff 1993; Spiegel et al. 1988).

5 Common Pathological Events

If the anatomical aspects are integrated into the various functions, such integration also characterizes pathological events that may affect effectors with a consequent impact on related functions (Fig. 1): in consideration of the high integration of these functions, dysfunctions may therefore be due to *noxae* localized at various levels and differently influenced by various pathological events.

Diseases related to voice and swallowing disorders may therefore be due to lesions of the nervous system in all of its components, autoimmune/dysreactive, iatrogenic (surgical operations, chemotherapy, radiotherapy, drug interaction) pathologies, as well as nonorganic ones, if not overtly psychic or psychiatric components, which may sometimes explain certain clinical pictures. Table 1 briefly summarizes

Table 1 Events related to voice production

Voice production	
Central nervous system	Planning, activation, control
Peripheral nervous system (PNS)	Transfer of information
Thoracic bellows	Volume, pressures, flows
Larynx	Energy vibration: longitudinal and vertical direction
Vocal tract	Energy distribution in the speech spectrum

the events underlying voice production, whereas Table 2 illustrates the pathogenetic events that may affect it.

Table 2 Pathophysiology of voice disorders

Pathophysiological events	Site
Lack of planning, activation, control	CNS
Information transfer from centers to effectors	PNS, lack of motility, sensation
Breathing disorders (volumes, pressure, flows)	Thoracic bellows
Glottic insufficiency	Larynx, CNS, PNS
Vibratory alterations of the mucosa (qualitative and quantitative)	Larynx
Pathological posture of intrinsic and/or extrinsic laryngeal muscles	CNS, bellows, larynx, vocal tract
Breath-phonation incoordination	CNS, bellows, larynx
Phonation-resonance incoordination	Larynx, vocal tract
Incorrect posture	Posture, respiratory function

5.1 Vocal Alterations

Dysphonia is defined as a disorder characterized by altered vocal quality, pitch, loudness, or vocal effort that impairs communication or reduces voice-related QOL (Schwartz et al. 2009). Voice disorders may be differently classified. In the literature there exist only a few works on the topic (Milutinovic 1966; Rosen and Murry 2000), but the most recent orientations identify two main categories: organic dysphonia (Table 3) (Blitzer et al. 1992; Bouchayer et al. 1985; Sataloff 1997; Schindler 1980; Segre 1976; Ursino 1995) and nonorganic (dysfunctional or muscle tension) dysphonia (Table 4), characterized by structural or functional changes in the organs involved in voice production (Aronson 1980; Remacle and Lawson 1994; Sataloff 1997).

The interaction between form and structure (Fig. 1) explains the rich variety of related symptoms (dysphonia syndrome), including acoustic signs (alterations in volume, frequency, pitch, texture), clinical signs (inspection; endoscopic: morphological and dynamic findings), and/or subjective physical signs (phonastenia, pharyngolaryngeal paraesthesia), psychological signs

Table 3 Organic dysphonia

Organic dysphonia	
Thoracic bellows	Restrictive, obstructive, mixed lung disease
Laryngitis	Acute, chronic nonspecific and specific
Glottic plan alterations	Epithelium and lamina propria, arytenoid mucosa, anterior commissure
Postsurgery	Laryngeal structures (epithelium, muscles, framework)
Dysmobility	Ankylosis, peripheral nerve injury
Neurological disorders	Cortical, subcortical, cerebellar, peripheral nerve pathways
Muscle disease	Myasthenia, dystrophies, dermatomyositis, myofibromatosis, muscle tumors, intrachordal hematoma
Drugs	Testosterone, steroids, antihistamines, spasmolytic, atropine, drugs, high doses of vitamin C, diuretics
Hormonal disorders	Dysthyroidism, premenstrual hyperestrogenism, dysmenorrhea, pregnancy, menopause, andropause, hyperpituitarism, hypogonadism/hyperestrogenism in prepubertal male and hyperandrogenism in prepubertal female, diabetes
Tesaurismosi	Amyloid, lipids, mucopolysaccharides
Pitch alterations	Primary (change of sex, androphonia), secondary
Vocal tract alterations	Nasality, volume resonators, feature walls

Table 4 Nonorganic (dysfunctional or muscle-tensive) dysphonia

Nonorganic dysphonia	
Primary	Overuse, misuse, difficulties in pitch discrimination, imitation of incongruous vocal models
Secondary psychogenic	Conversion disorder, vocal cord dysfunction, disorders of the voice moult, pathological anxiety, depression
Secondary to organic disease	Audiogenic

(own voice perceived as unpleasant or inadequate), which are occasionally or constantly present in all or only in certain communication situations (Bergamini et al. 2002).

5.2 Deglutition Alterations

From a brief overview of the conditions that may be related to the onset of dysphagia (Table 5), many common pathogenetic events can be identified, with a combination of swallowing and voice disorders.

5.3 The Effects of Reflux

One of the main causes of comorbidity involved in voice and swallowing disorders is the laryngopharyngeal reflux (LPR), which is treated in a separate chapter of this volume. The topic will therefore be taken into account only as a concausal factor.

The laryngopharyngeal reflux involves different anatomical sites, including the lower esophageal sphincter, esophagus, upper esophageal sphincter, laryngeal structures, oral cavity, trachea, and lungs. LPR represents the expression of the locoregional involvement of a gastroesophageal reflux disease (GERD), whereas reflux laryngitis (RL) is a more circumscribed expression of the local problem. LPR was characterized as a nosological entity in the 1980s (Wiener et al. 1989; Koufman 1991) at the same time as laryngeal

Table 5 Oropharyngeal dysphagia (Cook and Kahrilas 1999)

Oropharyngeal dysphagia
Iatrogenic medication side effects (chemotherapy, neuroleptics, etc.)
Postsurgical muscular or neurogenic
Radiation
Corrosive (pill injury, intentional, cytomegalovirus, candida, etc.)
Infectious: diphtheria, botulism, Lyme disease, syphilis, mucositis (herpes)
Metabolic: amyloidosis, Cushing's syndrome, thyrotoxicosis, Wilson's disease myopathic
Connective tissue disease (overlap syndrome)
Paraneoplastic syndromes
Neurological diseases:
Myasthenia gravis, myotonic dystrophy, oculopharyngeal dystrophy dermatomyositis, polymyositis, sarcoidosis, cerebral palsy, Guillain-Barré syndrome
Metabolic encephalopathies
Neurological brainstem tumors
Head trauma
Stroke
Huntington's disease
Multiple sclerosis
Polio postpolio syndrome
Tardive dyskinesia
Amyotrophic lateral sclerosis
Parkinson's disease
Dementia
Elderly
Structural disease:
Cricopharyngeal bar, Zenker's diverticulum, cervical webs
Oropharyngeal tumors
Osteophytes and skeletal abnormalities
Congenital (cleft palate, diverticula, pouches, etc.)

signs correlated to it gained greater attention (Belafsky et al. 2001; Belafsky et al. 2002). Hidden signs of gastroesophageal reflux are an etiological factor often reported in patients with ENT problems, especially in relation to voice. In 1989, Wiener reported 78% of LPR cases documented with dual-probe pH monitoring in a series of 32 patients (Wiener et al. 1989). This is a highly frequent problem in professional voice users and

singers. In 1991, Sataloff et al. described reflux laryngitis in 265 out of 583 voice professionals (45%), including singers, who had required medical treatment over the previous 12 months (Sataloff et al. 1991). However, reflux laryngitis is often an occasional finding during medical consultation for other disorders and not the only cause of the voice problems complained of by the patient. The incidence of a posterior laryngitis is lower in patients without dysphonia but is present in 78% of patients with hoarseness and in 50% of patients with general voice problems (Koufman et al. 1988). Other data on the prevalence of LPR were published in the following years (Koufman 1991; Koufman et al. 2002). LPR is often associated with aspiration. This may be clinically irrelevant or be associated with chronic cough, reactive airway disease, difficulty in controlling asthma, distal phlogosis, and bronchiectasis. Laryngeal involvement in GERD is often associated to hyperkinetic phonation in those patients who try to compensate for an inflammatory condition of the larynx. Several issues are particularly interesting for voice professionals. In the first place, the age of the patients: many are young and need a long period of pharmacological treatment (pump inhibitors or H2 antagonists). They neutralize the refluxate and many related symptoms, but not the effect of neutral or alkaline substances (biliary salts) or enzymes that cause in any case damage to the larynx, pharynx, and lungs. In professional voice users these substances may continue to cause local symptoms, such as clearing the throat, burning in the throat, and cough (Sataloff et al. 2006).

6 Recent Contributions in the Literature

Although the correlations between the respiratory and digestive tracts are so closely interlinked and overlapping, and in spite of the vast literature existing on voice and deglutition disorders when considered separately, only a few studies have been conducted on their association in specific populations and even less with respect to professional voice users.

A bibliographic research using the major search engines actually confirmed the above. Results from a PubMed search for articles over the last 15 years including key words such as "dysphagia" or "swallowing disorders" and "singing voice" or "professional voice," found only 25 articles in which sometimes the association between singing or professional voice and dysphagia is actually not strictly relevant. For instance, Sereg-Bahar et al. (2005) evaluated in a prospective study the acoustic characteristics of an/a/ produced by a sample of 43 patients with LPR before and after treatment with esomeprazole. The group was compared with another group of patients with vocal fold polyps. In addition to this acoustic parameter, further parameters were evaluated: medical history, and laryngostroboscopic and esophagogastroscopic findings. The conclusion was that the tested drug was effective for LPR management, whereas for LPR diagnosis, medical history and videolaryngoscopy proved to be superior to esophagogastroscopy.

Acoustic voice analysis and laryngoscopic investigation can also be found in the work by Vashani et al. (2010) who evaluated the effectiveness of voice therapy in a group of 32 patients with GERD and dysphonia. The sample was subdivided into two groups: voice therapy combined with omeprazole and omeprazole alone, with follow-up evaluation after 6 weeks. Voice analysis included jitter, shimmer, harmonic-to-noise ratio (HNR), and normalized noise energy (NNE). Esophageal and laryngeal signs were assigned according to the reflux symptom index (RSI). The authors reported an improvement in all voice parameters and better results of the pharmacological treatment if combined with vocal therapy.

Similarly Siupsinskiene et al. (2009) considered six parameters of the voice range profile (VRP) and five parameters of the speech range profile in a group of 60 female dysphonic patients with LPR compared with a sample of 66 subjects with normal voice. In their conclusions the authors reported a reduced vocal capacity as documented by VRP measures in LPR patients and underlined the usefulness of these measures in the pre- and posttreatment quantitative assessment

of voice performance. Similar conclusions were drawn by Oguz et al. (2007) and Pribuisienë et al. (2005). In an Italian study, the correlation between LPR and dysphonia was assessed in a sample of 62 patients without significant laryngoscopic findings and vocal abuse history by using a questionnaire validated for typical reflux signs versus a sample of subjects without voice problems. Electroacoustic, laryngostroboscopic, and 24-h pH monitoring data of the two samples suggested a correlation between the amount and duration of the reflux (in patients with pH-metry suggestive of LPR) and a dysfunction of arytenoid muscles causing laryngeal compensatory stress which was in turn responsible for chronic fatigue (Cesari et al. 2004). On the contrary, no significant variation in electroacoustic parameters was found by Handman et al. (Hamdan et al. 2001) in a sample of 22 patients with GER-induced laryngeal signs treated for 4 weeks with pantoprazole 40 mg b.d. and cisapride 20 mg twice daily. The treatment actually determined a quick disappearance of vocal symptoms (vocal fatigue and excess mucus production) and endoscopic signs.

The association between hoarseness and LPR has also been studied by Ozturk et al. (2006) in a sample of 43 subjects presenting hoarseness for over 3 months and 20 control subjects. All subjects underwent videolaryngoscopic evaluation and 24-h double-probe pH monitoring. The results obtained by comparing data from the two methods in the two populations showed that in the study group 27 patients out of 43 (62.8%) presented laryngeal reflux episodes, whereas in the control group only 6 out of 20 (30%). The average of pharyngeal reflux episodes was 7/24 h (SD 8.8) in the study patients versus 0.9/24 h (SD 1.9) in the control group, with $p = 0.003$. In the study group the average of laryngopharyngeal reflux episodes in upright position was 5.8 (SD 7.0) vs. 1.2 (SD 3.3) in supine position, both values being significantly higher than those found in the control group ($p = 0.005$ and $p = 0.014$, respectively), thereby demonstrating that LPR is significantly greater in patients with hoarseness than in the control subjects, although presenting LPR as well. The results of this study have further shown that the most common symptoms in the study group were heartburn and persistent throat clearing, whereas the endoscopic clinical finding was pachydermia. This may suggest that the severity of LPR rather than its presence may be the factor that triggers the onset of symptoms.

Some works found in the bibliographic research are epidemiological studies. Among these, Roy et al. (2005) evaluated a random sample of 1326 subjects interviewed with a questionnaire and reported that the lifetime prevalence of a voice disorder was 29.9%, with 6.6% of participants reporting a current voice disorder. The logistic regression correlated such data with some risk factors: sex (female), age (40–59 years), conditions and demands of vocal usage, esophageal reflux, exposition to chemical agents, and frequent colds and sinus infections. Paradoxically, the consumption of tobacco or alcohol was found not to increase the chances of developing a chronic voice disorder. Voice disorders proved to have a negative impact on work performance (4.3%) and work attendance: 7.2% of interviewees reported that they were absent from work one or more days in the course of the previous year and 2% more than 4 days due to voice problems.

Abnormal laryngeal findings that can be correlated to reflux were identified in a sample of 65 asymptomatic singing students who underwent videostroboscopic evaluation. Five students (8.3%) exhibited benign vocal fold lesions (2 with nodules and 3 with cysts) and 44 (73.4%) posterior erythema, suggesting possible reflux (Lundy et al. 1999). This correlation was considered useful to plan preventive measures in young singing professionals with high vocal demands.

Similar considerations were made by Elias et al. on a population of 65 professional singers who voluntarily underwent strobovideolaryngoscopic evaluation after observing 58% laryngeal abnormalities in six different clinical entities. The authors confirmed the usefulness of standardizing normal strobovideolaryngoscopic findings in professional singers being aware of the variability of laryngeal behavior in this population (Elias et al. 1997). Similarly, Heman-Ackah et al. studied 20

singing teachers who voluntarily underwent strobovideolaryngoscopic evaluation, of whom 7 reported voice problems and 13 a normal voice. The presence of organic lesions (vocal fold masses) was a common finding in asymptomatic teachers, whereas reflux laryngitis was found in both symptomatic and asymptomatic teachers. Movement asymmetry was more common in singing teachers with voice disorders (Heman-Ackah et al. 2002). Dysphonia and LPR findings were associated in a group of eight singers with bulimia, leading to the conclusion that LPR may be a factor that contributes to the development of vocal disorders in singers with bulimia (Rothstein 1998).

What is more interesting is the association between functional dysphonia and LPR. The correlation between the two entities has been investigated by several authors. Kerkos et al. (2007) studied 23 subjects with dysphonia for over 3 months, by comparing them with eight healthy volunteers. Of the initial sample 22 dysphonic patients and 6 healthy subjects completed the protocol that included a 24-h dual-probe pH-metry. Of all the studied parameters, the longest duration (in seconds) of reflux episodes in supine position and the time fraction in which the pH was <4 in supine position were significantly longer in dysphonic patients than in control subjects ($p < 0.05$). This led the authors to conclude that there is a correlation between LPR and the two parameters, although many more parameters may determine functional dysphonia, including "medical" and psychological causes.

A 30-month retrospective review of 150 subjects (60% females and 40% males, mean age 42.3 years) with muscle tension dysphonia was carried out by Altman et al. (2005). Medical history showed the presence of gastroesophageal reflux (49%), high stress levels (18%), surmenage (63%), and malmenage (23%). Instrumental clinical evaluation performed in 82% of patients showed the presence of anatomical abnormalities in 52.3% of subjects (vocal fold edema, or paralysis/paresis). Speech-language assessment identified a poor phonatory support to breathing, improperly low voice pitch, and visible neck tension in most patients. Adequate voice volume was observed in 23.3% of patients. This range of factors indicates the presence of multiple factors in the genesis of muscle tension dysphonia.

The association between dysfunction factors, such as extrinsic laryngeal muscular tension (ELMT), muscle misuse dysphonia (MMD), and GER, was investigated also by Angsuwarangsee and Morrison (2002). A sample of 465 patients (65% females and 35% males) were sequentially evaluated and ELMT results were analyzed in relation to GER diagnosis. A close relationship ($p \leq 0.01$) was found between the thyroid muscle in GER patients and MMD, indicating that there might be a correlation between the extrinsic and intrinsic laryngeal muscular tension, useful in the diagnosis of MMD.

A professional susceptibility to GER related to professional singing was suggested by several authors. The first work dates back to 2003 (Cammarota et al. 2003), reporting on the experience conducted with four professional singers who showed decreased respiratory muscle functioning during reflux episodes during performances. Reflux episodes were related to the quick and prolonged need of increasing intra-abdominal pressure due to the need of reducing subglottic pressure. According to the authors this was the first case described in the literature of a worsening of GERD symptoms in professional singers during performances.

This study was followed by another work by the same author (Cammarota et al. 2007) with the purpose of studying the prevalence of GER symptoms in a group of professional opera choristers versus a control group of non-singers. Three hundred and fifty-one opera choristers belonging to professional lyrical choruses from various Italian regions were compared with 578 subjects resident in the same areas with a similar age and sex distribution. By means of a structured questionnaire, the occurrence of reflux symptoms in the course of the previous year, individual characteristics, and life habits of the two groups were investigated. Prevalence rate ratios, adjusted for sex, age, body mass index, smoking status, alcohol consumption, and other confounding factors, were computed.

In the sample of choristers a statistically significant increase in heartburn, regurgitation,

cough, and hoarse voice was observed versus the control sample, with adjusted prevalent rate ratios of 1.60 (95% confidence interval [CI], 1.32–1.94), 1.81 (95% CI, 1.42–2.30), 1.40 (95% CI, 1.18–1.67), and 2.45 (95% CI, 1.97–3.04), respectively. Multivariate analysis correlated regurgitation in a consistent way with the cumulative duration of singing activity ($p = 0.04$) and weekly singing performances ($p = 0.005$). The authors concluded by reporting a greater prevalence of reflux symptoms in opera choristers versus control subjects. They also underlined the need for further investigation to clarify whether GER in this population is stress related and may be considered as a professional disease. As to the relation with stress Marchese et al. (2008) described the case of a 49-year-old professional soprano with a 6-year history of regurgitation and pyrosis in association with an increased time to achieve adequate vocal warm-up, restricted vocal tone placement, and decreased pitch range. After the diagnosis of posterior laryngitis and a negative esophagogastroduodenoscopy, a functional study with esophageal manometry and pharyngeal pH monitoring was carried out. Esophageal manometry documented lower esophageal sphincter incompetence and isolated episodes of upper esophageal sphincter hypertonia. Pharyngeal pH monitoring (the patient was asked to carry out her normal singing and vocal warm-up activity) reported, during singing, 69 episodes of pharyngeal reflux equal to 10% of total reflux time, which is ten times higher than that previously described as the upper limit (0.9%) in healthy volunteers. This finding suggested a correlation between pharyngeal acid exposure and singing, thereby indicating that such a condition may be considered related to this professional activity. The authors agreed that further data are required to support this conclusion.

The latest work on this topic was carried out by Pregun et al. (2009), who considered the prevalence of GER symptoms in a population of professional opera choristers (202 subjects), wind players (71 subjects), glassblowers (43 subjects), and water polo players (54 subjects) in comparison with a sample of 115 subjects. By means of a questionnaire the occurrence of reflux symptoms, individual characteristics, and life habits of the two groups were investigated. Statistical processing of data showed a statistically higher prevalence of heartburn, regurgitation, and hoarseness in professional choristers than in control subjects ($p < 0.001$). Among professional wind players, heartburn and regurgitation were significantly more frequent compared with controls ($p < 0.05$ and $p < 0.01$, respectively). Glassblowers reported a significantly higher prevalence of acid regurgitation in comparison with controls ($p < 0.01$). The prevalence of reflux symptoms in water polo players was similar to that of controls. In opera choristers, wind players, and glassblowers, reflux symptoms appeared to be significantly correlated with the cumulative lifetime duration of professional singing, playing, and working activity, respectively ($p < 0.05$).

The results reported by the authors in agreement with Cammarota et al. (2007) demonstrated that professional opera choristers, professional wind players, and glassblowers presented a higher prevalence of reflux symptoms than control subjects. This work-related condition was found to have a negative impact on QOL and professional performances.

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Psychiatric Aspects of Dysphagia

M. Bülow

Contents

Abstract

Dysphagia with a psychiatric background is a rare condition, not so well understood, and presented with no structural or organic disease detectable. More research would therefore be of importance for more knowledge about this condition that in several cases affects the quality of life in a negative way.

Fear of swallowing, avoidance of swallowing specific foods, fluids, or pills seem to be the most frequent symptoms in psychogenic dysphagia, and may result in malnutrition and weight loss.

When psychogenic dysphagia is suspected a thorough swallowing evaluation is necessary, involving clinical as well as instrumental examinations. A multidisciplinary approach is required. Professionals from neurology, otolaryngology, speech-language pathology, radiology, and gastroenterology may be involved. The diagnosis of psychogenic dysphagia should, to avoid misdiagnosis, be reserved for patients with strong psychological symptoms and fear of swallowing. Most effective treatment of psychogenic dysphagia seems to be a combination of psychological treatment and dysphagia therapy. Anti-anxiety medications may in some cases be effective. A close collaboration between the dysphagia clinician and colleagues in psychology is necessary for an optimal management.

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1 Introduction and Terminology

In the management of dysphagic patients with acute or chronic problems where no structural or organic disease could be diagnosed, the etiology may be psychiatric. Dysphagia with a psychiatric etiology is a rare condition, and not so well understood. In the literature few scientific studies relevant to this topic could be found. More research is necessary to learn more about this condition, and thereby be able to help the patients to handle their pathologic fear of swallowing and also to improve their quality of life.

However, there are reports suggesting that persons with psychological conflicts in an attempt to reduce unacceptable emotional responses may convert them into more acceptable physical manifestations (Finkenbine and Miele 2004; Lehtinen and Puhakka 1976). It has also been suggested that patients with this condition may suffer from anxiety and depression (De Lucas-taracena and Montanes-rada 2006).

Several different terms are used to describe a condition of dysphagia with psychiatric origin where p*sychogenic dysphagia* is most well known. Sometimes the term *sitophobia,* from the Greek words sito (food) and phobia (fear, aversion), may be used to describe a condition with pathologic fear of swallowing. Other terms may be *choking phobia or swallowing phobia* (Seems et al. 2009; De Lucas-taracena and Montanes-rada 2006; McNally 1994), g*lobus hystericus* (Finkenbine and Miele 2004; Ravich et al. 1989; Stacher 1983, 1986), *hysterical dysphagia* (Ciyiltepe and Türkbay 2006; Nicasso et al. 1981), *phagophobia* (Ciyiltepe and Türkbay 2006; Shapiro et al. 1997), and *pseudodysphagia* (Bradley and Narula 1987).

2 Symptoms in Psychogenic Dysphagia

Psychological factors which inhibit normal swallowing and result in inefficient and/or disorganized swallowing are thought to be related to signs of psychogenic dysphagia. Nicholson et al. (2010) find that psychogenic dysphagia is a problematic diagnosis. The psychological mechanism and how it differs from conscious simulation seem to still remain unclear.

The most common complaints of patients with psychogenic swallowing problems may be fear of swallowing manifested as difficulties initiating the pharyngeal swallowing and thereby sometimes avoidance of eating. Certain foods, fluids, and pills may cause the patients huge stress and problems to swallow (Barofsky and Fontaine 1998; Ciyiltepe and Türkbay 2006; Leopold and Kagel 1997; Ravich et al. 1989; Shapiro et al. 1997). Also abnormal oral behaviors, with repeated deviant tongue movements, a feeling of throat pressure, and complaint of globus could be found in this patient group. Complaints reported by Bradley and Narula (1987) and Shapiro et al. (1997) are a globus sensation, general difficulties in swallowing, breathing problems, and fear of choking. Also malnutrition and weight loss may be associated with a swallowing condition with psychiatric origin (Barofsky and Fontaine 1998; Ciyiltepe and Türkbay 2006; Finkenbine and Miele 2004; Shapiro et al. 1997).

In some literature psychogenic dysphagia has been described as a *conversion disorder*. Psychological conflicts and anxiety are transformed into somatic symptoms and are regarded as an unconscious process. Already in 1935, Kanner described dysphagia as a primary conversion disorder. He presented a case with a 12-year-old boy that developed dysphagia to solid foods due to physical abuse from his father for eating improperly. In our swallowing clinic we have encountered similar cases. A young single mother, with a 5-year-old daughter, worked as a cashier in a grocer's shop. She was unable to take a normal lunch break due to customer demands which was a high stress factor in her working conditions. After a period of time she was unable to eat and swallow in a normal way. Her complaints were primarily orally in nature, along with difficulties in initiating the swallow. VFSE showed signs of oral dysphagia with intact pharyngeal function.

Another example is a middle-aged woman with an abnormal oral phase of swallowing and

fear of initiating the swallowing. She told us during one of her therapeutic sessions that she during her childhood was forced by a strict grandmother to always empty her plate. She experienced a great fear when she visited her, especially when forced to eat with her. When exposed to stress later in life, she reacted with an inability to eat and swallow normally.

Another form of conversion disorder described as a manifestation of both a physiological disorder and psychiatric illness may be the sensation of globus (Finkenbine and Miele 2004). Bradley and Narula (1987) have described the sensation of a "lump" or "fullness" localized to the throat in association with globus hystericus, hysterical dysphagia, or pseudodysphagia. Their conclusion is, when no evident cause was found, that the condition may be a "'primary globus pharyngeus', or a 'secondary globus pharyngeus' when the etiology was detectable" (p. 689). Okada et al. (2007) analyzed in a case study six children with phagophobia according to psychopathology and current treatment. Their results indicated that evaluation of premorbid personality is crucial to the prognosis.

Psychological factors have also been found to be associated with esophageal dysphagia. Esophageal contractions could result from psychological stress. Kronecker and Meltzer reported (1883) that esophageal contractions, not only due to emotional tension, but also in some cases due to cold or hot food, could react with nonpropulsive contractions. Other interesting observations have shown that stimuli not related to ingestion such as intense short sounds may influence esophageal contraction and are likely to form part of the defense reaction of a healthy organism (Stacher 1983).

Abnormal oral swallowing behaviors in the presence of intact pharyngeal stage function may be revealed at radiological swallowing evaluations. In some cases, such oral abnormalities may be associated with psychogenic dysphagia. Diffuse esophageal symptoms may also be related to psychological factors. According to Jones (2003) patients with psychogenic dysphagia may demonstrate a variety of swallowing signs during VFSE, including the presentation of small boluses, multiple tongue movements, and "complex oral motions such as rocking, swirling, bunching and pumping" (p. 97). Also a presence of a pharyngeal swallow delay without oral propulsion of bolus has been described by Jones (2003).

Even if reports regarding communicative symptoms associated with psychogenic dysphagia are not found in the literature an interesting case study describes a 63-year-old male "deglutition stutterer." The man developed myoclonus of the tongue and contractions of the hypopharyngeal muscles in the moment of deglutition. The history was remarkable for pharyngeal spasms in his youth, which reemerged as described above in stressful situations (Escher 1983).

At our swallowing clinic we have during the years 2002–2010 completed 2084 VFSE studies, and psychogenic dysphagia has been diagnosed in 25 cases. The most frequent complaints regarding swallowing signs and symptoms are listed below. The patients often presented more than one symptom. Those patients with complaints of globus without pharyngeal dysfunction or with suspected esophageal dysfunction were referred to either an otolaryngologist or a gastroenterologist for further clinical or instrumental evaluation.

Fear of swallowing	13/25
Experienced difficulties in swallowing specific consistencies	13/25
Problems in initiating the pharyngeal swallow	10/25
(The patient experienced a feeling of being unable to swallow. At VFSE we could document a normal pharyngeal swallow.)	
Oral abnormalities	8/25
(Such as multiple tongue movements with difficulties in propelling the bolus posteriorly to pass the base of the tongue and initiating the pharyngeal swallow.)	
Globus complaints	6/25
Normal pharyngeal swallow	25/25

3 Epidemiology

From different swallowing clinics has been reported that psychogenic dysphagia is a minor group of the patients complaining of swallowing

problems. Among patients referred to the Johns Hopkins Swallowing Center 13% of the patients had been labeled with psychogenic dysphagia or globus hystericus. However, when this group later was reevaluated, more than half of the group was found to have an organic etiology for their dysphagia (Ravich et al. 1989). From a large sample of patients seen in a swallowing center and complaining of swallowing difficulties, a normal pharyngeal swallow has been revealed on VFSE (with additional abnormal oral behaviors in some cases) accounting for approximately only 3% of the group (Barofsky et al. 1993). Malcolmson et al. (1966) diagnosed 231 patients with globus hystericus, and negative clinical and radiological evaluations were found in 20% of the patients. Patients with different psychosomatic disorders of gastrointestinal tract were studied (612 pts) by Korkina and Marilov (1995). In 70% of the 612 studied cases, patient relatives also had psychosomatic diseases, suggesting the possible influence of genetic and environmental factors in this condition. Choking phobia was found to be more frequent in females (two-thirds of cases) and had a high comorbidity with anxiety disorders. Life events such as a divorce, disease in the family, or unemployment, as well as traumatic eating antecedents, were also frequently present (De Lucas-Taracena and Montanes-rada 2006). Prevalence studies have shown that 45% of young and middle-aged people have been estimated to suffer from symptoms of globus, often in combination with strong emotion (Thompson and Heaton 1982).

4 Swallowing Evaluation

A diagnosis of psychogenic origin must be used with caution and only after a thorough evaluation. At the Johns Hopkins Swallowing Center, Ravich et al. (1989) performed a reevaluation of 23 patients with the diagnoses of psychogenic dysphagia or globus hystericus. They subsequently found that more than half of these patients had an underlying physical explanation for their difficulty swallowing. In 65% (15 of 23) of the patients pharyngeal dysfunction, structural obstruction, or esophageal dysmotility were found. Due to those findings they suggested that when any changes or progression of symptoms were reported, a careful reevaluation should promptly be performed. Stacher (1986) also recommended caution when attributing symptoms of dysphagia to psychogenic origins and emphasized the importance of performing instrumental examinations:

> It is not justifiable to label dysphagic symptoms, for which no organic etiology can be detected, as psychogenic or psychosomatic. Patients with such symptoms should be studied by means of esophageal manometry and/or pH-metry to reveal the nature of their disorder and to enable adequate therapy (p. 502).

A careful and thorough evaluation must be completed, and may also include psychological assessment when a psychogenic dysphagia is suspected. Okada et al. (2007) have studied psychopathology and treatment in children with phagophobia, and they found that an evaluation of premorbid personality was crucial to the prognosis. The diagnosis of psychogenic dysphagia should, to avoid misdiagnosis, be reserved for patients with strong psychological symptoms and/or fear of swallowing (Jones 2003). A positive dysphagia history consisting of different complaints associated with the moment of swallowing is often found in patients with psychogenic dysphagia. The patients may report the feeling of a lump or pressure in the throat, fear of choking, and/or the inability to swallow solids. A complete and careful medical history is crucial and should therefore be the first part of the swallowing evaluation (Castell and Donner 1987). Important considerations in the medical story include the patient's symptoms, when they occur, under what circumstances, duration of swallowing difficulty, and determination regarding a history of eating disorders, weight loss, and family history of dysphagia. Following the medical history, a physical examination should be performed to rule out any organic causes for the symptoms. A multidisciplinary approach may be required, involving professionals from neurology, otolaryngology, speech-language pathology, radiology, and gastroenterology. Next step, often indicated for a complete evaluation, is an instrumental assessment of swallowing (i.e., VFSE to evaluate oropharyngeal

swallowing, barium swallow/esophagram to assess esophageal function). Esophagoscopy, manometry, pH monitoring, and endoscopy may also be of value. Laboratory tests to rule out disturbances as hypo- or hyperglycemia, systemic infections, or toxins may also be of importance in establishing the diagnosis of psychogenic dysphagia. Another technique discussed by Vaiman et al. (2008) is to use surface electromyography (sEMG) of deglutition to investigate suspected psychogenic dysphagia (Table 1).

5 Treatment of Psychogenic Dysphagia

A multidisciplinary approach including professionals from psychiatry, psychology, otolaryngology, neurology, speech-language pathology, radiology, and gastroenterology may be required in the treatment of psychogenic dysphagia. A combination of psychological treatment and dysphagia therapy seems to be the most effective treatment of psychogenic dysphagia (Ball and Otto 1994; De Lucas-taracena and Montanes-rada 2006). In a case report from Ciyiltepe and Türkbay (2006) a 13-year-old boy suffering from psychogenic dysphagia treated with such an approach is described. A psychological behavior management program has to consist of behavior modification, insight-oriented therapy, and family therapy. The dysphagia therapy sessions should include therapeutic eating trials with various consistencies, as well as oral motor exercise programs. Also relaxation exercises, breathing support, and functional coughing could be of benefit for the patient. In a report from Shapiro et al. (1997) the benefit of behavioral techniques

Table 1 Treatment of psychogenic dysphagia

Evaluation of psychogenic dysphagia	Professionals commonly involved
History	
A thorough history often obtained in a multidisciplinary fashion emphasizing:	Otolaryngologist Gastroenterologist
Patient complaints	Psychiatrist
Symptoms and when they occur and under what circumstances	Psychologist
Duration of swallowing difficulty	Speech-language pathologist
Determination regarding a history of eating disorders	Radiologist
Weight loss	Laboratory staff
Family history of dysphagia	
Clinical examinations	
Physical examinations may be performed by a multidisciplinary team of professionals including	
Otolaryngologist	
Speech-language pathologist	
Gastroenterologist	
Psychiatrist	
Psychologist	
Instrumental examinations	
Radiology:	
VFSE	
Hypopharynx esophagus examination (a morphologic swallowing examination)	
Videomanometry (examination for analysis of quantitative intraluminal pressure changes in the pharynx and the esophagus)	
Gastroenterology:	
pH-metry (24 h pH recording)	
Gastroscopy (assessment of the morphology in the esophagus and stomach)	
Surface electromyography (sEMG)	
Different laboratory tests (to eliminate electrolyte disturbances, sideropenic anemia, or iron deficiency)	

and the use of hypnosis in a single case were discussed. In a new case study from REID (2016) the author also describes the benefit of hypnosis, in this case for a 13-year-old female suffering from phagophobia. Also other studies emphasize the positive effect of behavioral therapy; for example Nicasso et al. (1981) described behavioral therapy as a beneficial and even a life-saving approach for hysterical behavior. The importance of explaining normal swallowing mechanisms, the role of emotions, and the use of a holistic approach are pointed out by Bretan et al. (1996). A relationship of trust between the patient and clinician is essential (Finkenbine and Miele 2004). In some cases, family therapy may be of benefit (Oberfield 1981).

To treat patients with psychogenic dysphagia may be a challenge. However, we have also in our swallowing clinic experienced that a combination of psychological treatment and dysphagia therapy may be a successful treatment for some patients with psychogenic dysphagia. We have found that it may be of benefit for the patients if the dysphagia therapy sessions involve education regarding normal swallowing physiology combined with breathing exercises. Such training involving the coordination of breathing and swallowing necessary for safe swallowing could help the patient to understand the physiology of the swallowing and thereby hopefully increase the fear of swallowing. Therapeutic eating sessions starting with the consistency easiest to swallow may also be of benefit. A close collaboration between the dysphagia clinician and our colleagues in psychology and psychiatry is, in our experience, necessary for optimal management.

Pharmacological treatment with anti-anxiety medications has been reported to be an effective treatment in some cases of psychogenic dysphagia (McNally, 1994). De Lucas-taracena and Montanes-rada (2006) have found that anti-panic drugs (alprazolam, lorazepam, bromazepam, imipramine, clomipramine, fluoxetine, paroxetine) have been of proven efficacy with a remission rate of 58.5%.

Surgical treatment is not appropriate in the management of swallowing disorders of psychogenic origin, though psychogenic dysphagia has been reported to result from surgical intervention. Nicasso et al. (1981) described a 60-year-old male with postoperative hysterical dysphagia s/p esophagectomy and cervical esophagogastrostomy secondary to esophageal cancer. Postoperatively, the patient complained of globus, though instrumental evaluations revealed that the patient was able to swallow safely and adequately.

Conclusion

Psychogenic dysphagia is an uncommon swallowing condition, most often characterized by fear of swallowing. At VFSE abnormal oral behaviors such as repeated deviant tongue movements may be present but the pharyngeal stage swallowing is revealed normal. Also esophageal dysfunction may at times be associated with psychogenic symptoms. To establish a diagnosis of psychogenic dysphagia a thorough evaluation must be performed. A careful medical history, clinical and instrumental examinations, and, if necessary, laboratory tests should be involved in the evaluation. Best therapeutic management approach appears to be a combination of a dysphagia therapy and psychological treatment. It has also been reported that the patient, in some cases, has benefited from anti-anxiety medications.

For best management of a patient with psychogenic dysphagia, evaluation and treatment should be performed with a multidisciplinary approach.

More research is however necessary to learn more about this condition to be able to help patients to handle their fear of swallowing, and thereby improve their quality of life.

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The Clinical and Radiological Approach to Dysphagia

Peter Pokieser and Martina Scharitzer

Contents

Abstract

The intention of this chapter is to introduce a multidisciplinary diagnostic workup, and, in particular, to present a practical and structured radiological approach to patients with dysphagia. Swallowing disorders are common and affect the quality of life in a large number of patients across all ages, with a prevalence of 30–40% in independently living older people and up to 60% in institutionalized older patients (Baijens 2016).

The swallowing tract crosses many anatomic regions. Liquid and solid foods have to be transported properly from the oral cavity into the pharynx and through the esophagus into the stomach. Thus, a wide variety of diseases may affect deglutition, necessitating a multidisciplinary workup of dysphagic patients. Videofluoroscopy (VF) is the method of choice with which to investigate the whole swallowing tract in a "one-stop-shop" fashion. The dynamic recording of deglutition can depict pathologic findings of morphology and function, as well as form a basis upon which to determine the necessity for and type of further specialized workup.

1 Introduction

Many various conditions may alter deglutition, including neurological diseases, tumors, metabolic disorders, infections, genetic pathologies,

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and others, which involve different disciplines in the management of patients with deglutition disorders. In addition to the clinical assessment, instrumental investigations are also mandatory to identify the cause and extent of swallowing disorders. Although many fluoroscopic procedures have been replaced by newer imaging techniques, such as computed tomography or magnetic resonance imaging, the radiological evaluation of swallowing remains a hallmark of fluoroscopy, especially in these times of the increasing importance and awareness of value-based imaging care. The videofluoroscopic swallowing study (VFSS), also known as the modified barium swallow, has been proven to reliably enable analysis of the whole swallowing tract and to serve as a method of choice for the evaluation of functional and morphological abnormalities as well (Ekberg and Pokieser 1997), Martin-Harris and Jones 2008). By using a high acquisition rate of 25–30 frames per second, rapid movements during the oropharyngeal phase of swallowing and visualization of the bolus flow related to structural movements along the esophagus can be stored and analyzed without the loss of important information. Although there are a number of established and new technologies for the evaluation of deglutition, each with its respective strengths and limitations, videofluoroscopy remains a practical, robust, and efficient instrumental imaging tool for dysphagic patients.

2 Symptoms of Swallowing Disorders

2.1 Taking the Medical History

Establishing the medical history is the first step in the investigation of patients with swallowing disorders to tailor the examination individually and to correlate the specific radiological findings to the patient's symptoms. Functional healthcare questionnaires reveal a large variability, including various limitations. Although the term dysphagia is simply defined as difficulty in swallowing, patients may present with a variety of signs and symptoms. Specific questions, such as onset and duration of dysphagia, severity and associated symptoms, general health information, and many others, may help to narrow the differential diagnosis. Procedure planning, diagnosis, and follow-up imaging often depend on the integration of relevant patient history. Studies have shown that a detailed exploration may help in discriminating different symptoms of dysphagia (Kim et al. 1993), as well as in differentiating between malignant and peptic strictures (Murray et al. 2012). Studies have also shown that insufficient clinical information may lead to misdirected referral of a significant number of patients to specialized gastroenterologic swallowing centers (Melleney et al. 2004). To obtain the clinical history thoroughly, a profound knowledge of the possible causes of swallowing symptoms and the clinical presentation of each disease is required.

A questionnaire helps to structure the patients' history and should include the duration and onset of swallowing disorders, the pattern of swallowing events, the location of symptoms, the consistency of foods that lead to swallowing difficulties, as well as a history of aspiration, regurgitation, coughing, pneumonia, and previous operations that may affect the upper gastrointestinal tract, and the presence of neurological diseases. Questionnaires vary largely among different institutions, most covering the oral and pharyngeal phase of swallowing. A survey among swallowing experts of different disciplines (Scharitzer 2016) showed that nomination and rating of questions categorized as "non-cardiac chest pain" and "globus sensation" were underrepresented and less common part of the communication with the patient. For an adequate workflow of diagnostic tests and therapeutic concepts, the patient's history must be differentiated into practical categories. With increasing experience with this patient group, the investigator may step further into the "art and science of history taking in the patient with difficulty swallowing" (Hendrix 1993). Despite time restraints, taking the clinical history should include a brief coverage of all subgroups of swallowing disorders (Table 1).

For the imaging specialist, the patient's history guides the design of the VF examination and must be integrated critically into the interpretation of

Table 1 Important specific questions helping the radiologist to discriminate different causes of dysphagia, plan the diagnostic procedure, and guide further diagnostic testing (extracts from Scharitzer 2016)

Basic pathway I: Dysphagia
Does food get stuck in your throat while you eat and where do you feel it?
Does food come back into your throat/mouth after you swallowed?
Do you have to cut your food into small pieces or take a drink after swallowing solids?
Do you have to vomit occasionally? If so, when?
Do you have problems swallowing your saliva or suffer from too much saliva?
Do you suffer from hoarseness or a gargling voice?
Do you suffer from any neurological impairment?
Basic pathway II: Suspicion of aspiration
Do you have to cough while drinking, eating, before drinking/after swallowing, or choking?
Do you have to choke while eating/drinking?
Are you able to cough?
Do or did you suffer from pulmonary complications?
How do you drink? Out of a bottle/from a spoon/by a straw?
Is the symptom connected with respiratory problems?
Basic pathway III: Globus sensation
Do you suffer from globus sensation or other related symptoms?
Are your symptoms present while you eat/without eating/both?
Do you suffer from a problem in your throat or too much phlegm in your throat?
Do you feel a lump in your throat or an urge to clear your throat?
Basic pathway IV: Non cardiac chest pain
Do you feel pain behind the sternum after a swallow?
Do you suffer from noncardiac chest pain or related symptoms, from heartburning sensations, from reflux?
Effect of live:
Did you lose weight? What is your body mass index?
Do you suffer from any mood changes?
Did other changes occur, e.g., in speech, walking, writing, cognition, and affection?
For how long do the symptoms impair your quality of life?
How much is your quality of life impaired by your symptoms?
Do you go out to eat and drink with other persons?
Can you eat by yourself or need someone's help?
How long does it take for you to finish a meal?
Others:
What treatment did you have so far? (medications, previous diagnostic studies, functional swallowing therapy)
What do you eat for breakfast/lunch/dinner?
Do you use compensatory strategies?
Do you suffer from nasal regurgitation or a dry mouth?
Do you feel the food going down when you swallow?
Assessment through health professional: Is the patient reliable or not?

the study. Do the VF findings or other test results explain the patient's symptoms? (Ekberg and Pokieser 1997). When the patient has addressed his problem, questions should focus on the presence of the symptoms or syndromes discussed in more detail in the following sections.

2.2 Dysphagia

Eating and drinking have to be performed without pulmonary compromise and serve many purposes, including personal and social pleasure, nutrition, and hydration. Any subjective feeling

of disturbance is called dysphagia (Buchholz 1996).

In oropharyngeal dysphagia, the patient has difficulties in swallowing. Isolated oral dysphagia is uncommon and is based on neurogenic disorders or diminished salivary flow. Drugs (anticholinergics, antihistamines, antidepressants, antihypertensives, diuretics) can also affect salivary flow, and neuroleptic drugs may slow or disrupt the oral phase of swallowing (Dziewas et al. 2007).

Pharyngeal dysphagia is often described by the patient as a sensation of difficult passage of the bolus through the region of the suprasternal notch, most frequently the result of neuromuscular disorders that cause weakness and/or incoordination of the striated muscles of swallowing (Buchholz 1987). Less frequently, structural narrowing, like a neoplasm, postoperative defects, Zenker's diverticulum, or a mucosal web, is found.

In esophageal dysphagia, the material seems to adhere along the swallowing tract, anywhere from the suprasternal notch to the epigastrium. Usually, patients cannot differentiate between a proximal or distal site of an esophageal lesion, but there is a tendency to localize symptoms of a distal pathology to the neck (Roeder et al. 2004); for example, a Schatzki ring at the level of the esophagogastric junction or achalasia often produce symptoms above the suprasternal notch. Intermittent esophageal dysphagia for solid food is typical for lower esophageal rings or strictures with a remaining lumen of less than 2 cm. Rapid progress of solid food dysphagia within 3 months is often found in esophageal carcinoma. If there is no sign or proof of aspiration, esophageal dysphagia for fluids only indicates esophageal motor disorders. Depending on the severity of the motility disturbance, the latter can produce solid food dysphagia as well. Regurgitation of previously ingested food can arise during a meal from any cause or location, and late regurgitation of undigested food is typical for a Zenker's diverticulum or achalasia. Complaints of sour and/or bitter material with heartburn are pathognomonic for gastroesophageal reflux (GER). Furthermore, gastroesophageal reflux disease (GERD) is the most common cause for "non-cardiac chest pain." After exclusion of a cardiac cause, the esophagus has to be evaluated. A 3-week therapy with proton pump inhibitors can be an effective diagnostic and therapeutic approach. Odynophagia means painful swallowing, and, when the pain is described as "sharp," usually indicates ulcerative mucosal lesions of the pharynx or esophagus, whereas dull or squeezing pain is associated with esophageal spasm.

2.2.1 Globus Sensation

Globus is a common problem, representing about 5% of general otolaryngology patients. A "lump in the throat," the sensation of a foreign body, sore throat, frequent throat clearing, and fullness are typical complaints of these patients. Symptoms tend to occur intermittently. Often, the symptom improves during eating, while a combination with dysphagia is often found. In 75% of 150 patients with globus as the only symptom, VF could depict pathological functional and/or morphologic findings, and evidence of an esophageal motor disorder was present in 47% (Schober et al. 1995). A high incidence of esophageal motility disorders in this setting was detected by manometry in 87% of patients (Moser et al. 1991). Globus sensation seems to be a symptom of laryngopharyngeal irritation, not specific to GERD, but in which GERD plays a role (Woo et al. 1996). There remains an open discussion about the pathogenesis of globus. However, the term "globus hystericus" should be avoided and pharyngeal and/or esophageal pathologies should be ruled out according to the specific history (Chen et al. 2007). If patients with chest pain do not show any evidence of cardiac disease, the term "non-cardiac chest pain" is often diagnosed.

2.3 Aspiration

Aspiration is defined as the entry of liquid or food into the airways below the level of the glottis. Choking and/or coughing immediately following a swallow, as well as recurrent pneumonia, is indicative of aspiration. Silent aspiration may

occur if the cough reflex is absent or diminished. Individuals who aspirate are at increased risk for the occurrence of serious respiratory sequelae, including airway obstruction and aspiration pneumonia. The quantity, the depth of aspiration (trachea or distal airways), and the physical properties of the aspirate influence the effects of aspiration (Palmer et al. 2000). Aspiration can occur as anterograde during or immediately after swallowing or as retrograde aspiration of gastric or esophageal contents. Radiologists must be aware of patients at risk of aspiration to ensure the most appropriate procedure or imaging technique. The tailored VF study avoids severe aspiration during the examination (Jones and Donner 1988).

3 Multidisciplinary Evaluation of Swallowing Disorders

The radiologist should be familiar with the specific techniques of different medical fields when investigating patients with swallowing problems. There is a considerable overlap with different clinical tests, which varies from country to country. We will try to better clarify the clinical interaction than the borders between clinical specialties.

General patient status includes mental and social function, physical mobility, as well as his/her nutritional and hydration status.

An examination of the chest can reveal problems with respiratory function related to aspiration or conditions in which aspiration might cause severe problems. The cardiovascular system has to be assessed for possible sources of emboli to the brain, impairment of the musculoskeletal system can affect normal mobility, and the swallowing mechanism can be affected by different systemic diseases, such as scleroderma or muscular diseases.

The protocol of otolaryngologists and speech/language pathologists includes a full head and neck examination. The neck should be evaluated for masses, especially for adenopathies, enlarged thyroid, and scars that might indicate surgery on the structures involved in swallowing. An inspection should be performed of the oral cavity, cranial nerve function, palate, pharynx, and larynx with indirect laryngoscopy or by fiber optics to assess for tumors, mucosal integrity, vocal cord motion, pooling of secretions into the vallecula or the piriform sinus, as well as sensation and voice (Sonies et al. 1987). Stridor is a sign of upper airway obstruction and may be audible only on auscultation over the trachea. The sounds of swallowing motility and the palpation of the elevation of the hyoid and larynx are part of the dynamic clinical investigation. Fiber-optic endoscopic evaluation of swallowing (FEES) is a well-established diagnostic test and also enables assessment of nasal, velopharyngeal, and laryngeal pathology with morphologic and functional changes. FEES is complementary to videofluoroscopy and the application and interpretation of results is an interdisciplinary task of otolaryngologists, speech/language pathologists, and radiologists. First, results of FEES and VF are "diagnostic studies." Second, they allow the clinician to design an appropriate diet and compensatory maneuvers designed to improve pharyngeal clearance and reduce aspiration, and are called "therapeutic studies," including investigations to determine the effectiveness of therapy.

FEES is also used by neurologists. However, the neurologic examination is a crucial part of the multidisciplinary approach to dysphagic patients. Cerebrovascular disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, poliomyelitis, myasthenia gravis, and dementia are examples of the wide spectrum of neurological disorders that can involve deglutition.

Invasive treatment of the upper esophageal sphincter (UES) is performed by otolaryngologists, as well as general surgeons, and is often used as therapy for Zenker's diverticulum. Different surgical strategies are under continuous discussion, including botulinum toxin injection to improve swallowing function, which is gaining in popularity. Myotomy of the UES with or without resection of the diverticulum itself, as well as myotomy with laser or with an endoscopic approach, has been applied to restore an adequate opening of the pharyngoesophageal segment.

Gastroenterologists and surgeons specialize in the diagnosis and treatment of esophageal

disease. Endoscopy reveals even subtle mucosal details and can obtain biopsies for pathologic diagnosis. But, endoscopy may overlook subtle rings or stenoses, which can be passed by the endoscope, but will hinder larger boluses of solid food. Furthermore, endoscopy cannot display the topographic relation of stenoses to the important anatomic landmarks in all cases and often cannot be forwarded distal to a narrow stenosis. VF is helpful in such instances, providing excellent topographic overviews, testing for subtle stenoses with a solid bolus, and examining the esophagus distal to the stenoses. Benign and malignant macromorphological changes of the esophageal tube are detected by endoscopy and VF (Scharitzer et al. 2002). In esophageal motility disorders, VF can detect a delayed transport for liquids and solid food as well, complementary to manometry, the gold standard for the diagnosis of esophageal motility disorders. Manometry can be combined with VF as videomanometry. This method synchronizes the videofluoroscopic record of bolus transport and the measurement of pressures. Evaluation of esophageal transport and gastric emptying can be obtained by scintigraphy. Delayed gastric emptying, well known in diabetic disease, may interfere with esophageal transport and contribute to symptoms like dyspepsia, epigastric fullness, or heartburn. pH probe studies can detect pathologic gastroesophageal reflux, while VF can describe the dynamic appearance of the esophagogastric junction during and after passage of a bolus. Intraluminal impedance monitoring offers the possibility to measure bolus movement in the esophagus without radiation. Combined with manometry or pH, pressure changes and bolus transit, as well as detection of all types of reflux episodes independent of the pH, can be evaluated. Therefore, these investigations offer new, additional methods for patients with persistent GERD symptoms after acid-suppressive therapy or with nonacid reflux. Comparison of impedance and videofluoroscopy has shown almost identical volume clearance of the swallowed contrast media (Simren et al. 2003). Impedance measurements can also be used for impedance planimetry to reveal cross-sectional areas in the esophagus in order to graduate esophageal stenosis. A comparison of videofluoroscopy, including a tablet test and impedance planimetry, has shown significant correlation for residual esophageal lumen (Scharitzer et al. 2017). Hiatal hernia, cardiac insufficiency, and status of the esophagogastric junction after operations such as fundoplication, myotomy, dilatation, gastric banding, and other operations are studied videofluoroscopically to rule out early and late postoperative complications, such as stenosis, leakage, or perforation. VF is the diagnostic test of choice to obtain a general overview of the whole swallowing tract, and to detect macropathologic changes and disordered function as well. Pertinent to the clinical problem, a tailored VF examination can be designed to serve as the basis for other diagnostic tests or to complete other results in a complementary way.

4 Imaging of Swallowing Disorders

4.1 Technical Considerations

Videofluoroscopy is performed with a fluoroscopy unit connected to a video recorder. The dynamic examination studies the motility of the oral, pharyngeal, and esophageal phases, whereas the spot film examinations demonstrate morphology. Any fluoroscopic unit that offers remote-control equipment is appropriate, as that allows a frame-by-frame analysis several times. The introduction of digital fluoroscopy and computer-based workstations offers a higher spatial resolution and new possibilities for interpretation, with lower radiation exposure at the same time, which is also achieved by pulsed fluoroscopy. Digital images obtained during a dynamic study can be post-processed and transmitted more easily. Modern fluoroscopy units offer a selection of various pulse rates with up to 30 pulses per second and frame rates to be set up to a maximum of 30 frames per second.

Acquisition rates of 25–30 images/second imply a higher temporal resolution with the disadvantage of a higher radiation dose. Comparative studies have shown that higher image resolution results in fewer missed penetration-aspiration events (since some aspiration event may be visible on only part of a second), a reduced number of swallows required to answer the clinical question, better distinction with regard to the onset of aspiration related to initiation of swallowing, and higher interrater agreement (Bonilha et al. 2013). An adequate protocol of oropharyngeal and esophageal transit can overcome problems of time resolution also in esophageal observations of transient visible stenosis like rings and subtle narrowing.

4.2 Examination Technique

The approach described by Ekberg and Pokieser (1997) is based on the patient's history and planning the investigation in detail. The radiographic examination must include all the structures involved in swallowing, from the lips to the stomach. Nevertheless, it is important to focus the examination on specific areas. In any patient with a high suspicion of laryngeal or pharyngeal disease, the laryngeal vestibule should be included in the image from the beginning. It is very common that the first swallow is the worst swallow and that only the first swallow will reveal dysfunction.

It is certainly very important to realize that there are two basically different examinations of swallowing. One is customized for the diagnosis, i.e., the search for why the patient has a specific symptom (diagnostic study). The test is basically concerned with finding that particular patient's worst swallow, and therefore might include maneuvers for decompensation of a compensated swallow (Buchholz et al. 1985). In contrast, we perform videofluoroscopy when the dysfunction in a specific patient is already known. Then, this investigation basically tries to reveal the patient's best swallow, and therefore always includes maneuvers for compensation of a decompensated swallow (therapeutic study). It is always important to observe as many swallows as possible, as dysfunction may be intermittent. Moreover, the benefits of therapeutic maneuvers are notoriously difficult to assess. Since FEES has become increasingly available and has gained importance in the assessment of aspiration and the value of swallowing manoeuvers, indications for a therapeutic videofluoroscopic swallow have decreased.

No special preparation is needed for the radiological examination of the upper gastrointestinal tract. The patient is examined with his/her dentures or other oral appliances in place so that the patient's swallow is as normal as possible. Nasogastric feeding tubes can be left on site due to discomfort during reinsertion of tubes, since the presence of a nasogastric tube does not substantially alter videofluoroscopic findings (Alnassar et al. 2011).

4.2.1 The "Seven Functional Units"

The systematic analysis procedure known from X-ray reporting proved to be useful for reporting film sequences as well.

The radiological substrate of this analysis is the movements of anatomical structures that cause the formation and continuous propulsion of the bolus of contrast medium. Physiologically, the act of swallowing is divided into three phases: the oral, the pharyngeal, and the esophageal phase. The duration of the oral phase may be determined arbitrarily. The pharyngeal phase takes less than 1 s. The esophageal phase takes approximately 10 s.

The esophageal phase is about ten times as long as the pharyngeal phase.

For radiographic analysis of the act of swallowing, it is useful to classify the involved anatomical structures into seven functional units (Pokieser et al. 1995, Fig. 1).

The description of normal and pathological functional findings of the seven functional units of the act of deglutition is a simplification of the subject, but does include the most important clinical findings needed by those embarking on routine diagnosis of the act of swallowing.

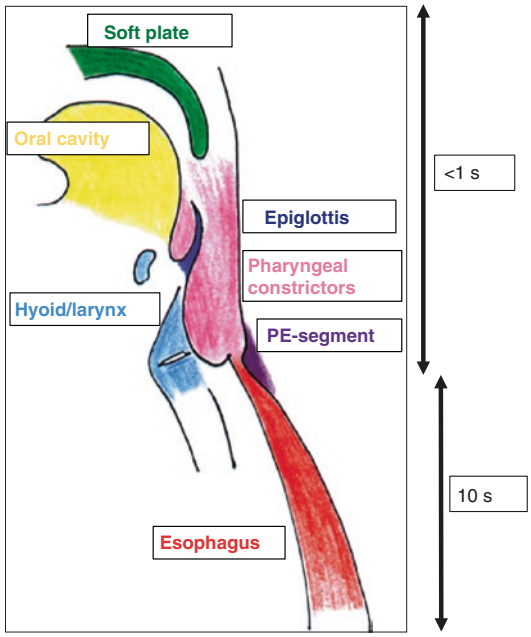


Fig. 1 This graph demonstrates the seven functional units of swallowing. Within 1 s, six of the units complete the pharyngeal stage of swallowing. Then, the esophagus bridges the long distance through the mediastinum to the stomach. A complete barium swallow of about 15 ml should reach the stomach within 10 s

4.2.2 Design of Videofluoroscopic Scripts

A standard examination of these seven functional units is performed by lining up various film sequences of the video recording of the act of swallowing and fluoroscopy. During the pharyngeal phase of swallowing, the functional units should be filmed in a stationary position, as the recording will be blurred and rendered unusable for study if the central beam is moved. During the esophageal phase, the central beam may follow the bolus, because the esophageal propulsion is relatively slow (~ 4 cm/s).

4.2.3 Swallowing Disorders Without Suspicion of Aspiration

Patients suffering from dysphagia, globus, chest pain, or other clinical conditions related to swallowing may have no clinical symptoms of aspiration. These patients should swallow boluses of a normal size and should be investigated in all standard positions, as mentioned below. The examination starts with films with the patient in the erect standard position, followed by tests of esophageal motility in the horizontal, supine, and prone positions. Plain films using a double-contrast technique should be added, based on the clinical question. Effervescent powder disturbs the standardized examination of the esophageal tube and should be given after studying the esophageal motility in the horizontal position. The passage of contrast material should be followed to the duodenojejunal junction.

4.2.4 Swallowing Disorders with Suspicion of Aspiration

The investigation is restricted to erect standard projections, if aspiration occurs. With increasing amounts of contrast material, severe aspiration can be avoided by stopping any increase when the patient aspirates. Different consistencies are applied in diagnostic studies pertinent to the symptom, and in therapeutic studies to determine the best consistency without aspirating. This is best done in collaboration with a speech and language pathologist, who has complementary clinical information and an interest in the therapeutic approach.

From a systematic point of view, every film scene may be defined by three characteristics: first, the selected section for imaging and the patient's *standard position*; second, the selected *type of contrast medium*; and, finally, third, the *amount* of contrast medium.

4.2.5 Standard Positions for Videofluoroscopy

The patient should stand or sit on the footboard of the fluoroscopic table. Esophageal motility can be best depicted in the horizontal position, when the contrast material is pushed mainly by esophageal motility.

Debilitated patients can be examined on a specially designed chair. Patients should not experience stress during swallowing, and the investigator has to take care to provide a quiet and comfortable environment during the study. Standard positions are shown in Figs. 2, 3, 4, 5, and 6.

Fig. 2 First standard position: Overview of the lateral oral cavity and pharynx. In this position, the pharynx is shown in the largest possible section of the image in such a way that the oral cavity, and, in the caudal aspect, also the upper esophageal sphincter are included. The patient is examined in an upright position, either standing or sitting. Usually, the patient is turned to the right side, slightly oblique. It is useful to repeat this scene after turning the patient left, if stenoses need to be ruled out

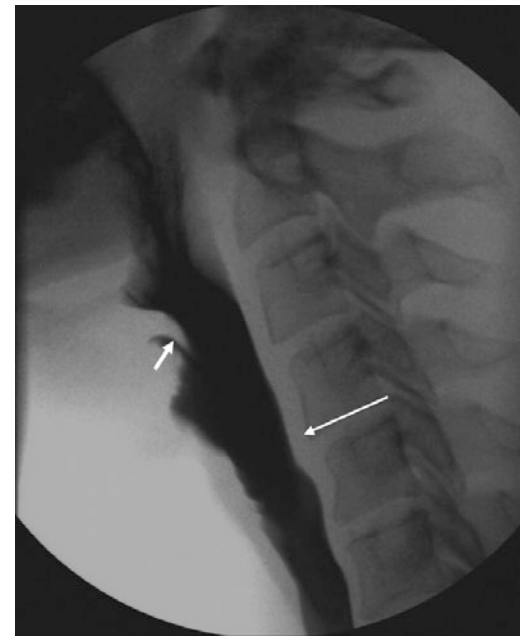


Fig. 3 Second standard position: This setting shows the upper esophageal sphincter in the lateral view, slightly oblique (*arrow*). The epiglottis is in an inverted position (*short arrow*). The upper esophageal sphincter can be evaluated especially well in this targeted image of the cervicothoracic junction

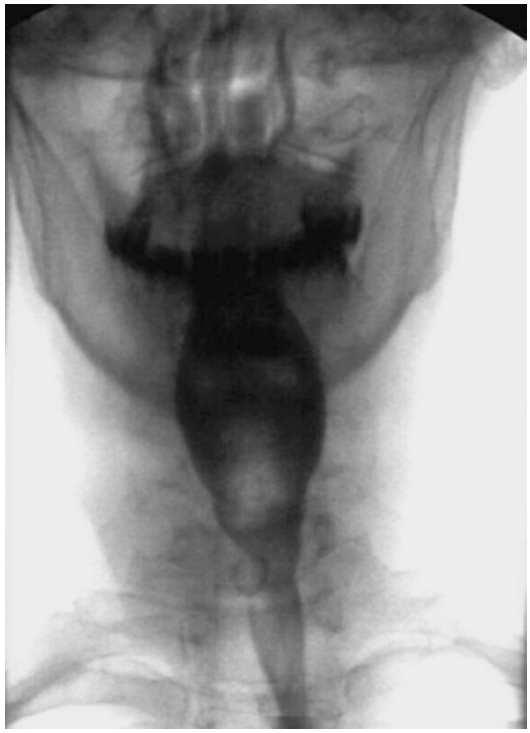


Fig. 4 Third standard position: Frontal view of the oral cavity, the pharynx, and the cervical esophagus. The symmetry of the passage must be documented

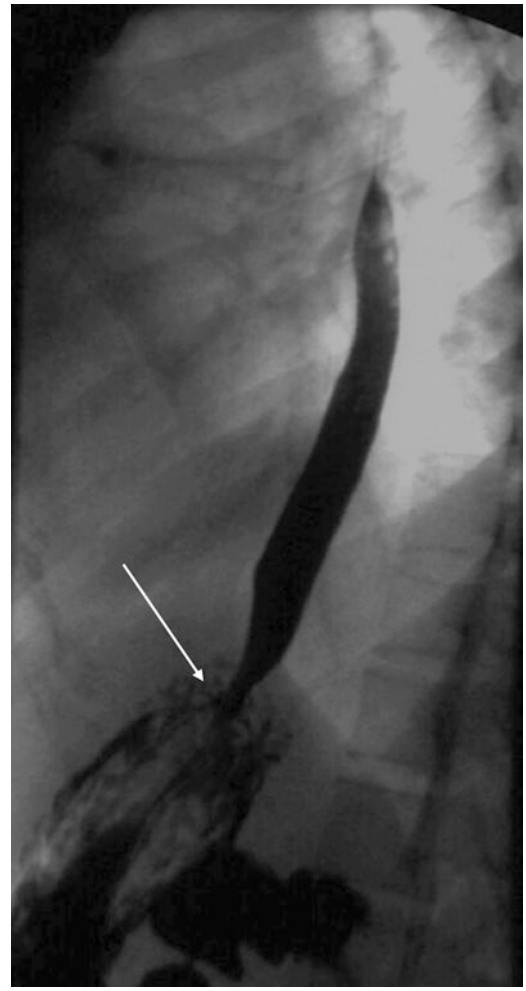


Fig. 5 Fourth standard position: This image shows the middle and lower esophagus in the erect left posterior oblique position. It is useful to repeat this scene in the right posterior oblique position to obtain two different projections of the esophageal phase. Gravity enforces the passage of contrast material in the erect position. With a single act of swallowing, the passage through the lower esophageal sphincter is shown (*arrow*). The patient is asked to swallow just once, to hinder repeated superimpositions of peristaltic waves. Practical advice: about 3 s after the pharyngeal phase in the first or second standard position, the fifth standard position is developed by following the bolus. This can be done when no abnormal findings were visible during the pharyngeal phase

4.2.6 Type of Contrast Medium

We use a high-density barium suspension to visualize the morphology and function from the oral cavity to the esophagus.

Nonionic, iodinated, low-osmolar, or isoosmolar water-soluble contrast material is necessary for patients with a clinical suspicion of aspiration or perforation. Hyperosmolar iodinated contrast medium is contraindicated in patients with suspicion of aspiration. In addition, solids are indicated to show a stricture, a solid-induced spasm or dysphagia, as well as for postoperative control studies. Therefore, a piece of bread with barium or placebo tablets with a 14 mm diameter can help in the evaluation of solid-induced abnormalities. The use of different consistencies is extremely helpful in patients with aspiration of only liquid boluses in order to assess the further therapeutic and dietetic management. A standardized protocol for the type, viscosity, and volume of oral contrast media is highly recommended for VF to match the rheology of swallowed material and ensure the correct interdisciplinary approach for therapeutic recommendations (Newman et al. 2016).

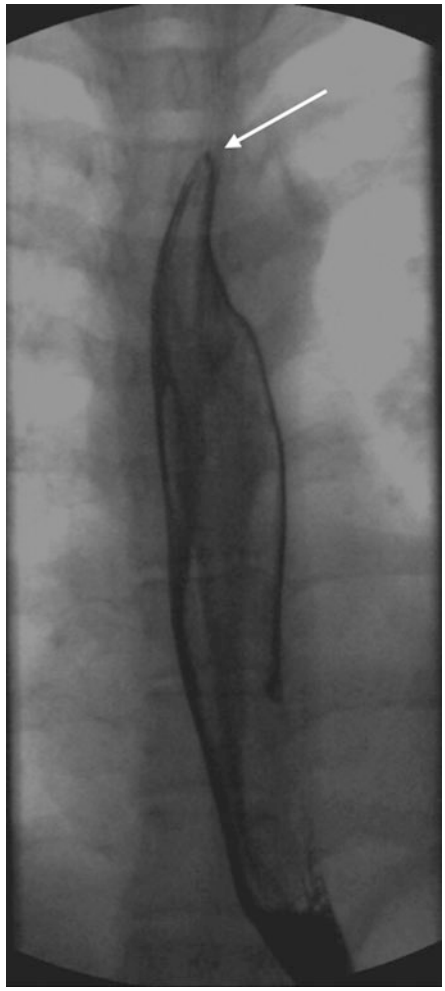


Fig. 6 Fifth standard position: The esophageal passage in the prone position allows the peristaltic wave of the esophagus to be visualized. Repeated in the supine position, the esophageal transport is visualized in a different way. Hernias, rings, and other findings are often seen in one position only—prone or supine. The cranially V-shaped peristaltic wave (*arrow*) is followed downward from the top. The peristaltic wave may be followed with the central beam, but the central beam should not be moved during visualization of the dynamic movements of the esophagogastric junction

4.2.7 Amount of Contrast Medium

The normal amount of a single swallow for an adult patient is about 15 ml. However, a healthy adult can manage liquid boluses up to 50 ml and more. The amount of contrast material should be varied according to the individual capabilities. The examination includes up to ten swallows of 15–30 ml of liquid barium sulfate. In the beginning, the amount of contrast media is 15 ml. In cases with suspected aspiration, it is lessened to 3 ml for the first swallow. If this bolus volume is tolerated, the bolus size should be increased to 5 ml and up to 15 ml. If liquid aspiration is observed, ingestion of a sample of pudding consistency is evaluated. The examination may also be started with nectar-thick consistencies, followed by thin consistencies and then pudding-thick consistencies. The contrast media may be mixed with barium preparations or water-soluble contrast agents can be prepared with thickening agents.

The contrast medium can be applied in many different ways, according to the abilities of the patient. Cups, drinking bottles, spoons, or straws may be suitable. The best way to administer contrast material orally can be determined by the feeding history and the clinical presentation of the patient.

4.3 Reporting on the Seven Functional Units of Swallowing

The basic principles of the functional physiology and pathology of swallowing constitute the actual radiological basis for reporting videofluoroscopy.

The seven functional units are a radiological approach based on the dynamic radiological information.

Often, there are several functional disorders of the same functional unit in a single patient. Countless combinations of findings occur, but typical "patterns of findings" are to be observed. Step-by-step analysis of the seven units may reveal malfunction. The strength of the method is the ability to see the entire swallowing action simultaneously, with its effect on bolus transport.

4.3.1 Tongue—Oral Cavity

Normal Function of the Tongue (Fig. 7)

Incompetent Bolus Manipulation. An inability to manipulate the bolus summarizes many different

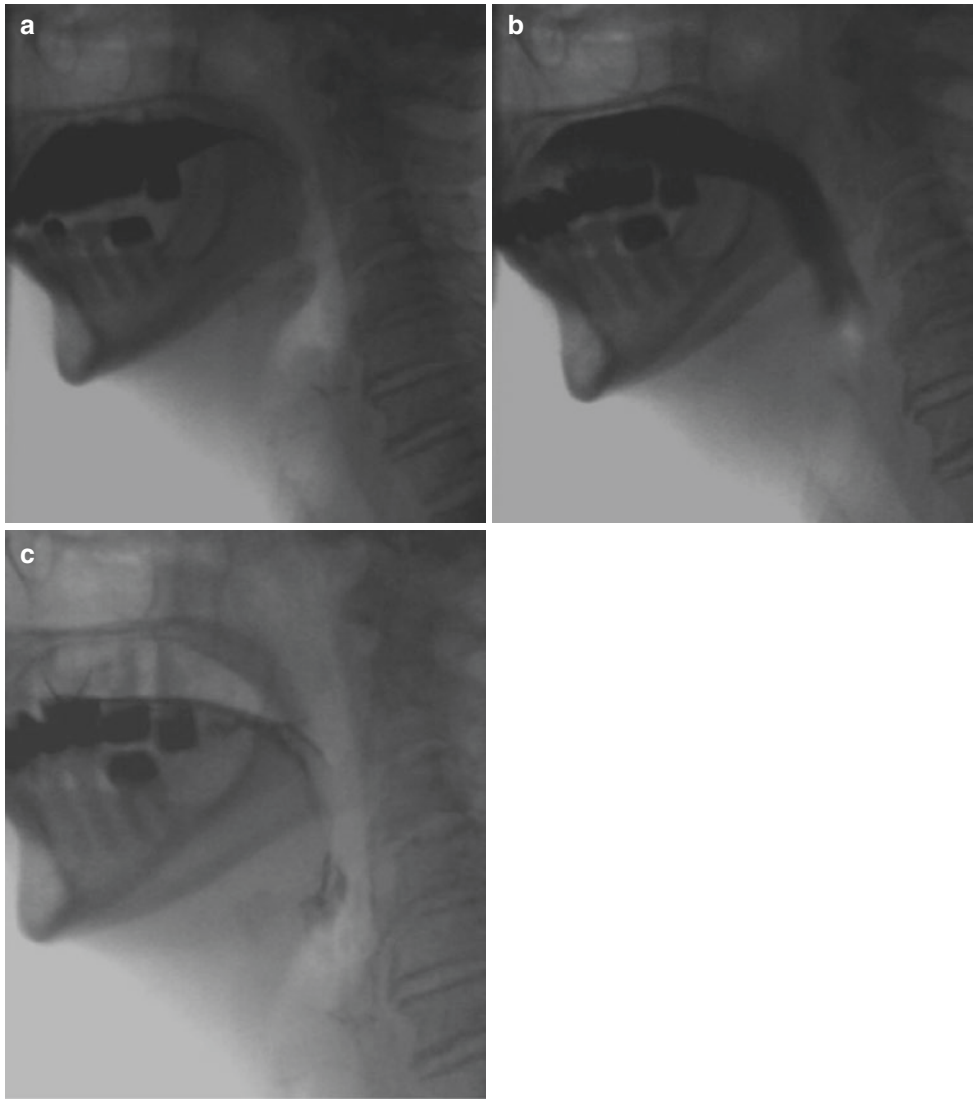


Fig. 7 (**a**) The oral phase starts with the intake of a beverage or the ingestion of food into the oral cavity. The lips close and seal the oral cavity anteriorly. To form the bolus, the substance is first loaded on the dorsum of the tongue. This process is under voluntary control. In this process, the tongue and soft palate together seal off the posterior part of the oral cavity (*arrows*). (**b**) When the involuntary act of deglutition is started, the tongue performs a wave-like movement and presses the manipulated bolus along the hard palate backward into the pharynx. (**c**) After swallowing, only the barium coating remains in the oral cavity

dynamic findings. The inability of the tongue to hold the bolus on its upper surface, fragmentation of the bolus, and uncoordinated movements, such as tremor or undulations, may be visible. When lip closure is insufficient and material runs out over the lips, this is called "drooling."

Weakness of the Tongue. Weakness of the tongue is often combined with pharyngeal weakness, retention in the valleculae can be caused by both, and overlaps cannot be differentiated.

When weakness of the tongue is present, a thicker consistency of the contrast material

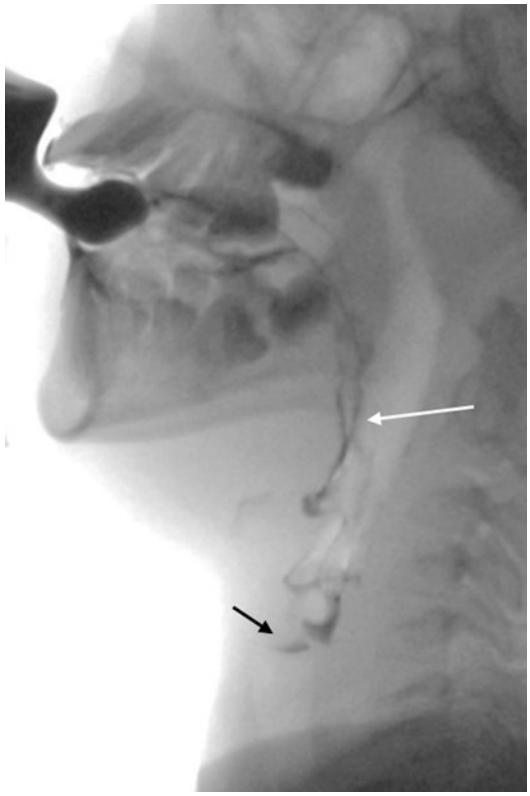


Fig. 8 Posterior leaking. Eight-year-old girl with psychomotor retardation. Videofluoroscopy shows weakness of the tongue, the dorsal closure of the oral cavity is disturbed, and contrast medium prematurely passes into the pharynx (*arrow*)—so-called leaking. This leads to predeglutitive aspiration (*short arrow*)

proves to be more sensitive, like a barium paste or bread with barium. Water-soluble contrast material can be propelled more easily, thus masking a weakness of the tongue.

Incompetent Tongue–Palate Seal. Incompetence of the apposition of the soft palate and the tongue leads to leakage of the bolus into the oropharynx (Fig. 8). Weakness or postoperative defects of the tongue, the soft palate, or both can cause this functional deficit. The differentiation between leakage and late triggering of the involuntary swallow can be difficult when the oral transit time is short. This might be the case when the patient reclines the head to compensate for difficulties with oral transport.

4.3.2 Soft Palate

Figure 9 shows the normal function of the soft palate. Incomplete elevation and insufficient velopharyngeal closure (Fig. 10) are the most common pathological findings of this functional unit of swallowing.

4.3.3 Epiglottis

In contrast to normal function of the epiglottis, an incomplete epiglottic tilt is almost always combined with retentions in the valleculae, and often with hypopharyngeal retentions and numerous other disturbances of the pharyngeal phase (Fig. 11). Tumors, swelling after radiation (Fig. 12), or inflammatory diseases, such as epiglottitis, and postoperative structural deficits should be considered.

4.3.4 Hyoid and Larynx

Normal function of the hyoid and larynx is shown in Fig. 13. Tracheostomy, pharyngeal or laryngeal resections, radiation therapy, or muscular weakness are common causes of poor movements of the epiglottis and the larynx. Over time, this condition contributes to pharyngeal retentions and aspiration.

Penetration. Penetration is defined as the entrance of contrast medium into the laryngeal vestibulum above the vocal cords and may indicate neuromuscular swallowing disorders if assessed as the only pathological finding. Single penetrations, especially during passage of the first swallow, may also occur in healthy individuals. Aspiration is defined as contrast medium entering the trachea and may be differentiated into pre-, intra-, and post-deglutitive, referring to the involuntary act of swallowing and the rapid, automatic motion of the larynx, hyoid, and pharynx. Thus, aspiration may occur before, during, or after the rapid swallowing movement.

Pre-deglutitive. Aspiration occurs during preparation of the swallow and leads to the entry of the bolus into the airway before triggering of the pharyngeal phase of swallowing (Fig. 8).

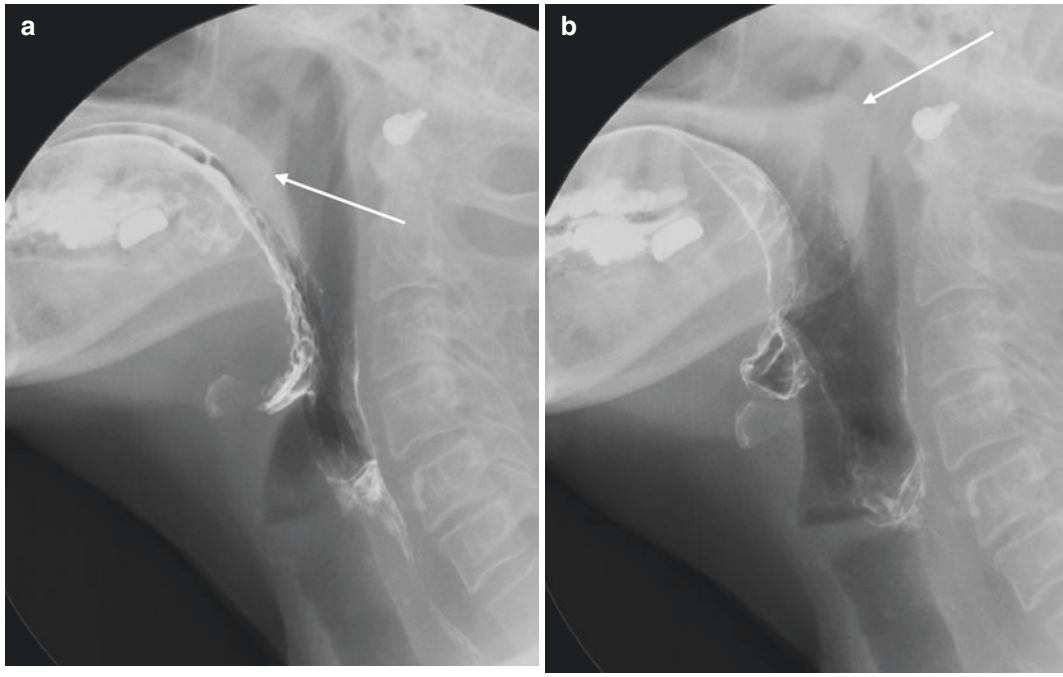


Fig. 9 Sometimes, it is useful to view the oral cavity separately. In doing so, the movement of the soft palate during speech can be visualized. However, the pharyngeal phase is largely eliminated in this setting. While speaking (words beginning with "k" such as "Kathy"), the soft palate rises from its resting position (**a**) (*arrow*) up to a right angle and tightens the nasopharynx (**b**), and the latter is called Passavant's cushion (*arrow*)

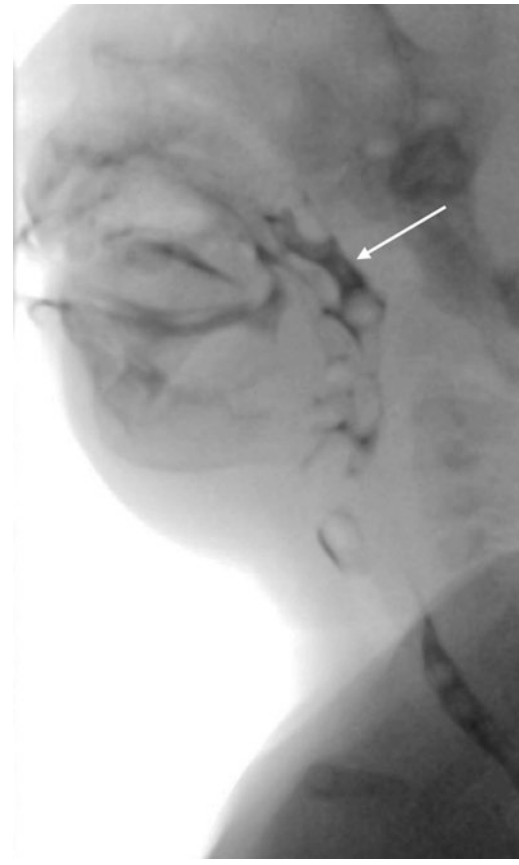


Fig. 10 Nasal regurgitation. Five-year-old girl with congenital neurologic disease and suspicion of aspiration. Videofluoroscopy reveals failure of the closure mechanism between soft-palate elevation and contraction of the upper pharyngeal sphincter muscles (*arrow*) and shows spillage of contrast material into the nasopharynx. Additionally, aspiration can be seen

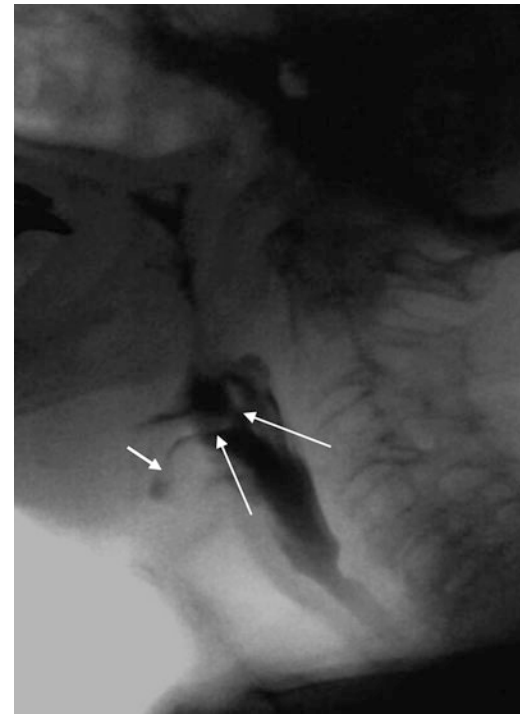


Fig. 11 Incomplete epiglottic tilt. Reduced epiglottic movement with lack of epiglottic inversion (*arrows*) and infraglottic penetration (*short arrow*) as a result

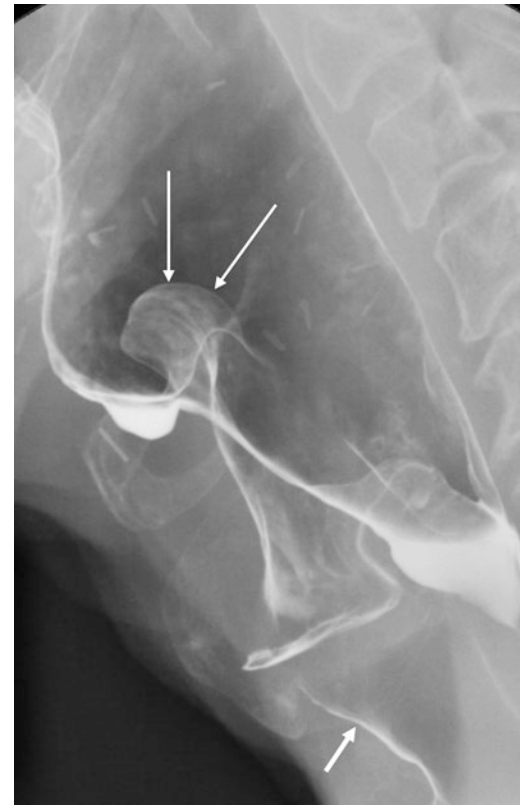


Fig. 12 Thickened epiglottis. In this patient with base of tongue cancer and radiation therapy, the epiglottis is markedly thickened (*arrows*) and prohibits regular laryngeal closure and intra-deglutitive aspiration can be observed (*short arrow*)

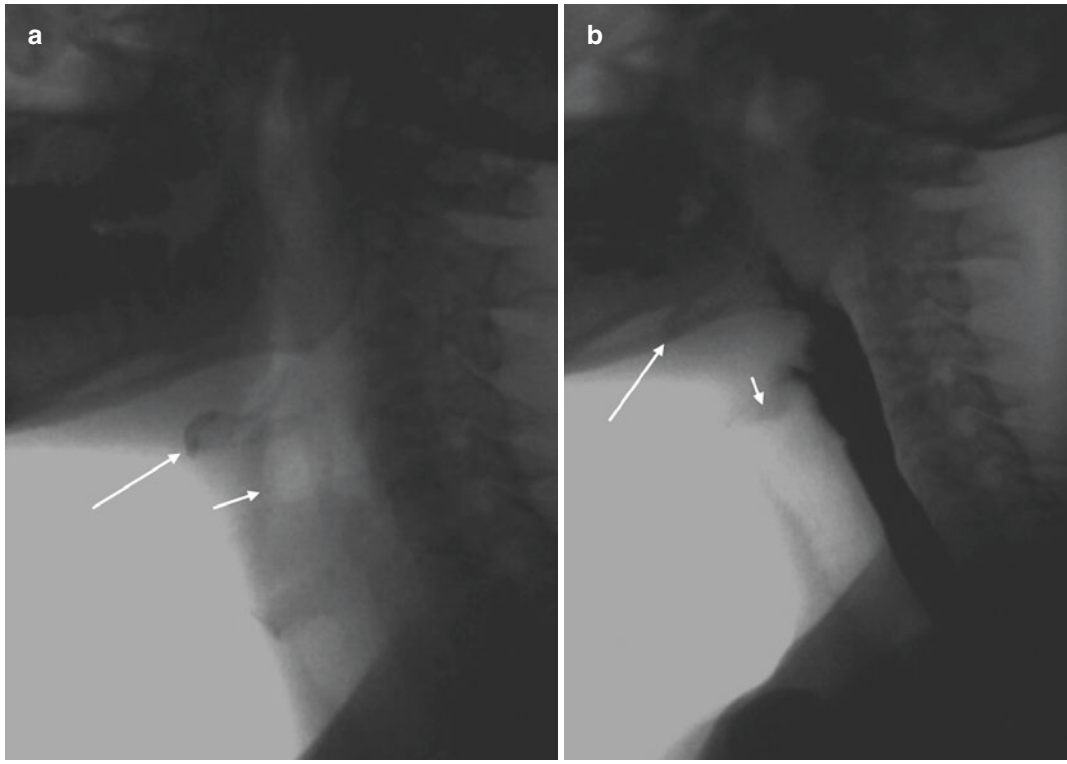


Fig. 13 Hyoid bone and air column in lateral projection. (**a**) The hyoid is visible as a bony structure (*arrow*), while the larynx is represented by an air column (*short arrow*). (**b**) To protect the respiratory tract, the hyoid and larynx move cranially and ventrally at the beginning of the involuntary act of swallowing (*arrow*). The elevation of the larynx is visible fluoroscopically. The laryngeal vestibule is tightly closed during the movement of the larynx, and the air column of the trachea is visible up to the horizontal end at the level of the vocal cord (*short arrow*). Elevation of hyoid and larynx can be estimated by correlation to the height of a cervical vertebral body

Intra-deglutitive. Aspiration is observed during the rapid involuntary act of swallowing (Fig. 14).

Post-deglutitive. Aspiration occurs during incomplete swallowing, which causes retention in the pharynx. Frequently, this is due to weak pharyngeal muscles (Fig. 15).

Severity of Aspiration. An important aspect of the evaluation of aspiration is its severity. Videofluoroscopy can be quite valuable here. However, it should be mentioned that any decision with regard to prognosis and therapy can be made only by considering all clinical data. For gradation, the Penetration-Aspiration Scale described by Rosenbek et al. (1996) has gained wide interdisciplinary acceptance. When the coughing attack has subsided, or is entirely absent, this always signifies a high grade of aspiration and a great likelihood of bronchopulmonary complications.

4.3.5 Pharyngeal Constrictors

The fifth functional unit includes the activity of the pharyngeal constrictors. The pharyngeal wave of contraction starts at the level of C1 on the lateral projection. The rapid upward movements of the hyoid and larynx also occur at the beginning of the involuntary act of swallowing. As the voluntary act smoothly passes into the involuntary one, the physiological

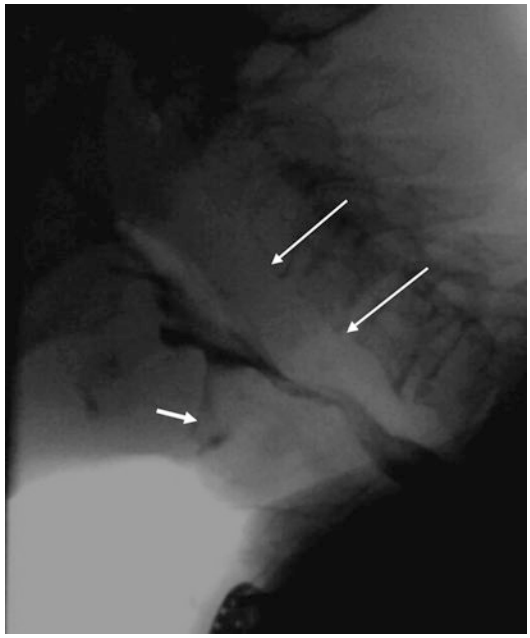


Fig. 14 Patient with hypopharyngeal cancer and PEG tube. Videofluoroscopy shows massive thickening of the posterior pharyngeal wall (*arrows*) with stenosis and intra-deglutitive aspiration of contrast medium (*short arrow*)

beginning may be difficult to determine. In the normal act of swallowing, there should always be a rapid and continuous passage through the pharynx as soon as the angle of the jaw has been passed or the valleculae have been reached (Fig. 16).

Delayed Swallowing Reflex. Delayed triggering of the involuntary act of swallowing is an important and common finding. Delay occurs when the contrast medium has reached the level of the valleculae before the involuntary act of swallowing is triggered. Pre-deglutitive aspiration may be present, when the closure of the laryngeal vestibule is also delayed. Several swallows can show a different length of the delay. Often, the delay is worst in the first swallow and may improve during the examination. Delays from 0.5 s up to 3 s are frequent in neuromuscular disorders. The swallowing reflex is absent if the reflex does not trigger for 30 s.

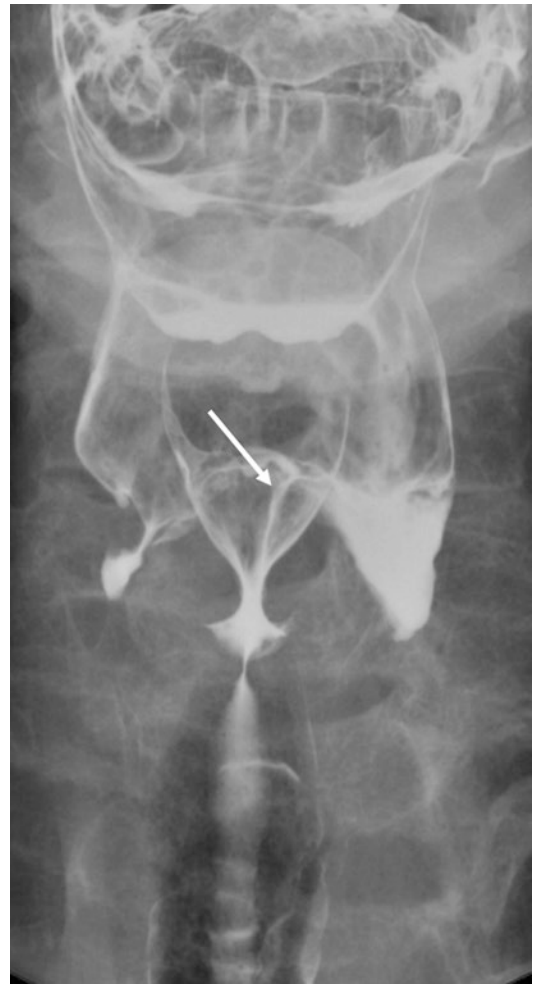


Fig. 15 Post-deglutitive aspiration. Patient with pharyngeal cancer and absent unfolding of the right piriform sinus. Severe retentions in the left piriform sinus after swallowing with overflow of contrast medium into the laryngeal entrance (*arrow*)

Symmetric Weakness of the Pharynx. Pharyngeal weakness is present when residues of contrast medium remain in the piriform sinuses and the valleculae after swallowing. The coating of the pharyngeal walls differs with the viscosity of contrast medium. Thus, the high viscosity of barium paste facilitates the detection of pharyngeal weakness (Fig. 17). The amount of pharyngeal retentions is a predictive factor for the

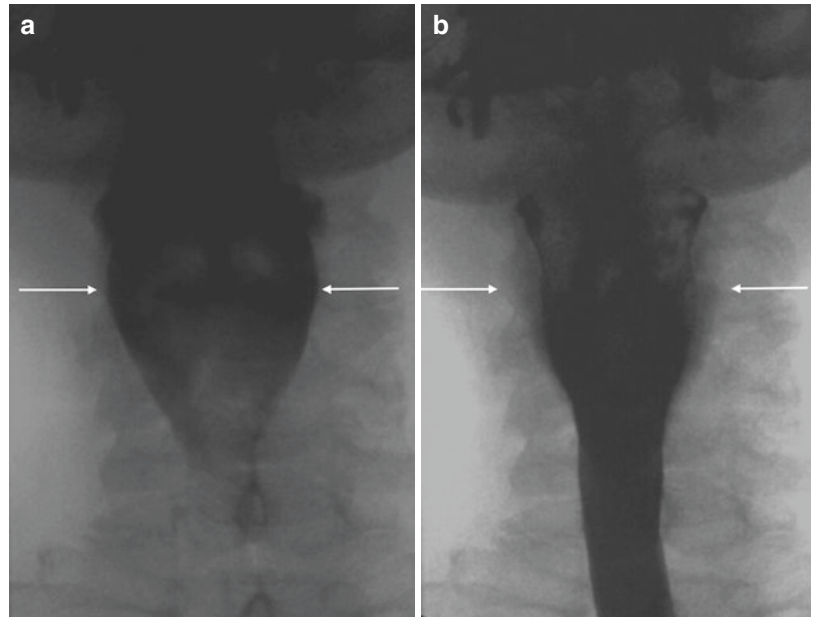


Fig. 16 (**a**) In the frontal view the lateral pharyngeal walls should move rapidly towards medial, with a symmetrical movement (*arrows*). (**b**) In the late intra-deglutitive phase the bolus is squeezed out of the pharynx (*arrows*)

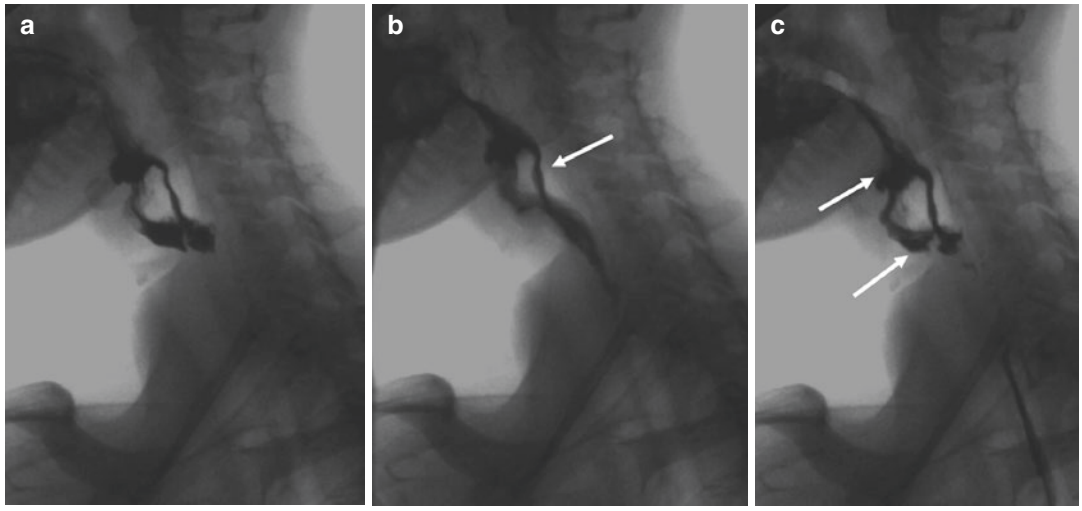


Fig. 17 Pharyngeal weakness. (**a**) Delayed triggering of involuntary act of swallowing, contrast medium has already reached the piriform sinuses. (**b**) Intra-deglutitive absence of the pharyngeal stripping wave seen as a straight line of the posterior pharyngeal wall during the swallow (*arrow*). (**c**) After swallowing videofluoroscopy reveals severe retentions within the piriform sinus and the valleculae (*arrows*)

incidence of subsequent aspiration (Eisenhuber et al. 2002).

Asymmetric Pharyngeal Weakness. This should be distinguished from unilateral or mainly unilateral pharyngeal weakness and a bilateral symmetric pharyngeal weakness, as the therapeutic alternatives differ. The frontal view is most suitable for radiographic diagnosis of a unilateral pharyngeal weakness, while, on oblique views, asymmetric retentions can be seen, with some experience (Fig. 18).

Pharyngoceles. These are usually harmless small out-bulgings of the pharyngeal wall, which may become symptomatic when

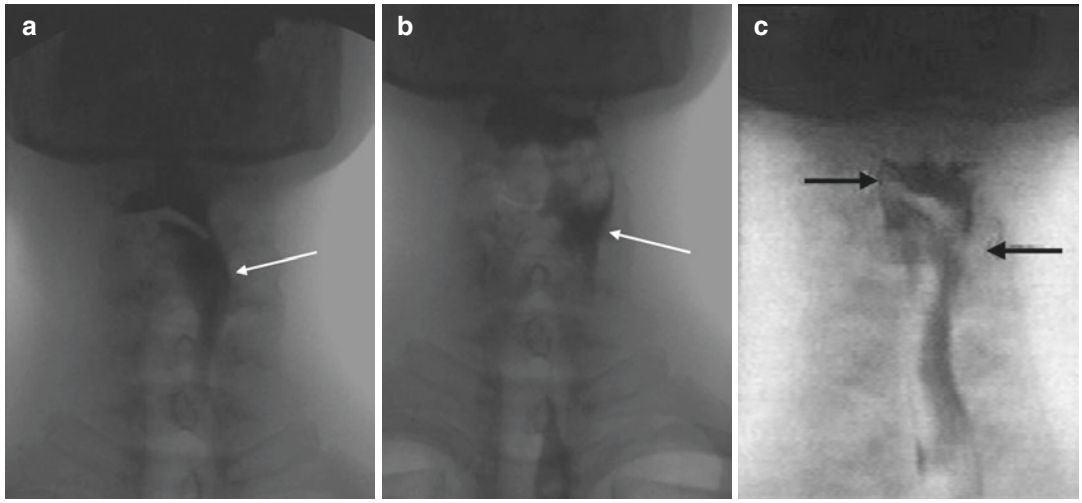


Fig. 18 Unilateral pharyngeal weakness. (**a**) Patient after traumatic injury of the right pharyngeal wall and surgical therapy. Videofluoroscopy reveals unilateral muscle weakness (*arrow*). (**b**) Post-deglutitive left-sided retentions in the piriform sinus as a result of swallowing impairment (*arrow*). (**c**) Another patient with unilateral pharyngeal weakness and incomplete epiglottic tilt (*arrow*). This is combined with retention in the valleculae and piriform sinuses (*arrows*)

they trap ingested food and cause mucosal irritation. Small pharyngoceles without retentions are common and harmless (Fig. 19). In rare cases, they can be enormously big (trumpeter).

Space-Occupying Masses. Even large cervical osteophytes can be compensated for without severe symptoms; for example, a cerebrovascular accident may lead to a decompensation in such cases. It is often very difficult to decide whether a resection of the osteophytic mass could improve a patient's swallowing function or not (Strasser et al. 2000) (Fig. 20).

Space-occupying masses may markedly hinder the pharyngeal passage. Seldom are pharyngeal or laryngeal tumors detected by videofluoroscopy or spot films, and, in symptomatic patients, endoscopy is usually performed first.

4.3.6 Pharyngoesophageal Segment

The pharyngoesophageal sphincter or segment (PE segment) is closed by its resting pressure between swallowing acts. Thus, it can be identified videofluoroscopically between the air column of the pharynx at rest and the air in the cervical esophagus. The PE segment consists of oblique parts of the inferior pharyngeal constrictor muscle, the cricopharyngeal muscle, and parts of the cervical esophagus (Fig. 21).

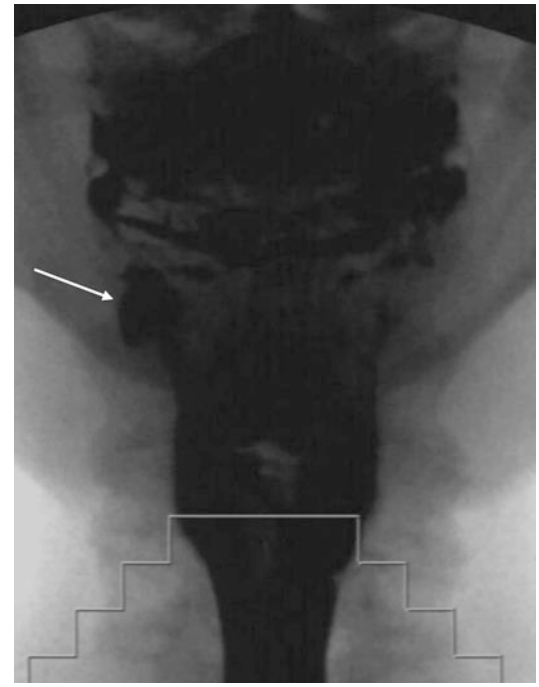


Fig. 19 Small pharyngocele on the right side in an asymptomatic patient (*arrow*)

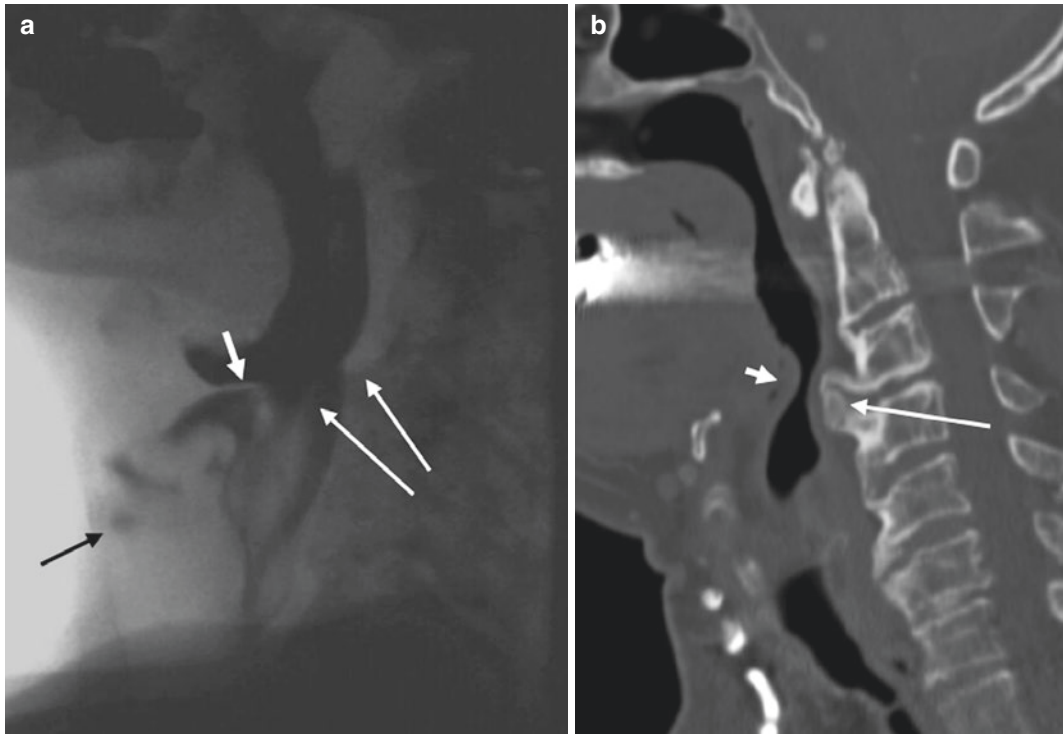


Fig. 20 Cervical hyperostosis. (**a**) Prominent osteophytes of the ventral spine (*arrows*) at the level from C3 to C4 hinder regular epiglottic tilting (*short arrow*). Consequently, aspiration is visible (*black arrow*) (**b**) CT of the cervical spine confirms anterior osteophytes (*arrow*) and the close anatomical relationship of cervical spine and the epiglottis (*short arrow*)

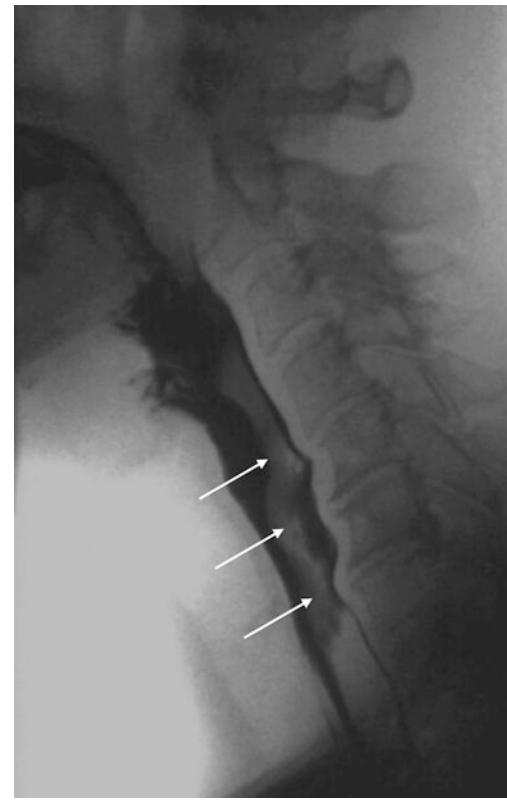


Fig. 21 When the contrast bolus reaches the level of the PE segment, the dorsal pharyngeal wall should have smooth margins, because the sphincter relaxes. A slight wavelike margin is normal—it is caused by the intervertebral disks (*arrows*)

Cricopharyngeal Bar. The best visualization of pharyngoesophageal dynamics is possible with videofluoroscopy. Especially in older patients, more than 30% of patients without dysphagia show a cricopharnygeal bar during videofluoroscopy (Leonard et al. 2004). There are conflicting opinions about the percentage of narrowing that enables the diagnosis of a sphincter disorder. Three different patients with varying degrees of incomplete opening of the upper esophageal sphincter are shown in Fig. 22.

In the case of mild dyskinesia, the dorsal indentation of the barium is discrete. The indentation of a cricopharyngeal bar may occur at various points of time during the passage of contrast medium. Furthermore, the indentation may be present for a varying period of time. Accurate assessment of an elevation of the larynx and hyoid is mandatory to make the decision about further myotomy treatment.

Gaping of the PE Segment. In cases of severe neuromuscular disease, the upper esophageal sphincter may reveal a gap, resulting from weakness. The resting pressure is no longer sufficient to close the sphincter (Fig. 23).

Web. So-called membrane flaps or webs are solitary or multiple, thin mucous membranes, most frequently located in the anterior wall of the upper esophageal sphincter and best seen on dynamic recordings. They are usually seen briefly on a few images (Fig. 24).

Zenker's Diverticulum. In the region of the pharyngoesophageal junction, we find the clinically significant Zenker's diverticulum, which

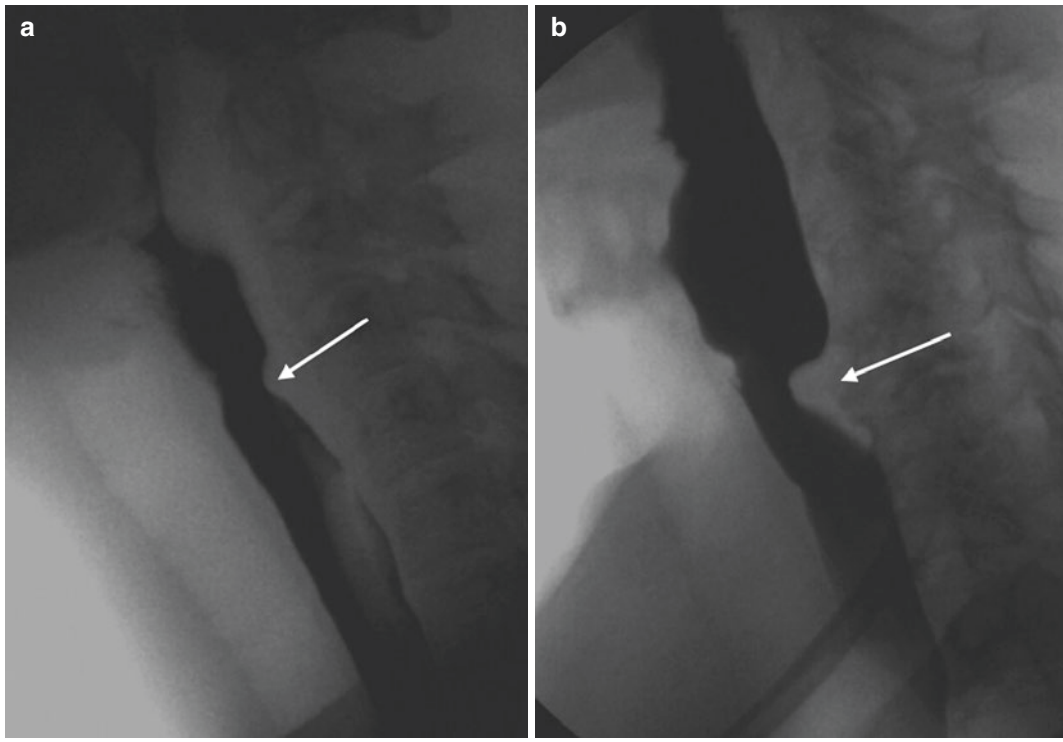
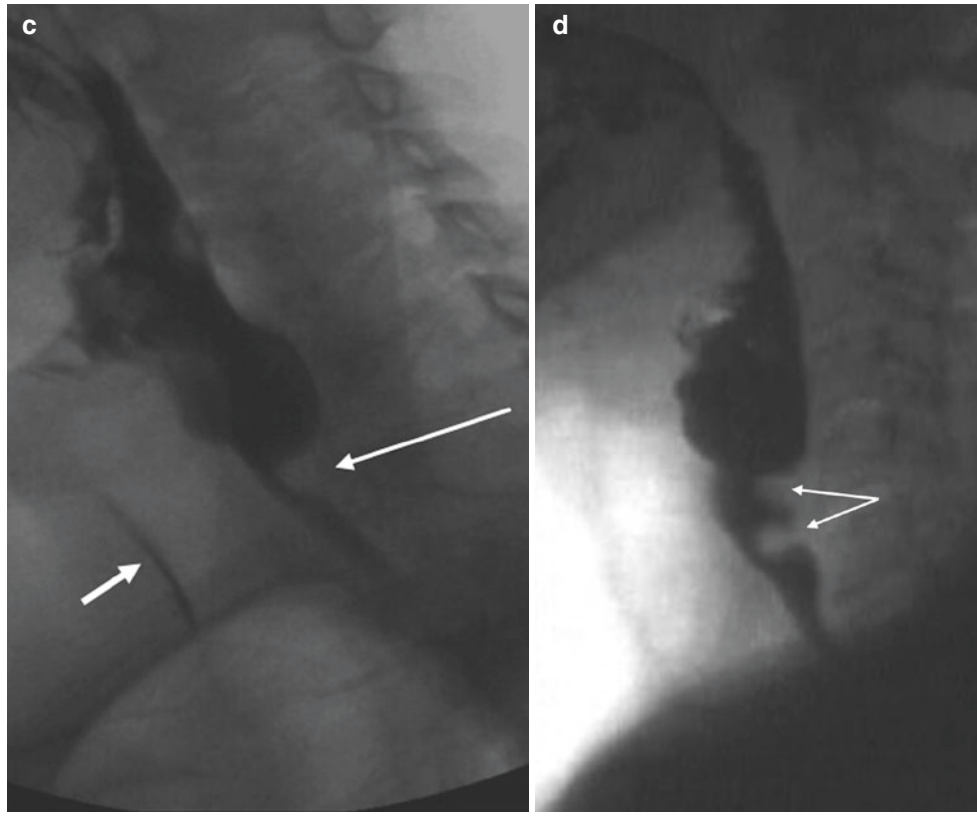


Fig. 22 Dyskinesia of the pharyngoesophageal segment. (**a**) A dorsal rounded impression of the column of contrast medium at the level of the PE segment can often be found in asymptomatic patients, representing a moderate cricopharyngeal bar with a narrowing of <30% (*arrow*). (**b**) Prominent dysfunction of the PE segment with a cricopharyngeal bar causing a 60% narrowing (*arrow*). (**c**) Extreme incomplete opening (*arrow*) with pharyngeal dilation and retention of contrast medium as well as little aspiration (*short arrow*). (**d**) Videofluoroscopy shows two indentations in terms of a double sphincter, which can be found in various neuromuscular disorders



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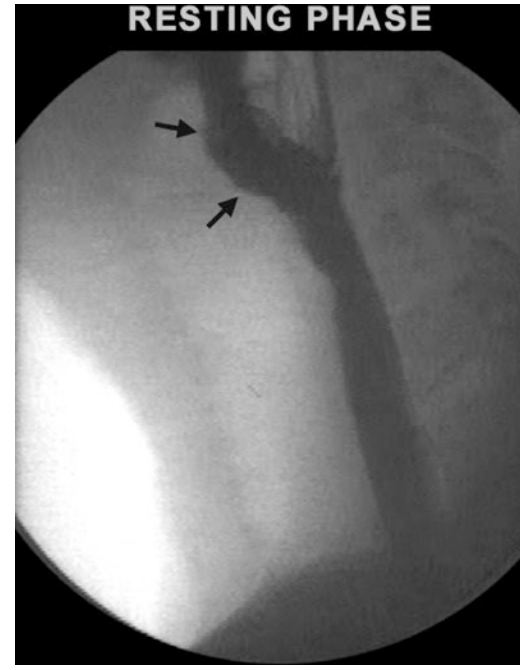

Fig. 23 In this 55-year-old woman with mixed connective tissue disease, the PE segment remains open during all the three phases of swallowing. In addition, there is always a weakness of the pharynx and retentions (*arrows*) in such patients

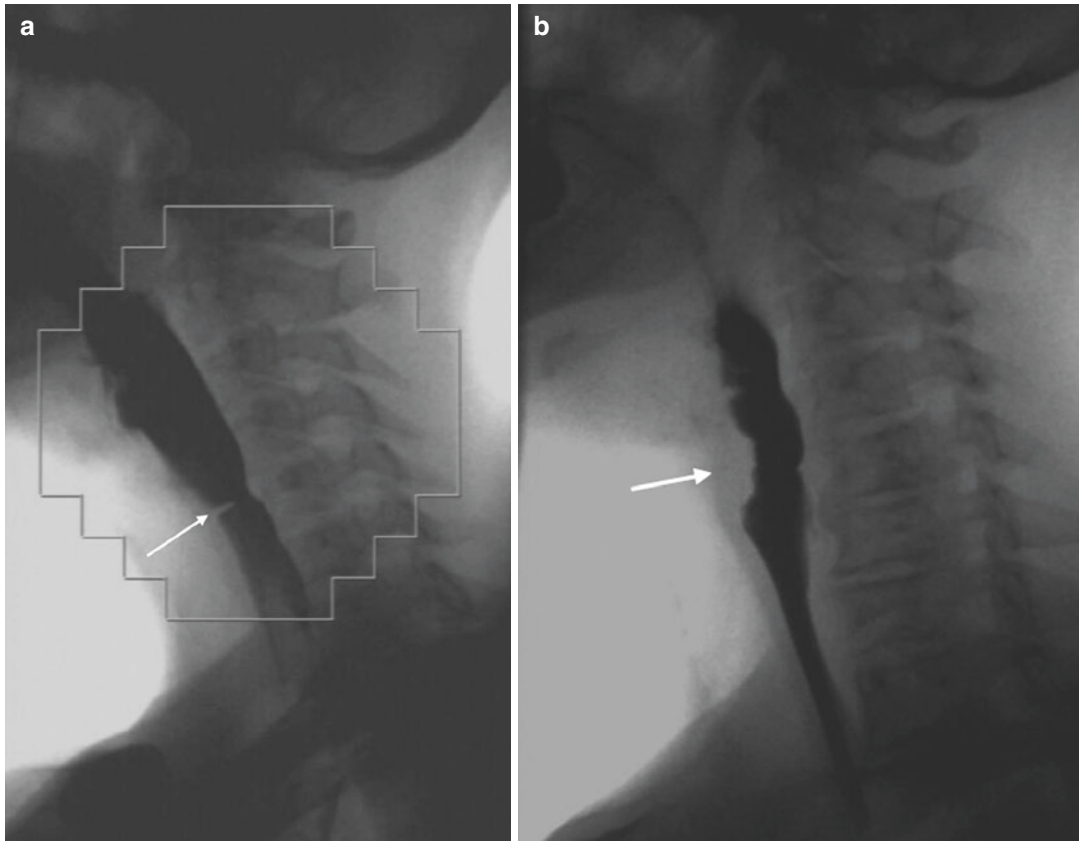

Fig. 24 (**a**) A 32-year-old woman with solid-food dysphagia worsening during the last year, pain after eating solids, and weight loss. Videofluoroscopy shows a cervical web (*arrow*) located ventrally in the lower PE segment and impeding bolus flow into the esophagus. The web is visible only for parts of a second. (**b**) Typical venous plexus at the postcricoid level (*arrow*). This normal dynamic appearance of an inconstant irregularity must not be misdiagnosed as a web. Webs are always thin and sharply delineated. This differentiates them from the retrocricoid venous plexus, which shows normal, movable, round mucosal folds

may substantially hinder bolus passage, depending on its size (Fig. 25). Small Zenker's diverticula or pseudodiverticula, in combination with a sphincter dyskinesia, may also cause problems.

4.3.7 Esophagus

The esophagus, the seventh functional unit, is very different from the others. The esophageal passage takes about 10 s—about ten times the duration of the pharyngeal passage. The examination technique is also different, as one moves the device along with the slow peristaltic wave of the tubular esophagus from cranial to caudal. The device is kept stationary only at the beginning and the end of the esophageal passage. The analysis is focused on the dynamic movements of the esophageal walls.

Delay of Transport in the Erect Position. One should keep in mind that pseudoachalasia [tumor stenosis of the esophagogastric junction (EGJ)] cannot be differentiated videofluoroscopically from achalasia with certainty—endoscopy must be performed (Fig. 26).

Delay of Transport in the Horizontal Position. The most frequent passage disorder is delayed esophageal transport in the prone or supine position. On oblique views, with a prone RAO position, a single swallow of 10 ml is partially transported.

Nonpropulsive Contractions. These contractions, also called tertiary contractions, are more or less strong constrictions of the esophagus that occur in addition to the wave of contraction. They are

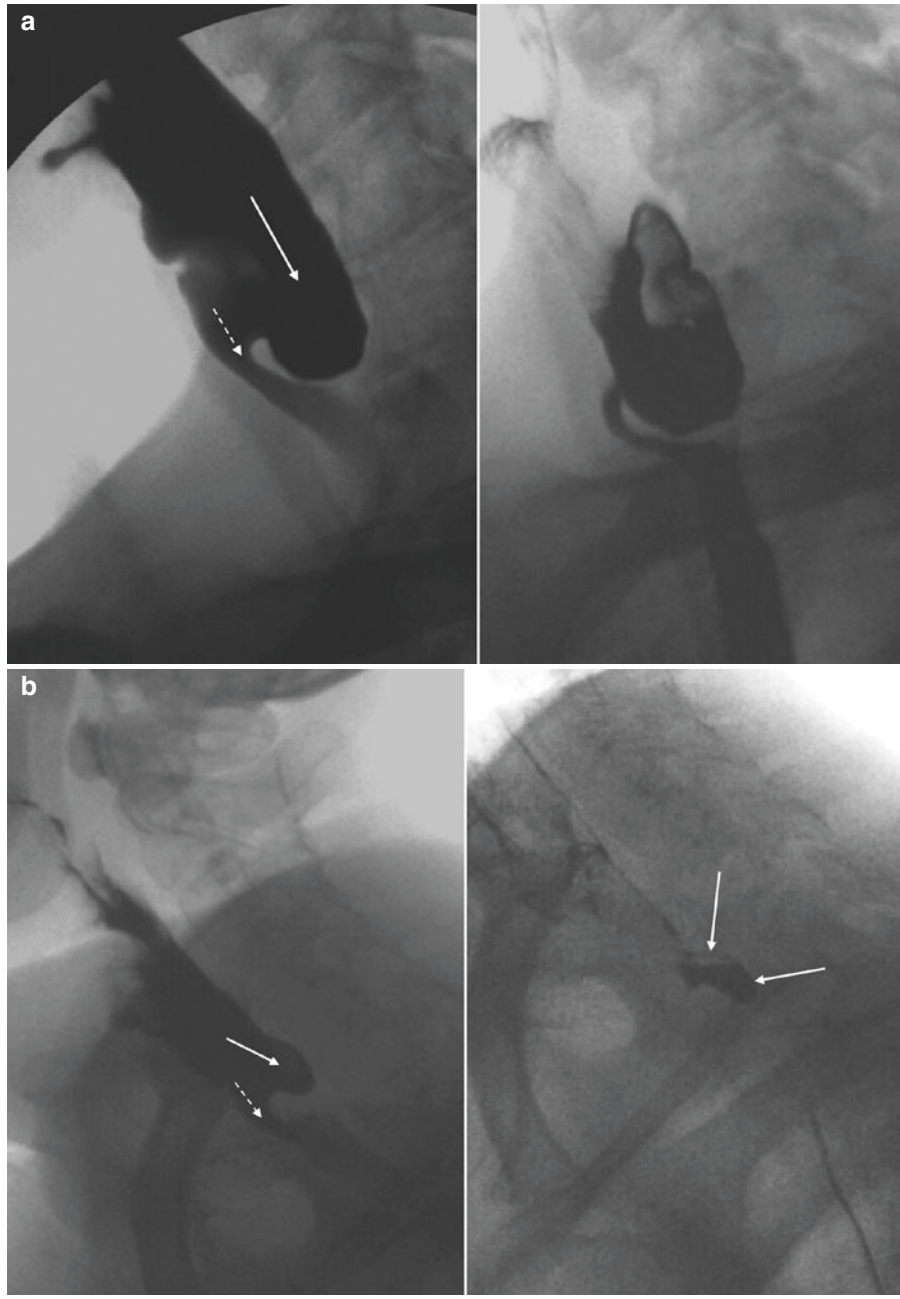

Fig. 25 Zenker's diverticulum. (**a**) During swallowing, a Zenker's diverticulum (*left, arrow*) can be observed as a sac originating above a cricopharnygeal bar. Large Zenker's diverticula are visualized as obstructions of passage even on ordinary static images (*left*, *dashed arrow*) and post-deglutitive retention of contrast media (*right*). (**b**) Also smaller diverticula may show a markedly wider point of entry into the diverticulum (*left, arrow*) than the esophageal pathway (*left, dashed arrow*), but a remaining smaller size after deglutition (*right*). (**c**) A very small collection of barium (*left, arrow*) trapped above a cricopharyngeal bar, also called a pseudo-Zenker's diverticulum, which cannot be seen during swallowing (*right*)

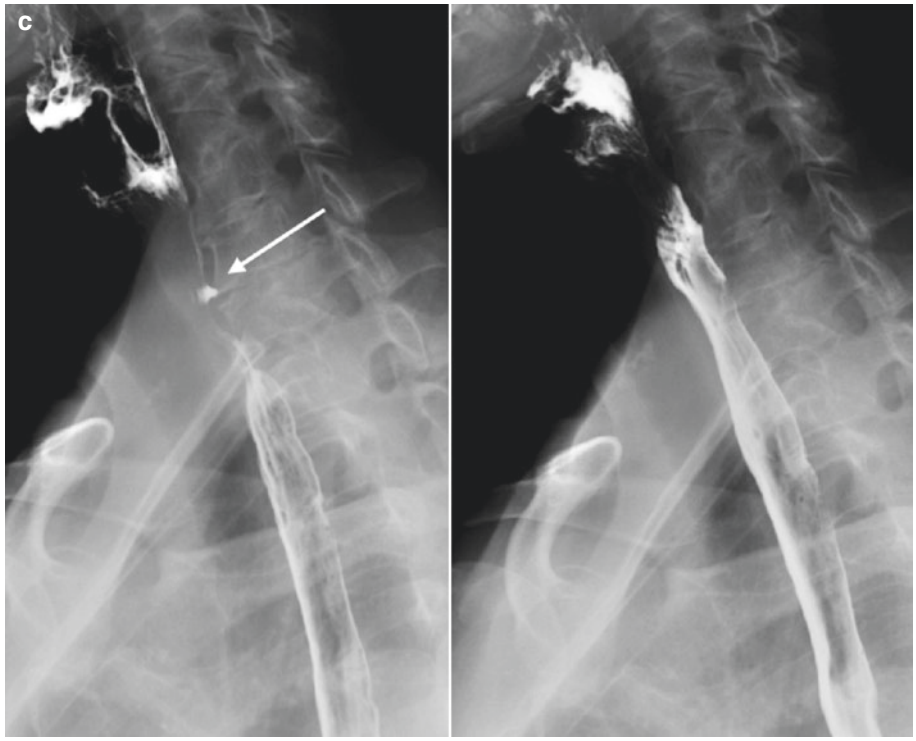

Fig. 25 (continued)

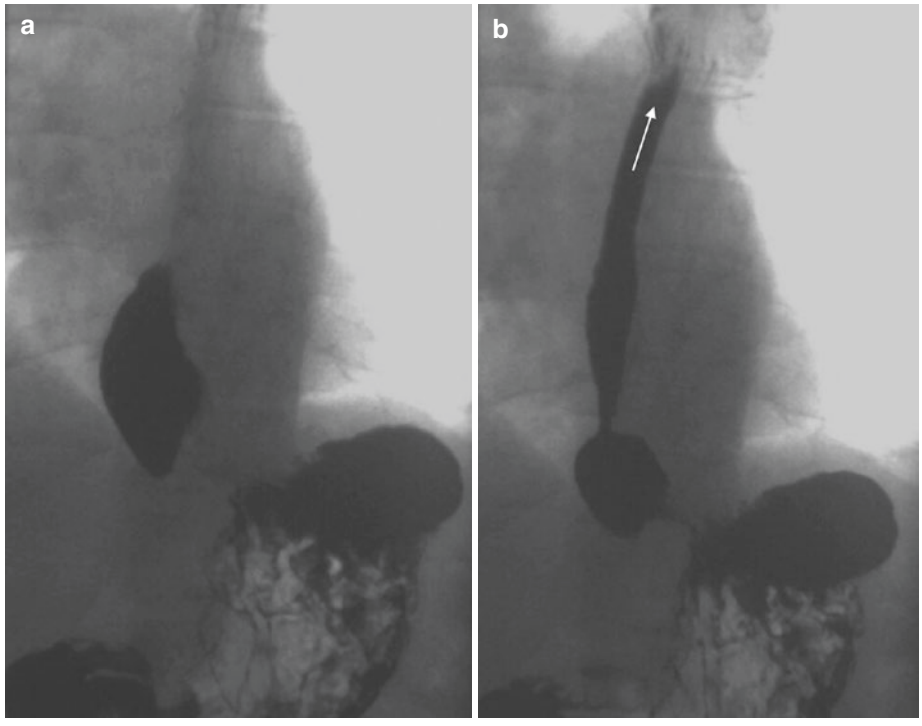

Fig. 26 Proximal escape. (**a**) In this 62-year-old man with globus sensation, the contrast medium is initially transported. (**b**) Having reached the EGJ, the contrast medium now flows back in a proximal direction (*arrow*), because the esophageal contraction is too weak to propagate 10 ml of barium. This indirect sign of reduced contraction strength is known as "proximal escape"

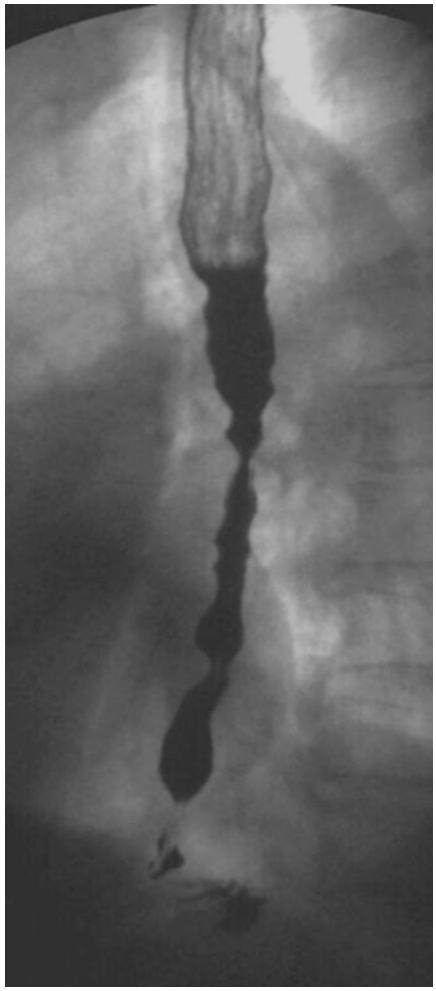

Fig. 27 This man suffers from achalasia. In severe achalasia a support level persists during the entire examination. Only small quantities of contrast medium are able to pass through a beak-like esophagogastric junction. In this case we also see strong nonpropulsive contractions—a further important functional finding

usually combined with a proximal escape of some barium or a support level of barium with the patient in the upright position (Fig. 27) (Schima et al. 1992).

Esophageal Stenoses. Stenoses of the esophagus, which are usually easier to diagnose on dynamic rather than on static X-ray images, can be tested for their diameters (Fig. 28). Placebo tablets of 13–14 mm diameter allow an exact measurement of the esophageal width. Furthermore, the tablet may produce symptoms that reproduce the patient's complaints.

If standard boluses of 10 ml do not obtain a clear delineation of the EGJ, about 150 ml of very thin barium can be applied through a straw—in the horizontal position. The patient may be advised to swallow repeatedly. This causes intra-deglutitive inhibition of the peristaltic waves, and the esophagus starts to fill up in monocontrast. This can help to diagnose subtle stenoses and rings as an adjunct or alternative to a placebo tablet. Videofluoroscopy enables the possibility to detect subtle esophageal stenoses not diagnosed by endoscopy (Figs. 29 and 30). Especially in young patients with dysphagia and a history of recurrent impactions, videofluoroscopy can reveal a small-caliber esophagus and ringlike stenotic margins, suggestive of eosinophilic esophagitis (Fig. 31).

Esophageal Diverticula. This is an important diagnosis. Whereas the Zenker's diverticulum may be easy to diagnose, the mid-esophageal and epiphrenic diverticula can be obscured by severe nonpropulsive contractions (Fig. 32). The esophageal tube above and below a mid-esophageal diverticulum shows an invariably delayed esophageal transport and nonpropulsive contractions. Incidentally, mid-esophageal diverticula may be found in non-dysphagic elderly people. This is crucial for further treatment, regardless of whether food impaction at the level of the diverticulum is present. Furthermore, it is important to note that epiphrenic diverticula are almost always combined with achalasia of the lower esophageal sphincter.

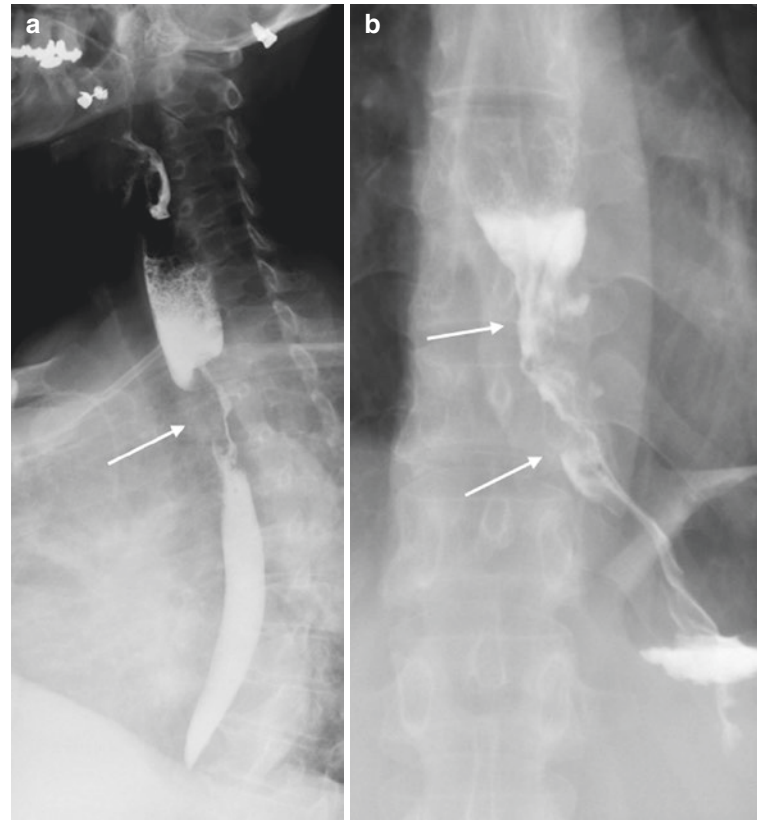

Fig. 28 Esophageal carcinoma (**a**) A 62-year-old woman with dysphagia and a carcinoma of the proximal esophagus. An endoscope could not be advanced, and videofluoroscopy was the first diagnostic test. (**b**) Example of a distal esophageal malignant stenosis (*arrows*) showing the impaired bolus flow with a support level above the tumor. The dynamic investigation is advantageous due to the extraordinarily useful time resolution, when esophageal stenosis has to be diagnosed. At a frame rate of three to four spot films per second, digital recording proves to be an alternative technique for structural lesions, but not for the dynamic evaluation of motility

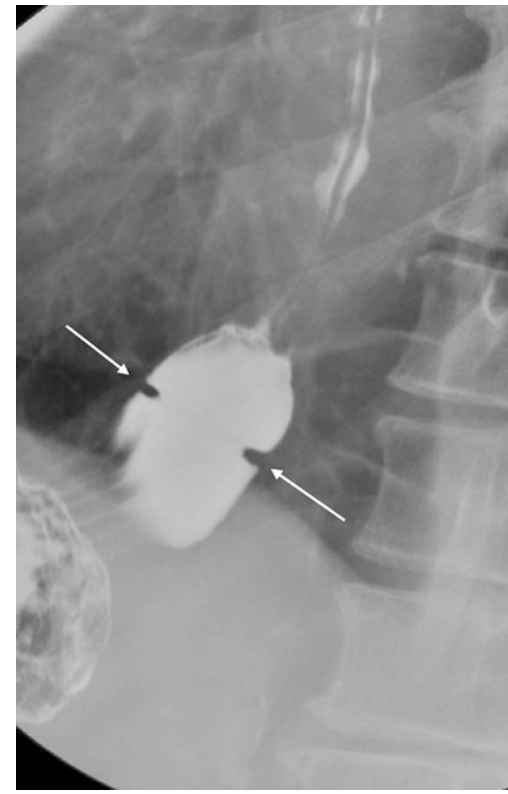

Fig. 29 In the supine position, the esophageal vestibule should be cleared completely when a 10 ml bolus of barium has been swallowed with the single-swallow technique. A subtle mucosal ring (*arrows*) delineates the proximally sited esophageal vestibule and a 3 cm hernia between the vestibule and the EGJ

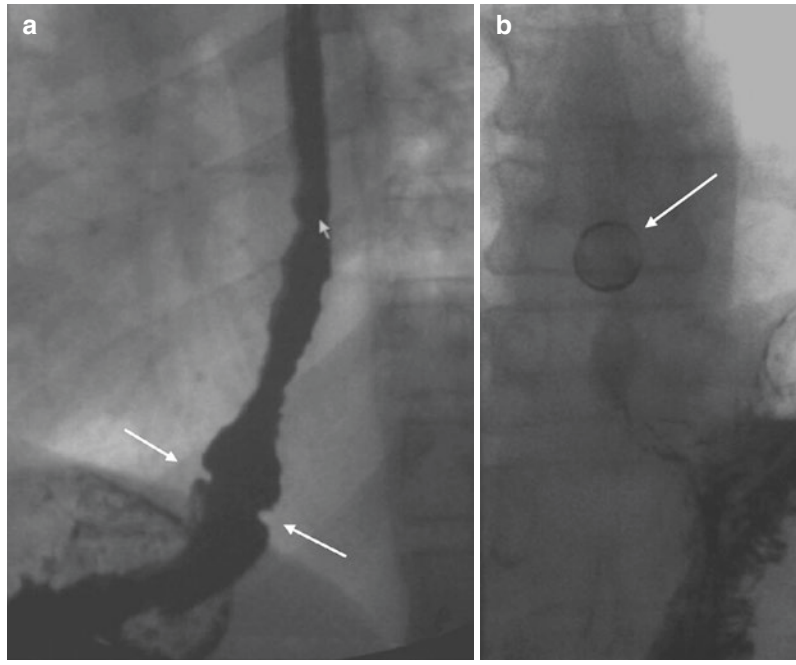

Fig. 30 Schatzki ring. (**a**) The most common stenosis of the esophagus is the Schatzki ring. A typical Schatzki ring in a 50-year-old man with dysphagia for solids (*arrows*). The ring is located exactly at the gastroesophageal junction and is nearly always combined with a hiatal hernia. It is crucial to investigate the patient in the prone and supine positions, since rings and hernias of the EGJ may be seen in the prone position only. The Schatzki ring acts as a diaphragm and can cause impaction of solid food. During bolus passage, the ring is only visible for a second or two, depending on the bolus volume. (**b**) A tablet (diameter of 14 mm) impacts at the level of the ring (*arrow*) proving clinical relevant stenosis

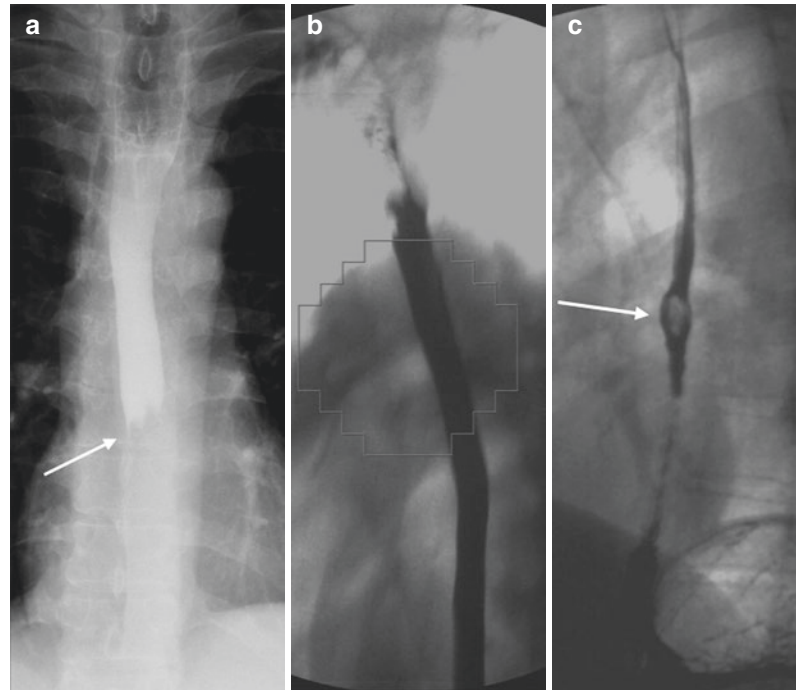

Fig. 31 (**a**) Young patient with repeated impactions of solid food in the middle esophagus (*arrow*) that requires endoscopic extraction. (**b**) Videofluoroscopy reveals a long-segment esophageal narrowing, also known as "small-caliber esophagus." (**c**) After ingestion of a tablet with a diameter of 14 mm it is impacted at the same esophageal level (*arrow*); histology confirmed eosinophilic esophagitis

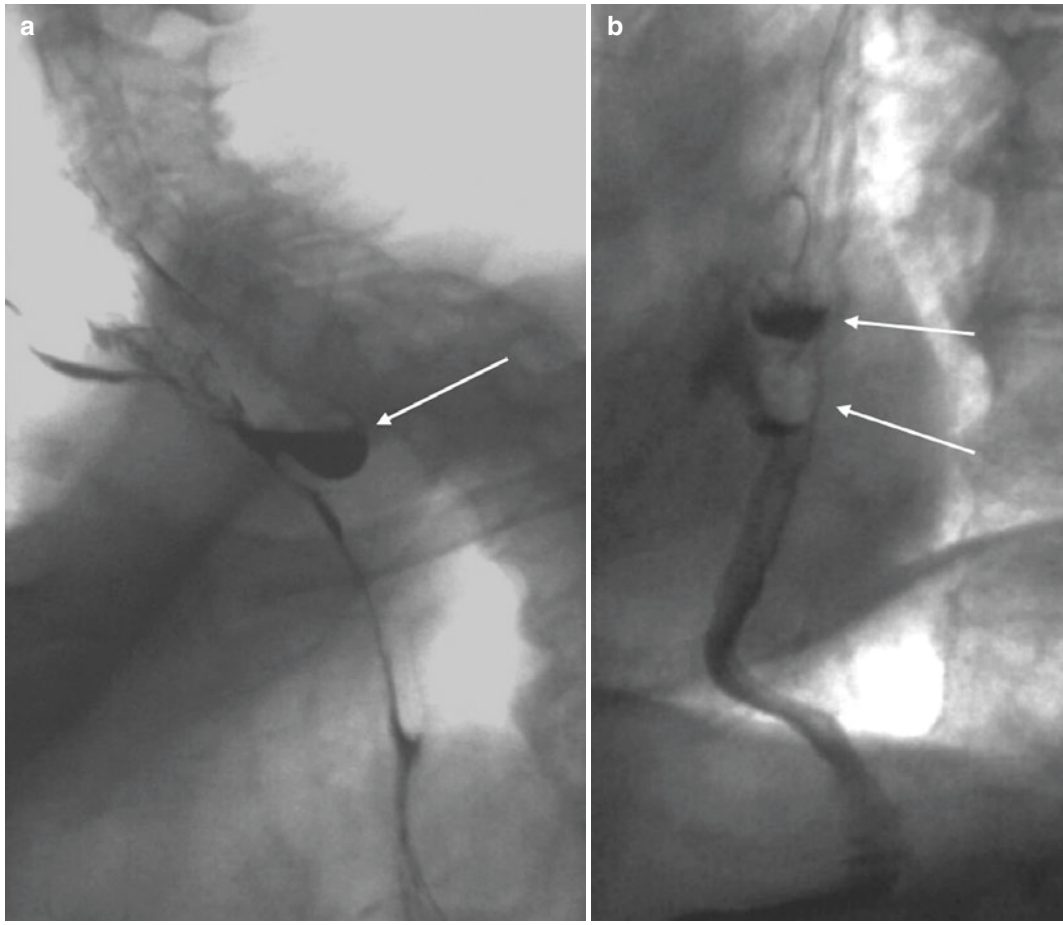

Fig. 32 (**a**) Typical Zenker's diverticulum (*arrow*) with dislocation of the esophagus and mild obstruction for bolus passage. (**b**) In the same patient, two mid-esophageal diverticula (*arrows*) are found during videofluoroscopy. These diverticula are usually small and asymptomatic and do not require intervention; in rare cases they may achieve a size causing symptoms and require invasive management

Esophagogastric Junction. In 80% of patients with reflux disease, a hiatal hernia is present, but only 50% of patients with a hernia suffer from reflux disease. The radiographic diagnosis of a small hiatal hernia is not of specific clinical importance; nevertheless, the radiographic examination of the esophagogastric junction is the method of choice by which to obtain pertinent topographic information (Fig. 33).

The radiologic contributions that suggest reflux disease by means of functional observations, such as reflux or the dynamic appearance of the EGJ, are controversial. This chapter does not intend to discuss provocative tests for reflux, such as the water-siphon test. Reporting on the dynamic EGJ can enrich the view of videofluoroscopy and suggest further workup with pH monitoring or endoscopy. Topographic information can also help in planning surgical therapy.

Most patients with heartburn can be managed symptomatically. With persistent, atypical symptoms, a more detailed investigation may be required. The dynamic evaluation can diagnose the presence of a hernia, its topographic relations, abnormal esophageal peristalsis, cricopharyngeal dysfunction, and suggestive observations, such as a cardia rosette, the angle of His, and the width of the EGJ.

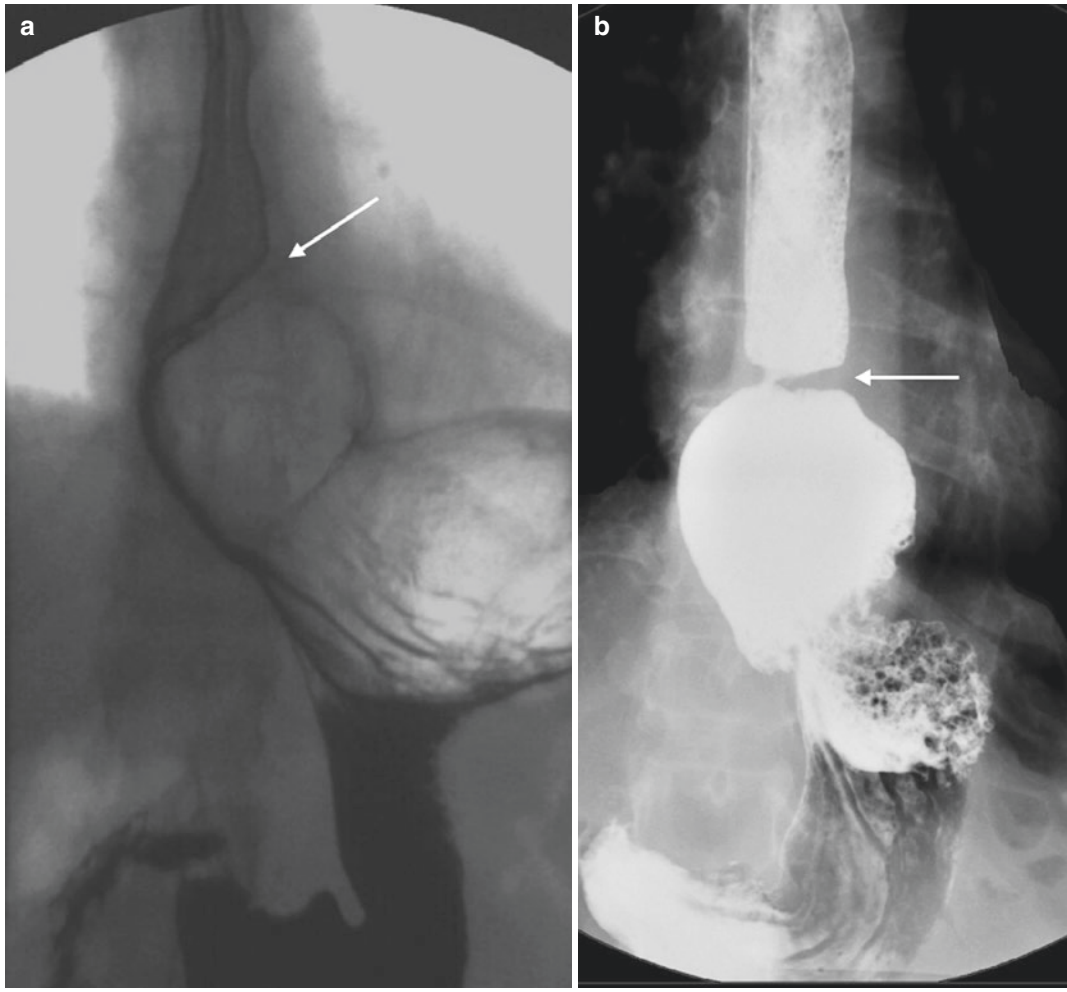

Fig. 33 (**a**) Large hiatal hernia in a patient with reflux symptoms and solid-food dysphagia. Videofluoroscopy reveals a large hiatal hernia and a wide diaphragmatic hiatus with a ringlike indentation above the hernia (*arrow*). (**b**) Maximum distension reveals the severity of the stenosis (*arrow*)

5 Summary

As swallowing is a highly complex process involving the coordinated effort of many muscles and nerves within the oropharynx and esophagus, dysphagia comprises a wide variety of causes and complex symptomatology. This underlines the need for a thorough history taking in patients with swallowing in order to adapt and to plan the radiological investigation and refer the findings to the patients' symptoms. A standardized approach for reporting videofluoroscopic swallowing studies is helpful to correctly assess pathological findings of morphology and function as well and to recommend further diagnostic procedures. The multidisciplinary workup ensures optimal evaluation of the individual symptoms and requires knowledge of all investigation modalities and their strengths in this particular patient group.

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Imaging Techniques and Some Principles of Interpretation (Including Radiation Physics)

Olle Ekberg

Contents

Abstract

Radiologic examination of the oral cavity, pharynx, and esophagus should focus on bolus transportation as well as on registration of morphodynamic events. The examination should be custom-tailored to the patient's symptoms but should also be performed in a rather standardized way. The radiologic findings should always be compared to the patient's specific symptoms.

1 Introduction

In the dysphagic patient the radiologic examination of the oral cavity, pharynx, and esophagus should be regarded as an extension of the physical and neurologic examinations. The mouth and the pharynx and larynx can be reached only partially during more conventional clinical evaluation. The result of the radiologic examination should thus be put in a broader context together with the clinical history and the result of the clinical and neurologic examinations.

2 The Symptom Dysphagia

Dysphagia, i.e., any abnormal sensation during swallowing experienced by the patient, may be caused by either morphologic abnormalities or dysfunction. The clinical history is often spurious and careful workup must be considered.

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The swallowing apparatus consists of the oral cavity, pharynx, and esophagus and symptoms from any of these three compartments may be present. Morphologic evaluation of these three compartments can be done by direct inspection (the oral cavity), by indirect inspection (the pharynx and larynx), or by endoscopy (the esophagus). However, for a proper functional evaluation, radiology is necessary. For the evaluation of transportation through the oral cavity, pharynx, and esophagus, the barium swallow is without doubt the most reliable test. It is used extensively and its accuracy has been well shown.

Any clinician interested in patients with dysphagia needs to make sure that his consultant radiologist has the means and interest to perform a proper examination. A carelessly performed examination interpreted as showing normal findings may give the clinician a false impression that the examination has been completed and misinterpretation of the barium swallow may lead to unnecessary further workup and delay correct diagnosis.

2.1 Does the Patient Really Have Dysphagia?

When properly performed, the radiologic examination should start with a careful penetration of the clinical history. The examination should then be custom-tailored to each patient's specific complaints. The patient who complains of difficulties with certain foods should be examined with such food. The patient who complains particularly of choking during eating must be carefully examined for misdirected swallowing. The patient who complains of heartburn should be examined with respect to gastroesophageal reflux disease. Patients who complain of pain or obstruction during solid bolus swallow need to be examined with some kind of standardized solid bolus. Therefore, a clinical history is of crucial importance for the radiologist and he or she needs to state in his or her report for what symptoms/purposes the study was designed. However, it is also important to always examine all three compartments of the swallowing apparatus, namely, the oral cavity, the pharynx, and the esophagus. What the clinical history does is to help the radiologist focus on one particular segment and sometimes on a specific food consistency. If the patient has undergone a careful endoscopic examination, before being sent for the radiologic examination, this should focus not on morphology but merely on function. However, most patients with dysphagia do not undergo endoscopy of the esophagus. Therefore, in most patients with dysphagia, it is important that the radiologist perform both a functional evaluation and a detailed double-contrast morphologic examination of the esophagus.

Most patients with swallowing symptoms have an abnormality that can be revealed during the radiologic examination whether it is morphologic or functional. However, many patients are sent for radiologic examinations of the swallowing apparatus without any real swallowing problems. These patients suffer from globus and their spontaneous clinical history always includes complaints or an inability to swallow. They feel a sensation of obstruction when swallowing and a constant feeling of a "lump" in the throat. This is the dominant and overwhelming symptom which bothers the patient considerably and this impresses many physicians. However, when a structured clinical history is taken, the patient admits that "he can eat and drink normally." This is the hallmark of globus. These patients localize their symptoms to the neck, but the symptoms should alert the radiologist to focus his or her examination on the lower esophagus in an attempt to reveal signs of gastroesophageal reflux disease. In fact, these patients, in addition to the inability to swallow "normally," also have heartburn and regurgitation. However, these symptoms are not the leading symptoms and are less alarming than the globus symptom. Therefore, globus should be taken seriously and these patients should be examined properly.

2.2 Findings Compared with Symptoms

The careful clinical history also serves another purpose, namely, to make an assessment of the clinical relevance of any radiologic finding. A comparison of the patient's symptoms and the radiologic finding should always be included in

the radiologist's report. The radiologic examination may reveal a host of abnormalities, most of which are irrelevant in that particular clinical setting. In our experience, the radiologist experienced in dysphagia evaluation is best suited to make this comparison between symptoms and findings. The radiologist knows how the examination was performed and may also add to the clinical history after the examination has been done. It may be true that many patients with dysphagia do not undergo a proper functional evaluation of the swallowing apparatus. However, the result of many barium studies is at the same time misinterpreted and not put into a proper clinical context.

2.3 Dysphagia During the Radiologic Examination

As well as the importance of the clinical history concerning symptoms and signs, it is also important to register symptoms during the radiologic examination. If misdirected swallowing occurs, the radiologist needs to observe if cough or other signs of the patient's subjective experience of that misdirected swallowing event occur. By and large, patients who do not cough during even minor events of misdirected swallowing have a more advanced disease than those who cough and have an increased risk of airway disease (Figs. 1 and 2).

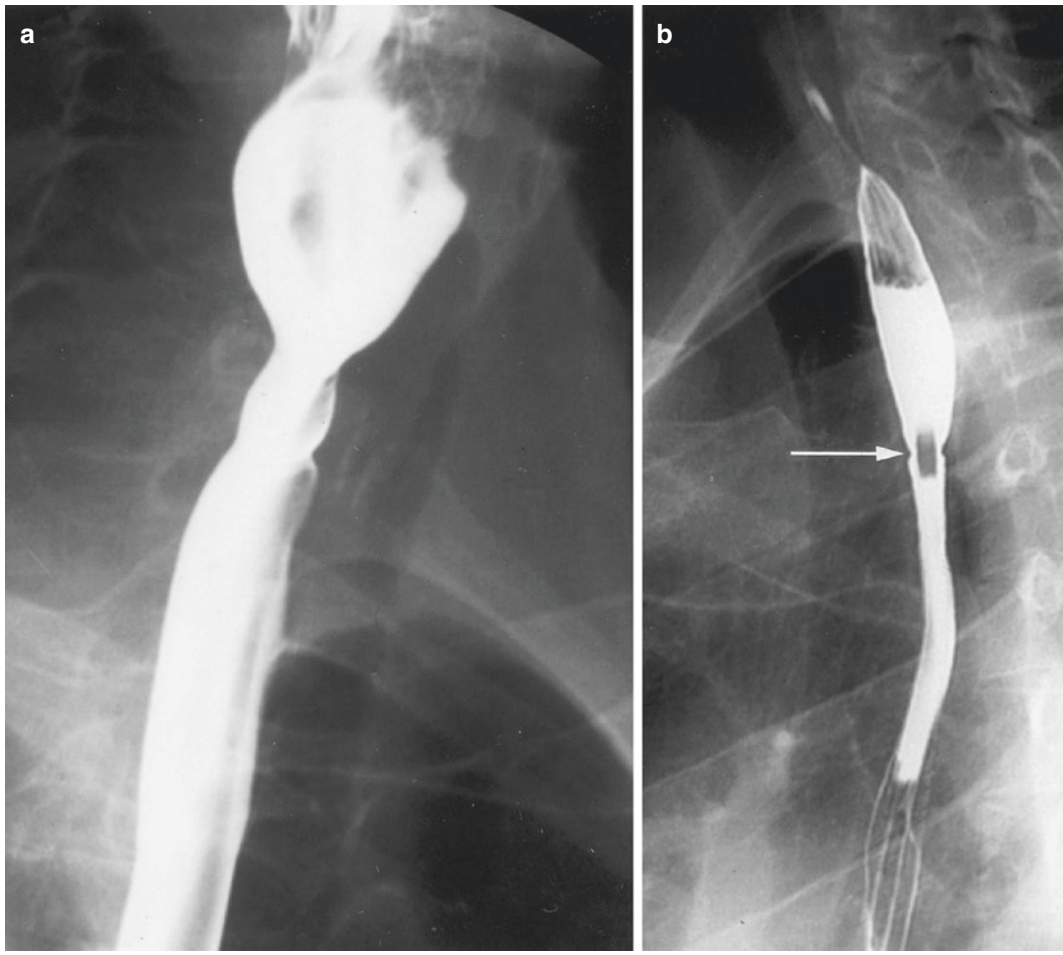

Fig. 1 A 46-year-old woman with solid bolus dysphagia. The findings of the initial barium examination were assessed as normal. A 13-mm-diameter antacid tablet used for stressing the esophagus became stuck in the proximal esophagus. A short asymmetric narrowing (assessed to be congenital in origin) was revealed (*arrow*) by the tablet. Balloon dilatation made the patient become asymptomatic

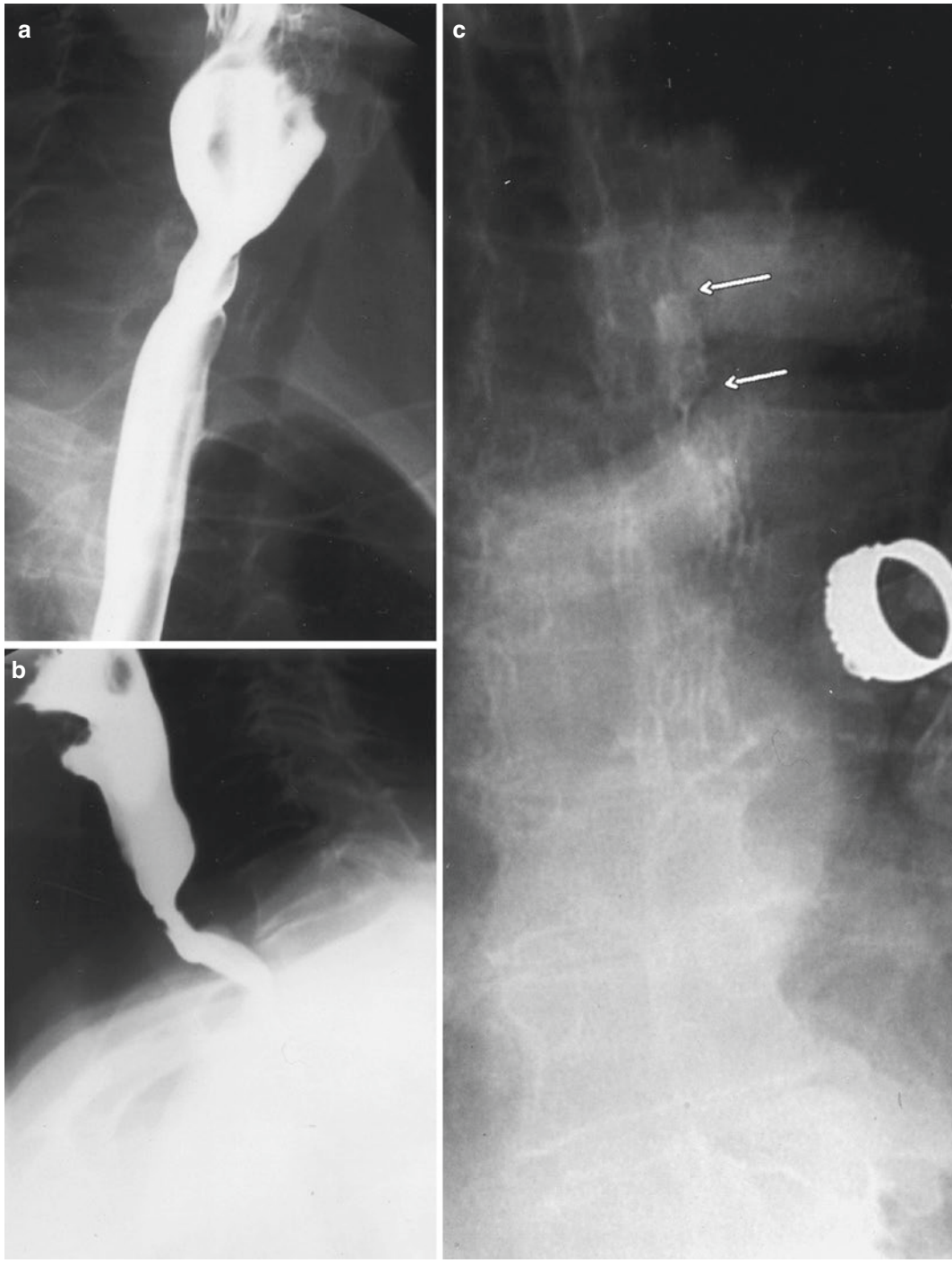

Fig. 2 An elderly patient with solid bolus dysphagia. (**a**, **b**) Single-contrast examinations of the pharynx and the pharyngoesophageal segment (PES). There is an incoordination in the opening of the PES and also small weblike narrowings. There is no misdirected swallowing. (**c**) As the patient indicated solid bolus dysphagia, she was given an antacid tablet together with thin liquid barium. The tablet passed the pharynx and the PES and became stuck in the upper esophagus. The patient immediately indicated that this created the same dysphagia symptom as she had had before. She indicated the level of the symptoms with her left hand. There is a ring on her index finger. The location of the tablet is indicated with *arrows*. Further evaluation revealed decreased peristaltic contrast pressure in this area but there was no morphologic abnormality

If a tablet is given to evaluate solid bolus dysphagia and if the patient does experience symptoms similar to the ones he or she experienced during normal eating and drinking, the tablet test can be considered diagnostic (van Westen and Ekberg 1993). However, even if the tablet gets stuck in the esophagus (excluding patients with strictures) for many minutes and the patient does not experience this, the tablet test has not revealed the cause of that particular patient's dysphagia. However, one needs to remember that patients usually do not spontaneously comment on symptoms during the test. This is often because symptoms provoked during the radiologic examination are much milder than those that occur during normal eating and drinking. This circumstance should alert the radiologist to carefully but casually ask the patient about swallowing symptoms during this test.

2.4 The Radiologic Examination (Barium or Iodine Swallow)

In the team of professionals taking care of neurologically impaired patients with swallowing difficulties the radiologist plays an important role. He or she must choose the correct imaging technique which will most expediently and accurately answer the clinical questions. This is not always barium swallow. For instance, in patients with the combination/constellation of neck pain and dysphagia, MRI can reveal soft tissue disease, such as retropharyngitis (Ekberg and Sjöberg 1995). The radiologist in the swallowing team must be aware of the limitations of radiology for assessment of the course and treatment of the disease process.

Radiology therefore offers a unique possibility to screen patients with swallowing symptoms. The barium swallow allows evaluation of both morphology and function, which is unique to this technique.

2.4.1 How to Perform the Barium Swallow Examination

The radiologic examination should be performed as a biphasic examination, i.e., both function (single contrast) and morphology (double contrast) should be evaluated (Fig. 3). All patients with dysphagia can be accurately examined

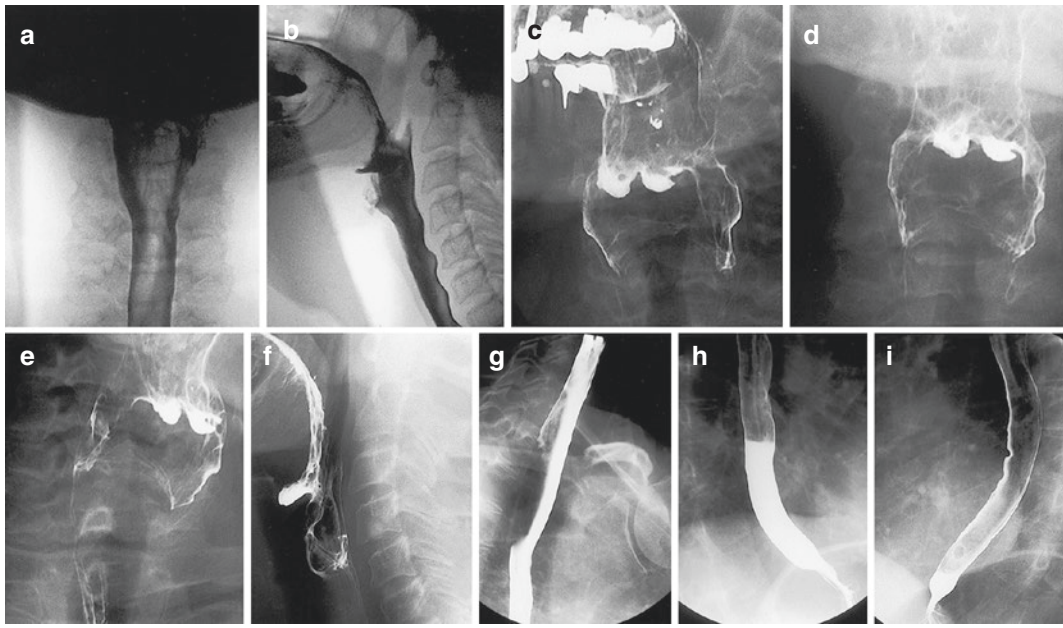

Fig. 3 Biphasic examination of the pharynx and esophagus. (**a**, **b**) Frontal and lateral projections of the pharynx. These images are digitally stored from the fluoroscopic images. (**c**) Double-contrast examination of the pharynx in slight left anterior oblique projection. (**d**) Frontal projection of the pharynx, double contrast. (**e**) Right anterior oblique projection of the pharynx examined with the double-contrast technique. (**f**) Lateral double-contrast examination of the pharynx. (**g–i**) Double-contrast examinations of the esophagus in different projections

radiologically! Even in the severely ill stroke patient the relevant clinical questions can be answered. In the very impaired patient it is often enough to demonstrate whether or not the patient can elicit the pharyngeal stage of swallowing and maybe also the degree of aspiration if this occurs. Such an examination is usually easy to perform. Cumbersome and time-consuming are examinations in ambulatory, alert, otherwise healthy young patients who complain of vague or uncharacteristic symptoms during swallowing.

The image should be centered at the important area whether this is the oral cavity, pharynx, or esophagus. Moreover, one should always use proper cone down, and most importantly, collimation. If wedge frames are available, they should always be used. A high voltage (110 kV) should always be used as this will shorten the exposure time, thereby minimizing movement artifacts.

The fluoroscopic intensifier should not be moved during exposure. Also, it should be kept steady during fluoroscopy. Moving the image intensifier around may save contrast medium but deteriorates image sharpness, thereby losing important morphologic information (Fig. 4).

Modern digital radiologic equipment offers the possibility to store the fluoroscopic image in digital form (Figs. 5, 6, and 7). This reduces the radiation dose administered to the patient (and the radiologist!). A digital fluoroscopy system is configured in the same way as a conventional fluoroscopy system (tube, table, image intensifier, video system). The analogue video signal is converted to, and stored as, digital data.

A frame rate of 25–50 frames per second may be achieved, but most studies use 12 frames per second.

It is important to perform fluoroscopy and obtain images in standardized projections. Fluoroscopy is used for assessment of function, and also for positioning. Especially in the pharynx the importance of meticulous positioning and projection is important (Figs. 8, 9, and 10).

All patients should be examined with them in an erect sitting or standing position if possible. We prefer to use high-density barium contrast medium (240% w/v) for the double-contrast evaluation of the oral cavity, pharynx, and esophagus.

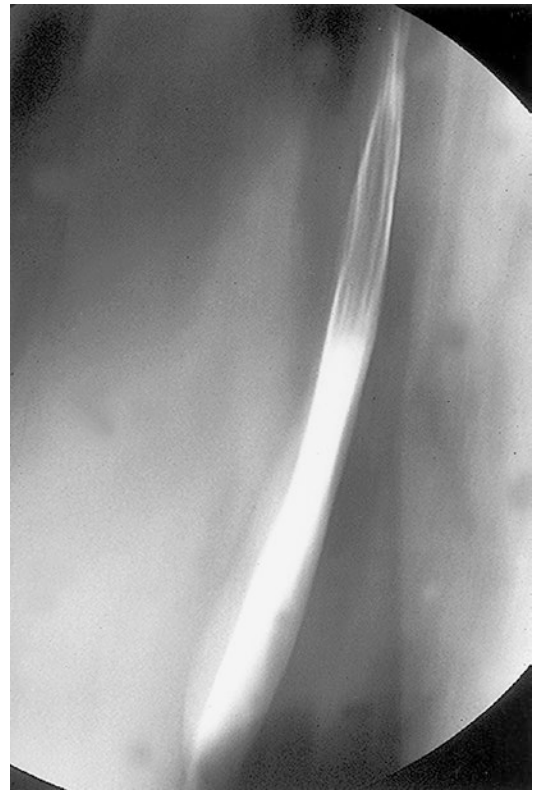

Fig. 4 The distal part of the esophagus filled with barium contrast medium and air. The image intensifier was moved during the exposure and this created lack of sharpness

The high density of the barium contrast medium also makes it relatively easy to register penetration of barium into the laryngeal vestibule (Fig. 11). However, such high-density barium contrast medium, probably owing to its high viscosity, is less likely to reach into the vestibule in patients with a defective closure. Therefore, sometimes penetration is revealed only when low-density barium contrast medium (40% w/v) is used. However, with the proper exposure technique, it should be possible to reveal even minute amounts of such contrast medium.

2.4.2 How to Perform the Iodine Swallow Examination

Only in patients in whom feeding must be strictly nonoral is it indicated to replace barium contrast medium with iodine contrast medium. The basic advantage with barium contrast medium is that it is radiopaque. It is also not harmful to the mucosa

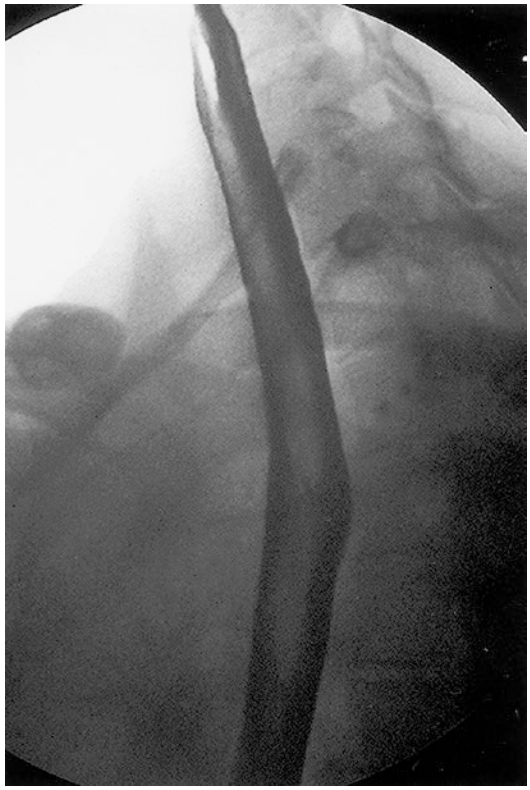

Fig. 5 Digitally stored image of the esophagus. This gives an image with inferior spatial resolution compared with an exposed image, but the radiation dose is much lower

in the airways. It is readily transported cranially in the airways by the cilia. However, in patients with emphysema and other chronic obstructive lung diseases, the transportation might be delayed and even absent from the most distal parts, i.e., the alveoli and emphysematous bullae. In such patients it might also be indicated to use iodine contrast medium. Iodine contrast medium generally used to be a hyperosmotic fluid with a very strong taste and smell. Nowadays, iodine contrast medium is usually nonionic, iso-osmolar, or has slightly higher osmolarity compared with plasma. Usually it has a sweet taste and no smell. The radiodensity of such a contrast medium (e.g., 350 mg I/mL) is appropriate for evaluation of morphology and function. Where iodine contrast medium has been chosen as the contrast medium, the clinical situation is usually that of a severely disabled patient with a very limited number of relevant clinical questions. One such question can be whether or not the patient can elicit a pharyngeal swallow. Therefore, the projections and number of swallows are much more individualized. It is usually sufficient to observe one or only a few swallows, and usually in lateral projection. Although double-contrast films may also be obtained with iodine contrast media, this is usually not indicated. However, even in a very limited examination it is important to ascertain that there is no obstruction for the bolus. Therefore, it is important to at least fluoroscopically examine the pharynx, PES, and esophagus in search for tumors or strictures. With the patient in the supine position, which is usually the only position that the patient can take, ample evaluation of esophageal motor function is also possible.

Other situations where iodine contrast medium is regularly used are in patients where there is a question of a leak and also in a postoperative situation where patency of anastomosis is evaluated (see Sect. 2.4.2).

2.5 The Oral Cavity and the Pharynx

As in most clinical circumstances the question of misdirected swallowing is the most crucial one and this should be carefully looked into. The patient should be in a lateral projection, preferably in an erect position, although the patient may also be recumbent. The field of imaging should include the oral cavity, soft palate, pharynx, and pharyngoesophageal segment (PES). In that position, the patient should be instructed to take a mouthful of liquid barium. The size of the ingestion should be according to the patient's own discretion. The radiologist should take time to explain this part of the examination. The volume ingested should then be evaluated and compared with the patient's swallowing capability. The ingested material should be observed in the oral cavity for at least 5–10 s. Any anterior or posterior leak should be observed during that period. It should also be possible to assess the volume of ingestion as many patients with oral apraxia or defective sensitivity ingest too big a bolus to be handled safely during swallowing.

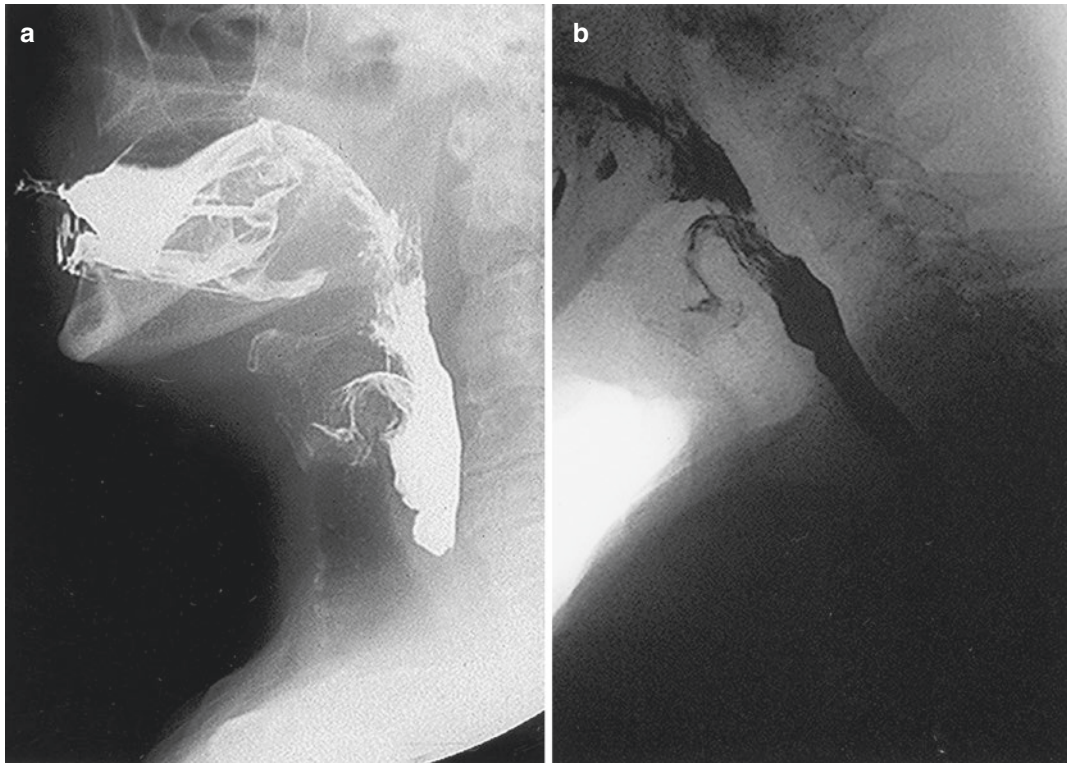

Fig. 6 The difference in image quality between the conventional (digital) exposure technique and the digital storage of a frozen fluoroscopic image is illustrated in this patient. (**a**) Exposure technique; (**b**) digitally stored fluoroscopic image. The spatial resolution is higher with an exposure technique. This is particularly important when assessing morphologic abnormalities. However, the detection of minor amounts of misdirected swallowing into the laryngeal vestibule can also be difficult using a fluoroscopic technique with digital storage only. However, the reduction in radiation dose is substantial

The fluoroscopy should be continued during the ingestion and until the bolus tail has passed into the cervical esophagus. Collimation and exposure techniques should be meticulously controlled and if possible wedged collimation should be used. This decreases flaring due to the air between the chin and the neck. A minimum of three swallows should be registered in this latter projection. However, if misdirected swallowing is a major concern and has not been revealed during these three swallows, it is important to observe additional swallows. We may observe at least 15 swallows in such patients (and even more if necessary). During such swallows provocation may be added. Patients may be able to compensate for defective closure of the laryngeal vestibule and/or misdirected swallowing. Alteration of the position of the head and neck may enable such a compensation to be decompensated, and thereby the cause of the patient's complaints is explained (Ekberg 1986). The easiest way to decompensate is to ask the patient to swallow with his or her neck extended. Patients with normal function should be able to close their laryngeal vestibule and misdirected swallowing should not occur during swallowing even if the neck is extended. Patients who have partial malfunction may decompensate during this maneuvers.

We have found that it is much easier to assess the video recording if a soundtrack is also recorded during the examination. Therefore, we have installed a microphone conveniently mounted on the X-ray shield. During the video recording all pertinent information, such as bolus viscosity, bolus volume, patient positioning, and perhaps most importantly any symptoms reported

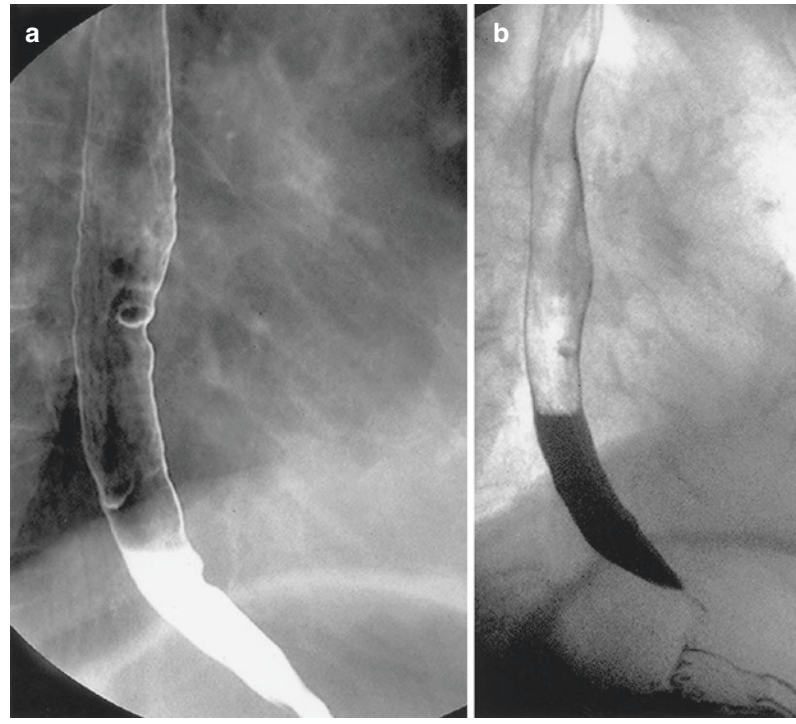

Fig. 7 Comparison between different techniques. (**a**) The exposure and (**b**) the storage of the frozen fluoroscopic image

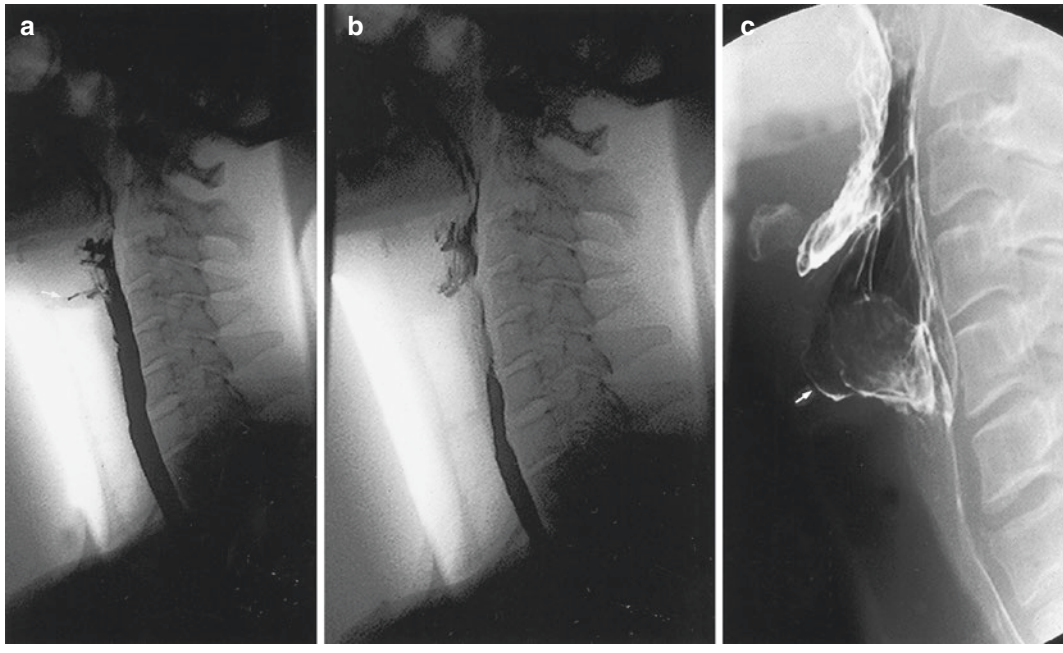

Fig. 8 The importance of correct projections/positioning. This patient was assessed to have contrast medium reaching into the laryngeal vestibule (*arrow*) (**a**). Contrast medium in one of the piriform sinuses in this slightly oblique projection mimics contrast medium in the laryngeal vestibule. However, this image was obtained in a slightly oblique projection. This was revealed during a more precise positioning of the patient (**b**). The same mistake can easily be made during double-contrast examination when contrast medium in one of the piriform sinuses may mimic contrast medium in the laryngeal vestibule (*arrow*) (**c**)

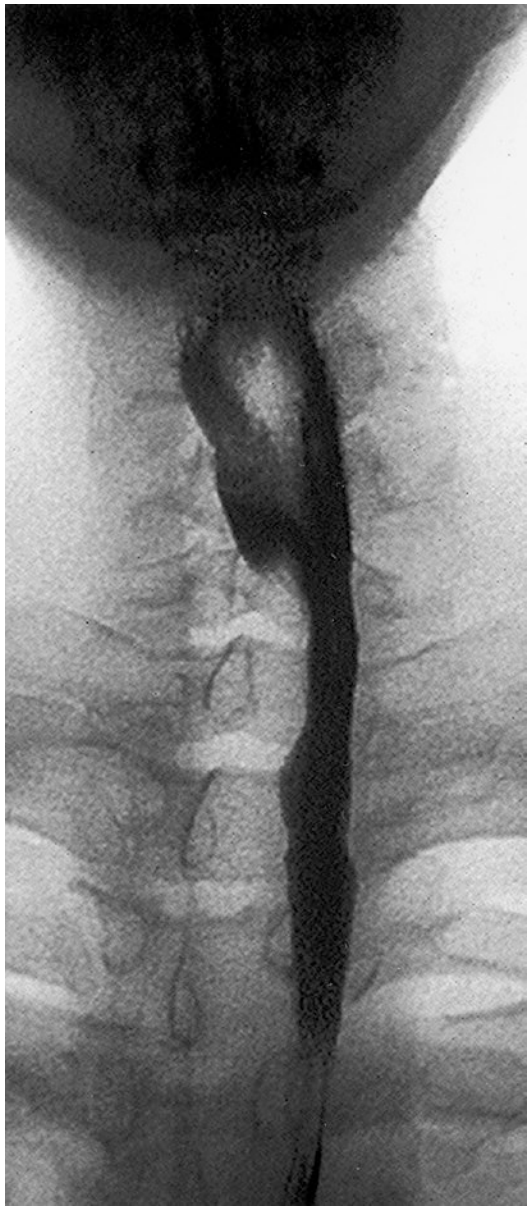

Fig. 9 Frontal projection of the cervical esophagus during barium swallow. There is a fusiform indentation from the right into the esophagus. This is the characteristic appearance of the effect of the kyphosis of a cervical spine. The esophagus is stretched over the kyphosis and deviates to the left. This gives a false impression of a "pseudotumor"

by the patient during the examination, is recorded and can be easily assessed during the review if a loudspeaker is included in the reading room equipment.

2.6 The Esophagus

For a detailed description of how to examine esophageal function, see Sect. 2.4.1. A short introduction is given here. It is of the utmost importance to always include the oral cavity, the pharynx, and the esophagus in the radiologic examination. However, in each patient the focus is usually on only one or two compartments.

We prefer to perform the double-contrast examination of the esophagus after the functional evaluation of the pharynx. The esophageal examination starts with effervescent tablets and the patient is asked to rapidly drink the high-density barium contrast medium (240% w/v). Double-contrast radiograms are taken in left and right oblique projections. Patients with painful swallow should be evaluated for esophagitis such as *Candida* esophagitis. The radiologist should always be careful in evaluating the patient for neoplastic lesions such as superficial carcinomas.

Evaluation of esophageal function often needs to be done with the patient in a recumbent position. However, if esophageal dysfunction has already been revealed with the patient in an erect position, it is usually not warranted to place the patient in a recumbent position as dysfunction in the erect position is not known to become normal in the recumbent position.

3 Solid Bolus Examination

All patients with a history of obstruction during swallowing should be examined with a solid bolus, especially if solid bolus dysphagia is present (see Figs. 1 and 2). The solid bolus used for the radiologic examination must be standardized. We prefer to use a radiolucent antacid tablet with a known diameter of 13 mm (van Westen and Ekberg 1993). This is swallowed together with thin liquid barium (40% w/v). Others have advocated the use of a barium tablet, a bread sphere, or a marshmallow (Curtis et al. 1987; Kelly 1961; Somers et al. 1986). Contraindications for tablet swallowing are known or suspected pharyngeal dysfunction with misdirected swallow. If this is suspected, the patient should first undergo evalu-

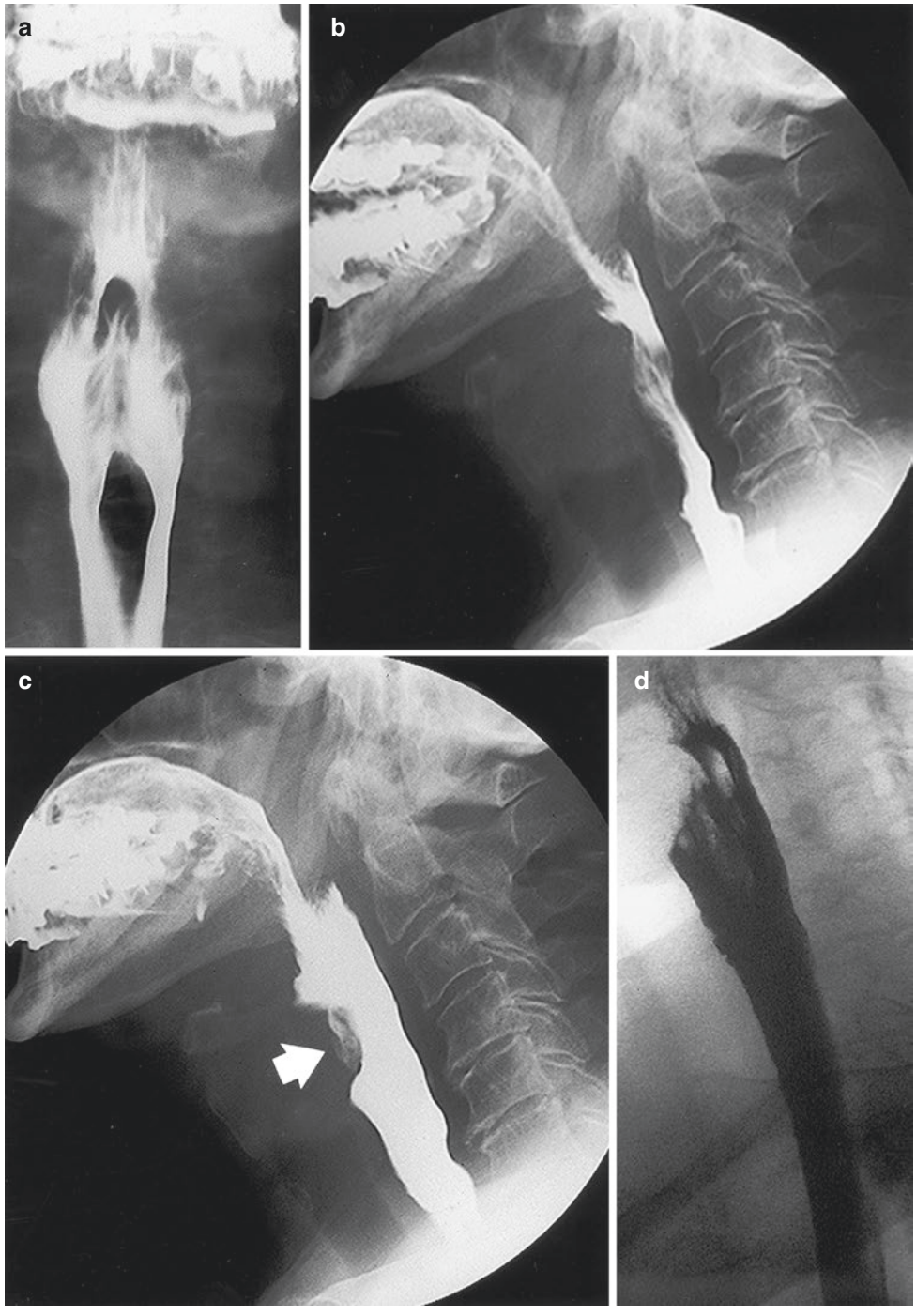

Fig. 10 (**a**) A single-contrast examination of the pharynx. The folded appearance of the epiglottis creates a hole in the contrast medium. This image also shows the medialization of the lateral pharyngeal wall as an indicator of normal function of the constrictors. (**b**) This is much more difficult to assess in lateral projection. (**c**) The characteristic, irregular in-bulging of the arytenoid region and the down-folded epiglottis is seen creating an irregular impression in the anterior wall of the midpharynx (*arrow*). (**d**) For proper evaluation of the PES, it is often necessary to obtain images in oblique projection

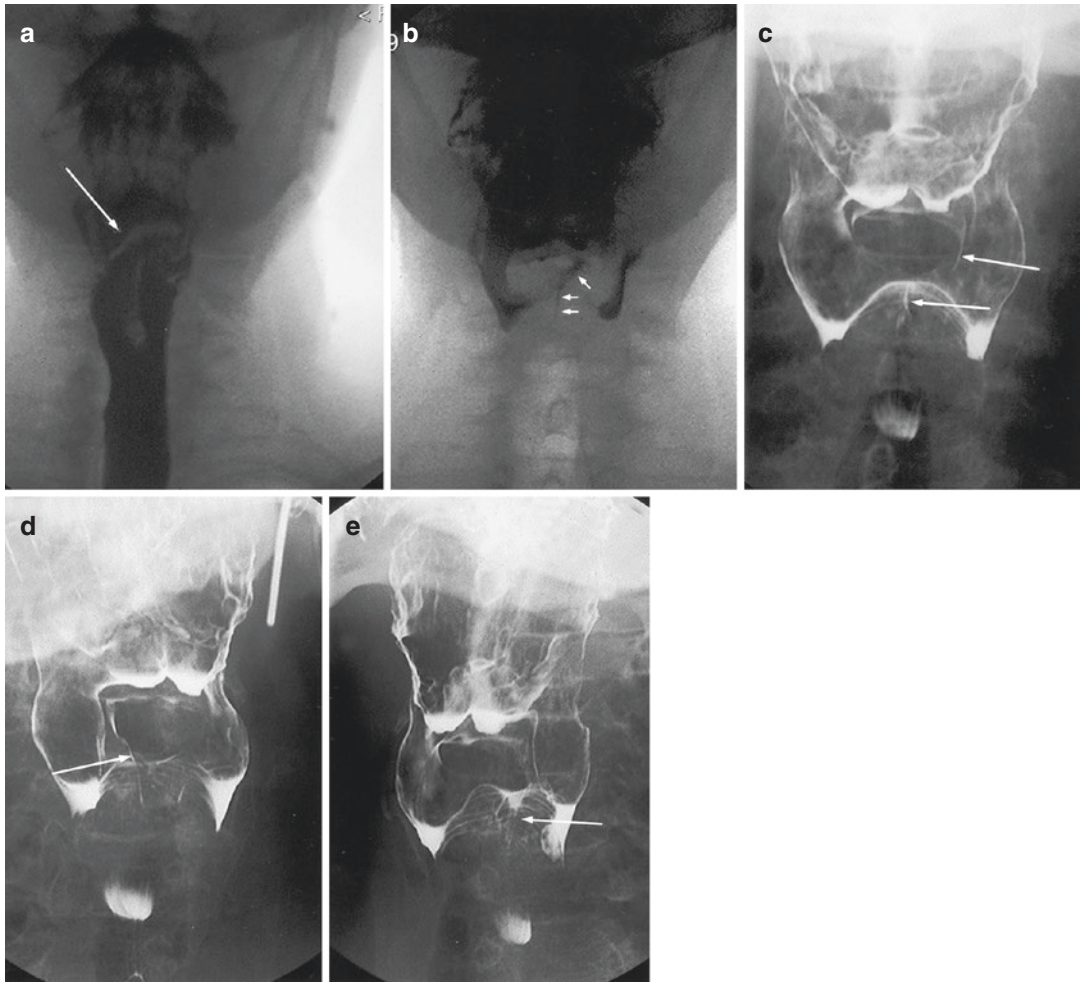

Fig. 11 It is important to be able to identify misdirected swallowing also in a frontal projection. During the full column examination, also called the single-contrast technique, the laryngeal vestibule is obscured in the frontal projection. (**a**) The oblique epiglottis (*arrow*) can be seen. This is per se not a functional abnormality. (**b**) Retention of barium in the pharynx showing that there is also contrast medium outlining the characteristic shape of the half-opened laryngeal vestibule (*arrows*). The shape resembles a tapered glass. (**c**) Contrast medium on the inside of the laryngeal vestibule up to the aryepiglottic folds (*arrows*). There is also contrast medium between the opposed arytenoids (*lower arrow*). The same is seen in left anterior oblique (**d**) and right anterior oblique (**e**) projections. Barium seen in the laryngeal vestibule, as in this patient, indicates misdirected swallowing. This finding is always abnormal but may or may not be symptomatic

ation of the pharyngeal stage, and if misdirected swallowing is present with barium reaching below the vocal folds, a solid tablet should not be given. This is because of the risk of choking. However, the best way to triage patients for the tablet test is to show them the tablet and the thin liquid barium and ask them if they can swallow the tablet. In our experience this easily excludes patients who should not undergo the tablet swallow. In fact, that particular group of patients who do not think they can swallow the tablet are the ones who should be examined because of suspected stricture or other obstructions.

Tablet arrest may or may not be symptomatic. When the tablet becomes stuck above a stricture, symptoms are usually absent. This is in contrast to when the tablet arrest is due to dysmotility. In the latter cases, the patient is often symptomatic.

However, the symptom is often much milder than the symptoms that arise during a meal.

Solid bolus arrest in the esophagus is due to either dysmotility or a narrowing. Dysmotility is due to either spasm or hyperperistalsis, two entities that are hard to separate fluoroscopically. As assessed by manometry, most of these patients have hypomotility and only rarely spasm.

4 Aspects of Radiation Physics/Safety

Radiologic examination relies on the ability of photons of a certain energy (X-rays) to penetrate opaque materials such as the human body. Since their discovery by Wilhelm Conrad Röntgen in 1895, they have made a major contribution to medicine as well as other industrial applications. However, such radiation means that energy is transported through the body. Only 1–20% of the given energy from the X-ray tube reaches the detector, i.e., the image-intensifying screen or the film–screen combination. The rest of the energy is absorbed in the patient. It is this absorbed energy, which is sometimes called radiation dose, that is the main hazardous aspect of radiation. Such ionized radiation, when absorbed in the body, might interfere with water molecules and cause free radicals to be produced. The ionizing radiation may also interfere with proteins and other important substances within the cell. This reaction may cause cell death or induce serious late side effects. It is therefore necessary that all radiations, including that used for swallowing studies, are used with care.

One important aspect to remember is that it is only when the X-ray tube is irradiating, namely, when the current is applied, that there is radiation from the tube and in the room. At the same moment as the current stops, the radiation primarily from the X-ray tube (secondarily from the patient) stops and there is no hazard within the room or to the patient, nor to the personnel in the room. Radiation always and only traverses linearly, i.e., it does not bend around corners.

The X-ray equipment must undergo regular scheduled quality controls according to each country's regulations. It is also important that personnel responsible for the equipment ascertain that all functions are checked for proper function on at least a weekly basis.

The most important consideration is that an X-ray examination should never be performed unless it is necessary. It should be contemplated beforehand what the referring clinician is expecting to find and what therapeutic or prognostic consequences that may have. Once this is clear, the risk of radiation damage is always far smaller than the benefit that can be achieved from the X-ray examination. This means that the X-ray examination needs to be necessary in the clinical setting and then that the performance of the study must be optimized. The risk of damage is far greater in children and young adults. In individuals older than 40 years, the risk is basically negligible. There is a positive correlation between patient dose and personnel dose. It is important to cone down on the pharynx and/or esophagus and thereby avoid irradiation of extensive volumes. The distance between the patient and the image intensifier/screen should be as small as possible.

You should try to stay as far away as possible from the patient; however, you must be close enough for assistance or manipulations. Lead aprons must be worn. Sometimes an apron over the thyroid or lead eyeglasses have been advocated. Most importantly, if you do not need to stand close to the patient, step away. If you double the distance from you to the patient, the radiation dose reduces to one quarter. Remember that it is not radiation from the X-ray tube that radiates the personnel in the room, it is the patient who radiates secondary radiation. It is also important to carefully perform the study, meaning that it is better to do one proper radiologic examination than to have to redo studies or even exposures because of bad technique. It is also important to realize that the fluoroscopy time contributes to most of the radiation dose. Fluoroscopy for 1 min is roughly equivalent to one exposure. This is, however, relative and depends on the situation. In a study by Chan et al. (2002), they found that if a videoradiographic swallowing study had a duration of 18 ± 8 min (and this is very long from my own perspective), the scattered radiation dose (measured 30, 60, and 100 cm from the patient's

neck) received by the examiner varied tenfold, i.e., 34–3 μSv. This should then theoretically permit an examiner to perform 2583 examinations per year given the annual effective dose limit of 20 mSv. It should be noted that since lead aprons are always worn, the additional protection they provide further reduces the scattered radiation dose to negligible levels.

If you have access to digital radiology, you may also have access to pulsed fluoroscopy. If possible, you should use as few pulses (usually two) per second as possible. However, this might sometimes be unsuitable for evaluation of function. It is better to use continuous fluoroscopy than to have to redo the swallowing studies. You should use a fluoroscopy time as short as possible. You should ensure that the patient does not move around, and if necessary you should have the patient hold his or her breath during exposures. You should avoid flaring by using wedge frames. Modern equipment also has the possibility to save the fluoroscopy image digitally. This may in fact lower the dose considerably in comparison with conventional exposures. These images may be enough for documentation of, for instance, misdirected swallowing. However, as stated above, it is better to make one proper exposure and to conduct one properly performed examination than to have to redo the study because of poor image quality. If studies are performed by speech-and-language pathologists, it is very important that they are familiar with radiation physics.

The effective dose of a radiologic dysphagia evaluation as described above is about 1 mSv. This can be compared with the effective doses for a chest X-ray (anteroposterior and lateral) of 0.1 mSv, an abdominal survey film (three images) of 5 mSv, and a barium colon examination of 5 mSv; the effective dose for coronary angiography with interventions as well as interventions in other parts of the body may easily exceed 100 mSv.

5 Other Techniques

Ultrasonography can be used for evaluation of the oral stage and hyoid bone movement (Hamlet et al. 1988; Brown and Sonies 1997). This technique is attractive because it does not rely on ionizing radiation. It can therefore be used unrestricted also in younger patients. It also enables visualization of the tongue surface. It could be the method of choice for monitoring oral function. However, the fact that the bolus is not visualized is a major drawback. Ultrasonography also requires considerable operator skills.

In recent years there has been growing interest in fiber-endoscopic evaluation of swallowing. During fiber-endoscopic evaluation of swallowing, the endoscope is inserted through one of the nostrils and the pharynx and larynx are observed before and after swallow (Langmore et al. 1988). Any posterior leak before swallowing over the tongue base can be observed, as well as movement of the pharyngeal wall. Also, laryngeal structures during breathing are observed. Sensitivity may be tested by touching the walls of the pharynx with the tip of the fiber endoscope. When the pharynx is elevated during swallowing and the bolus is brought into the pharynx, the endoscopist's view is obstructed. However, retention in the pharynx after swallowing can be observed and also whether or not the bolus has reached into the larynx. As a bolus one usually uses intensely colored water in order to better visualize the bolus.

The repetitive oral suction and swallowing test was introduced in the mid-1990s. With use of a multimodality and simultaneous technique (ultrasound, pressure, scale, temperature) it was possible to measure suction pressure, bolus volume, respiration and feeding–respiratory coordination and pharyngeal transit time (Nilsson et al. 1995).

A "swallowing safety index" can also be calculated (Nilsson et al. 1997); however, his technique has not gained widespread use.

The most promising "new technique" is MRI. With fast gradients and short acquisition times an "almost real-time" fluoroscopic technique is possible. This allows analysis of bolus transport but also, and more importantly, movements in anatomical structures, i.e., the tongue and pharyngeal constrictors (Buettner et al. 2001).

Dynamic cineradiography and videoradiography (videomanometry) of pharyngeal barium swallow provides morphological as well as quali-

tative functional information on the swallowing sequence. However, dynamic barium swallow relies mainly on functional qualitative judgment, failing to quantify the results. This is, for example, the case when trying to assess pharyngeal paresis in terms of the degree of barium retention in the pharynx.

In this context, intraluminal pharyngeal manometry is capable of providing a more quantitative analysis of pharyngeal muscle function in terms of intraluminal pressure registration (McConnel 1988; McConnel et al. 1988a, b; Olsson and Ekberg 1995; Olsson et al. 1994, 1995, 1996). Concurrent barium swallow and pharyngeal manometry combine qualitative assessment of bolus transport with quantitative registration of the contractions of the pharyngeal wall. Our experiences with this simultaneous technique have revealed that there is a substantial longitudinal asymmetry in pharyngeal pressure response in normal individuals. There is also a wide variety in the timing of PES opening/relaxation, where the pressure registration is extremely dependent on sensor positioning. Furthermore, the radiologic finding of a CP bar is often only an indicator of a more widespread dysfunction around the PES easily evaluated with the simultaneous technique. In many patients with a posterior CP bar the major abnormality is weak constrictors with outpouching of the lumen above and below.

The simultaneous technique provides new diagnostic information in dysphagic patients and we suggest the addition of pharyngeal solid-state manometry, preferably with simultaneous videoradiography, in cases where routine radiologic workup does not reveal any abnormality.

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Morphologic and Kinematic Analysis of Swallowing Using Multislice CT

Yoko Inamoto and Eiichi Saitoh

Contents

Abstract

Dynamic swallowing computed tomography (CT) is a novel technology with superior spatial (0.5 mm voxel) and sufficient temporal resolution (10 frames/s) that produces the dynamic three-dimensional images and quantitative kinematic analysis of swallowing. This technique has provided new insights into swallowing morphology and kinematics in two primary ways: precise 3D dynamic imaging and quantitative measures. This has in turn promoted the treatment-oriented evaluation in dysphagia rehabilitation.

1 Introduction

Imaging tools are essential in dysphagia evaluation and have opened the door to dysphagia rehabilitation. Visualization of aspiration allows clinicians to move beyond risk management to an accurate understanding of swallowing physiology and treatment-oriented evaluation. Videofluorography (VF) and videoendoscopy (VE) are currently the standard imaging techniques for dysphagia evaluation. During diagnostic and treatment-oriented evaluations, these techniques depict the immediate effects of alternations in bolus textures, posture adjustment, or therapeutic maneuvers. Although they are commonly used tools, VF can only provide a two-dimensional vision of the three-dimensional swallowing process and VE lacks quantitative data acquisition

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due to the variable lens-to-field distance. These methodologies limit the appreciation of the dynamic volumes of oropharyngeal spaces and trajectory of oropharyngeal structures that moves simultaneously along multiple places. Novel multidetector computed tomography (CT) has recently provided new insights into overcoming these limitations. CT provides dynamic three-dimensional (3D) images and allows for quantitative kinematic analysis of swallowing. CT has revolutionized the whole-swallow examination and expanded the understanding of swallowing morphology and kinematics in two primary ways: precise 3D dynamic imaging and quantitative measurements.

2 Overview of Swallowing CT

2.1 Profile of Dynamic Swallowing Computed Tomography

CT provides superior spatial resolution of hard tissue and has been effectively used to detail morphologic diagnoses. The appearance of multidetector CT in the 1990s enabled the acquisition of 3D images, and CT was added to achieve functional diagnostics in many areas. The use of CT was subsequently considered for the swallowing field; however, the inability to acquire dynamic imaging with helical scanning limited the clinical application of CT. Later, 320-row area detector computed tomography (320-ADCT) (Aquilion ONE; Toshiba Medical Systems Corporation, Tochigi, Japan) was developed for multidetector CT imaging and was the first to enable 3D dynamic evaluation of swallowing evaluation. This technique is called swallowing CT and has been used to evaluate swallowing in both research and settings.

320-ADCT systems is equipped with 320 rows of 0.5 mm detectors along the body axis, corresponding to a total detector width of 160 mm. A 160 mm range can cover almost all of the organs in the human body including the skull base to the upper esophagus, or the range which is necessary for swallowing assessment. (Fujii et al. 2011). Due to the specified detector width, nonhelical scanning is performed with a 0.35 s tube rotation speed and produces dynamic 3D images.

By high-speed single-phase volume scanning (single-volume scan) in which the tube is rotated once, static 3D images of targeted structures within a 160 mm range can be acquired. By multiphase scanning (dynamic volume scan), in which the tube is rotated repeatedly, dynamic 3D images of the motions of structures within this range can be acquired. Scanning is performed during swallowing, and dynamic images of swallowing are thus acquired (Fujii et al. 2011; Fujii and Inamoto 2015).

The 320-ADCT technique was upgraded in 2011 and the tube rotation speed of the new Aquilion ONE Vision Edition (new edition) is 0.275 s. In 2015, it was upgraded with an increased gantry tilt angle (Aquilion ONE GENESIS Edition).

2.2 Scanning Posture of Offset-Sliding CT Chair

Although CT examination is routinely conducted in the supine position, evaluation of swallowing is optimally conducted in an upright position. To overcome this limitation, a chair specifically designed for swallowing CT was invented (Tomei Brace Co., Ltd., Seto, Japan, and Aska Corporation, Kariya, Japan). The chair is placed on the opposite side of the CT table with the CT gantry tilted 22° toward the chair. The tilting of the gantry allows the patient to sit in a reclined position. The reclining angle of the seat is approximately 45°. After the patient is seated, the chair slides posteriorly into the gantry so that the patient's face falls within the scanning range. The chair is now available as a commercially produced CT system accessory called the offset-sliding CT chair (E-Medical, Chuoku, Tokyo, Japan) (Fujii and Inamoto 2015) (Fig. 1). With the new system, the gantry tilts to a maximum of 30°; therefore, the reclining angle can be increased to 60°, allowing for a more natural upright position.

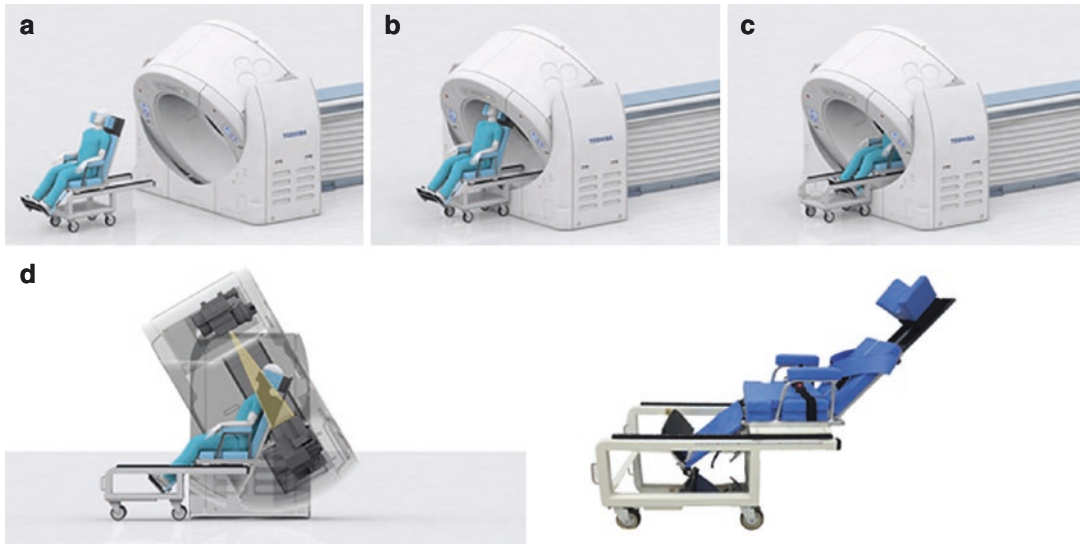

Fig. 1 Offset-sliding CT chair. (**a**) The subject is seated in the chair. (**b**) The seat slides backwards into the gantry. (**c**) The position is adjusted to acquire the target field of view. (**d**) Offset-sliding CT Chair

Table 1 Appropriate dilution rate of contrast medium (barium)

Consistency	(mPa)	w/v (%)	Water (mL)	Barium (mL)	Thicker (g)
Honey/spoon thick	1700	5	95	5	5
Honey thick	460	5	95	5	2.5
Nectar thick	140	6	94	6	1.25
Thin		7	93	7	0

2.3 Contrast Material

Barium is used as a contrast agent for swallowing CT. The optimal barium sulfate concentration is 5–7% weight/volume (Table 1). This allows the bolus to be visualized at 300–700 HU, distinguishing it from air, bone, and soft tissue. Iodine contrast medium can also be used with a similar concentration (5–7%).

2.4 Scanning Condition and Radiation Dose

The scanning time is set by adjusting number of tube rotations. For swallowing CT, 9 rotations (0.35 × 9 = 3.15 s) in the original system of 320-ADCT system or 12 rotations (0.275 × 12 = 3.3 s) in the new edition are normally used, but these values can be decreased or increased according to the total swallowing duration of each patient. With the original edition of the system, the maximum absorbed dose to the skin was 44.77 mGy and the effective dose was 1.65 mSV under the following scanning parameters: filed of view; tube voltage, 120 kV; current, 60 mA; and tube rotation time, 3.15 s (0.35 s × 9 rotations) (Kanamori et al. 2011). The new system is equipped with a low-dose image reconstruction filter (adaptive iterative dose reduction 3D: AiDR3D), which decreases the tube current to 40 mA. Under these conditions (120 kV, 40 mA, and 0.275 × 12 = 3.3 s), the maximum absorbed dose to the skin and effective dose were 28.07 mGy and 1.08 mSV, respectively (Table 2).

Table 2 Comparison of effective dose

		Tube voltage (kV)	Tube current (mA)	Scan time (s)	CTDI (mGy)	DLP (mGy.cm)	Effective dose (mSv)
Swallowing CT		120	60	3.15	34.7	554.9	1.65
Swallowing CT w/v low dose filter		120	40	3.30	26.2	419.0	1.08
VF	Lateral	75	1.2	270			1.05
	A-P	120	1.2	30			

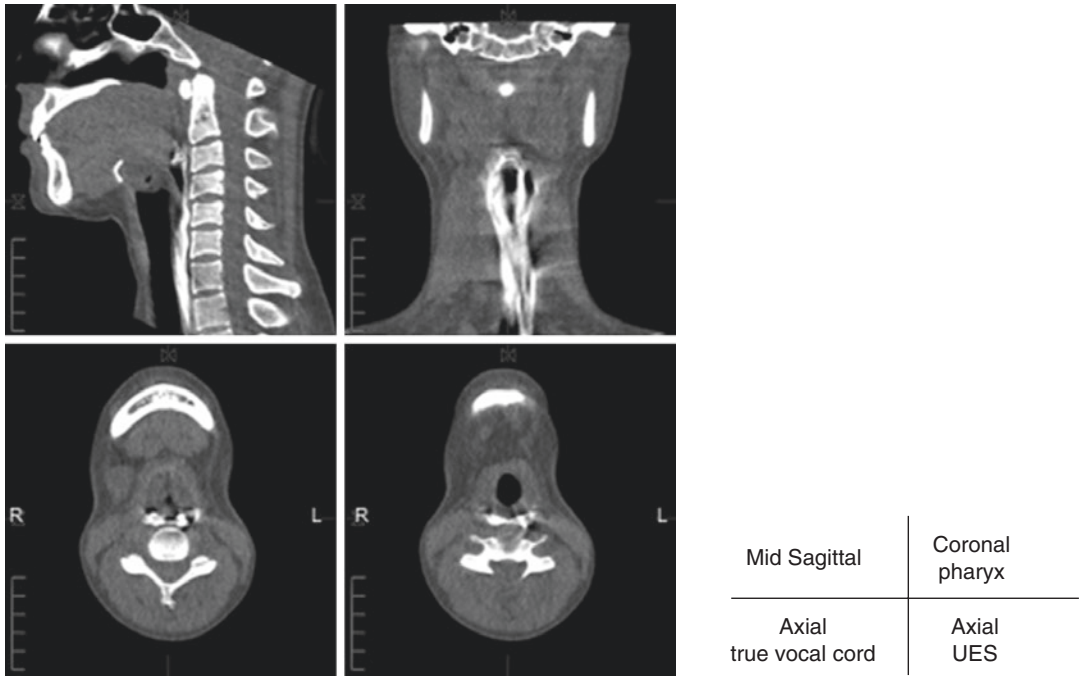

Fig. 2 MPR image. Healthy 28-year-old man swallowing 10 mL of nectar-thick liquid.

2.5 Advance Points

The primary innovation of 320-ADCT for swallowing include 3D visualization and quantitative evaluation.

2.5.1 3D Visualization

Images are reconstructed with a 0.5 mm slice thickness at 0.5 mm intervals and 3D CT images and multiplanar reconstruction images are generated using the software installed in the CT system. 3D CT images can display targeted structures from any directions (Fujii et al. 2011). Multiplanar reconstruction images allow for easy viewing of cross sections at any angles. Because the images represent isotropic volume data in which coronal (x), sagittal (y), and axial (z) are almost the equal at distance resolution (0.47 × 0.47 × 0.5 mm), structures can be accurately depicted at any arbitrary cross section (Fujii et al. 2011; Katada et al. 2001) (Fig. 2).

Dynamic 3D CT images are reconstructed at intervals of 0.1 s using a half reconstruction technique in which images are reconstructed using a data from a 180° X-ray tube rotation (0.175 s in the original system and 0.134 s in the new system) and using temporally overlapping image reconstruction, in which

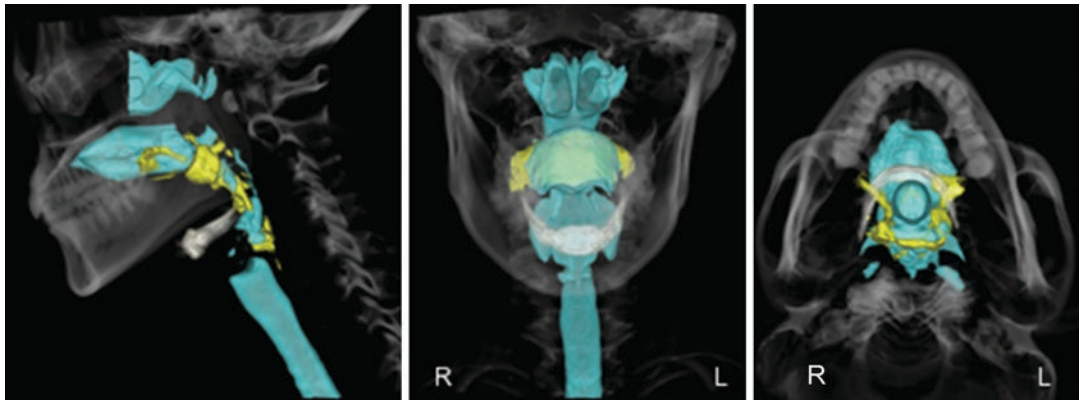

Fig. 3 3D CT images. Healthy 34-year-old woman swallowing 10 mL of thin liquid. *Left*: lateral view, *Middle*: anterior view, *Right*: inferior view

0.175/0.134 s data are reconstructed every 0.1 s. When the scanning time is 3.3 s (0.275 s × 12), images are reconstructed in 33 phases at intervals of 0.1 s. Continuous replay of these 33 phases produces four-dimensional images including a temporal dimension (Fig. 3).

The advantages of 3D imaging are its ability to depict structures simultaneously and to display the motion of the structures such as the true vocal cords (TVC) that cannot be viewed by conventional methods.

2.5.2 Quantitative Measurement

3D data acquisition provides several quantitative measurements and brings great potential for describing morphological and kinematical analysis.

(1) Reliability

In a study of temporal measurements of swallowing events using 320-ADCT in eleven healthy volunteers, the inter-rater reliability of 2 experienced raters was evaluated (Inamoto et al. 2012a). The interclass correlation coefficient (ICC) was calculated for the onset, termination, and duration of the swallowing events. The average ICC for all the measurement items was 0.98, indicating high concordance. This high ICC was supported by a high spatial resolution. Because the target structures can be captured with high precision, it is highly probable that any rater can obtain measurement results in the same manner once the definition of measurements and procedures are defined.

(2) Timing measurement

As in VF, the temporal measurement of the onset, termination, and duration of swallowing event can be measured in swallowing CT (Inamoto et al. 2011). Swallowing CT enables assessment of velopharyngeal closure, hyolaryngeal movement, laryngeal closure, upper esophageal sphincter (UES) opening, and bolus movement. Remarkably, with respect to laryngeal closure, both laryngeal vestibule closure and vocal cord closure can be measured. This promotes an understanding of the mechanism of laryngeal closure composed of three distinct events: laryngeal vestibule closure, TVC closure, and epiglottis inversion during swallowing. Additionally, the timing of UES opening can be accurately measured on axial sections (Figs. 4 and 5).

(3) Space measurement

Several spatial measurements are available using 320-ADCT: the hyoid and laryngeal trajectory, UES cross-sectional area, pharyngeal volume, and muscle length (distance between the muscular origin and the insertion of muscles). Standard values, which are essential for identifying clinical abnormalities, have been reported (Kendall and Leonard 2001).

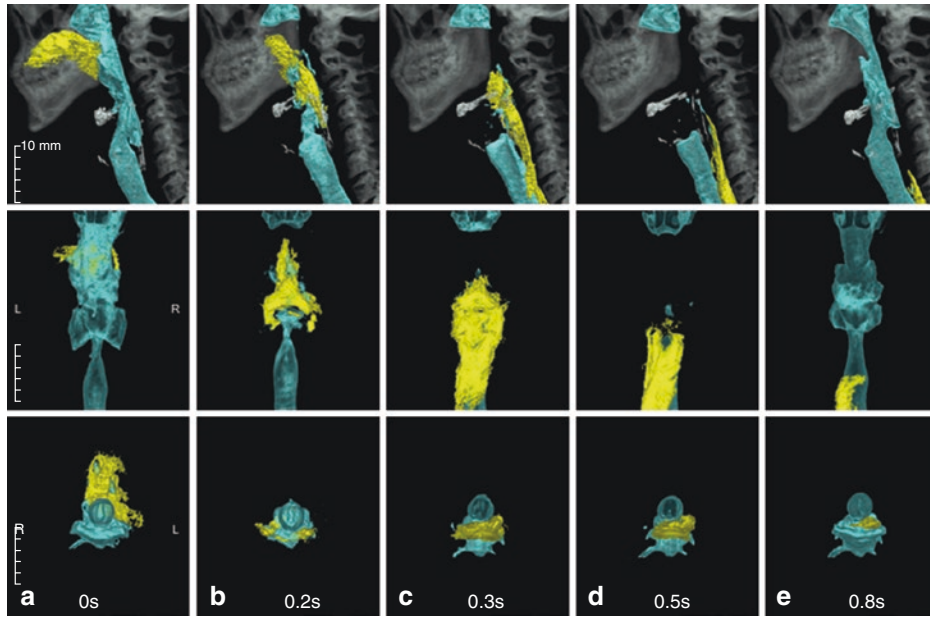

Fig. 4 3D CT images of swallowing. Healthy 36-year-old man swallowing 10 mL of nectar thick liquid. *Upper*: lateral view, *middle*: posterior view (posterior to anterior), *lower*: inferior view (viewed from below). (**a**) onset of hyoid anterosuperior movement; (**b**) onset of velopharyngeal closure; (**c**) onset of UES opening; (**d**) time of minimum pharyngeal volume; (**e**) end of swallowing

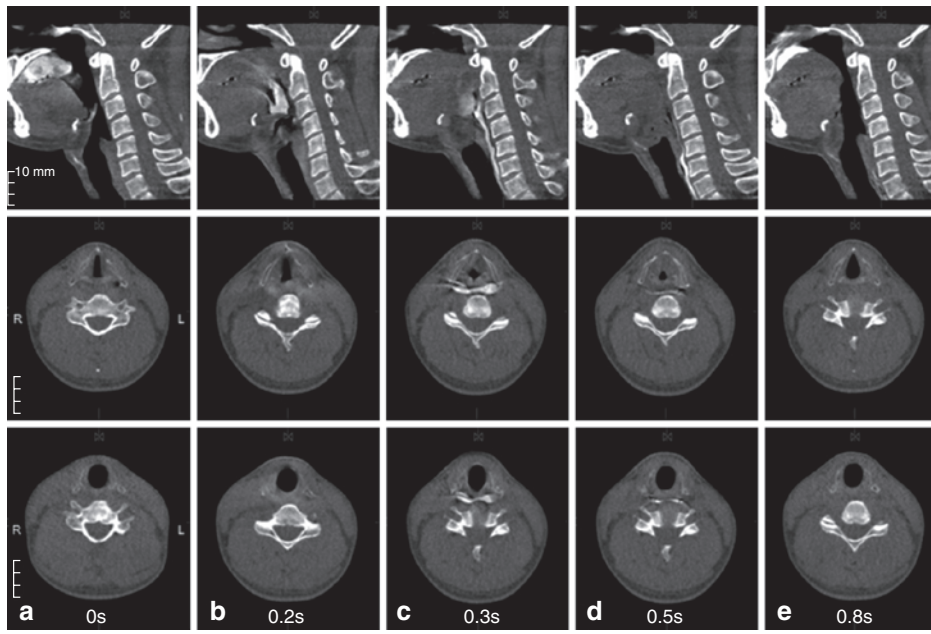

Fig. 5 MPR images of swallowing. Healthy 36-year-old man swallowing 10 mL of nectar thick liquid (same swallow of Fig. 4). *Upper*: midsagittal view, *middle*: axial view of true vocal cords, *lower*: axial view of UES. (**a**) onset of hyoid anterosuperior movement; (**b**) onset of velopharyngeal closure; (**c**) onset of UES opening; (**d**) time of minimum pharyngeal volume; (**e**) end of swallowing. TVC closed along folds entire length (between anterior commissure and most posteior bounrary of the folds). in **c** and **d**

A) Hyoid/Larynx Trajectory

One major advantage of 320-ADCT is its ability to display bone and cartilage. Thus, the hyoid bone and thyroid cartilage can be clearly depicted in 3D, and both hyoid and laryngeal motion can be tracked along with the thyroid cartilage trajectory. The *x* and *y* coordinates are used for calculation, with the *y*-axis is operationally defined as the plane made by the anterior-inferior corner of the second cervical vertebra and anterior-superior corner of fourth cervical vertebra. The zero point (0, 0) is the fourth cervical vertebra. The trajectory in two directions (anterior-posterior and upward-downward directions) and the distance of excursion (mm) can be measured.

B) UES Cross-Sectional Area

Measurement of the UES cross-sectional area is unique to CT. Using VF, the UES opening is evaluated primarily by the degree of anteroposterior opening on the lateral plane. Using 320-ADCT, the cross section of the UES can be visualized on the axial plane using the thyroid and cricoid cartilage as landmarks. The diameter and area can be measured with a digital image measurement tool to directly circumscribe the UES region as it opens (Fig. 6).

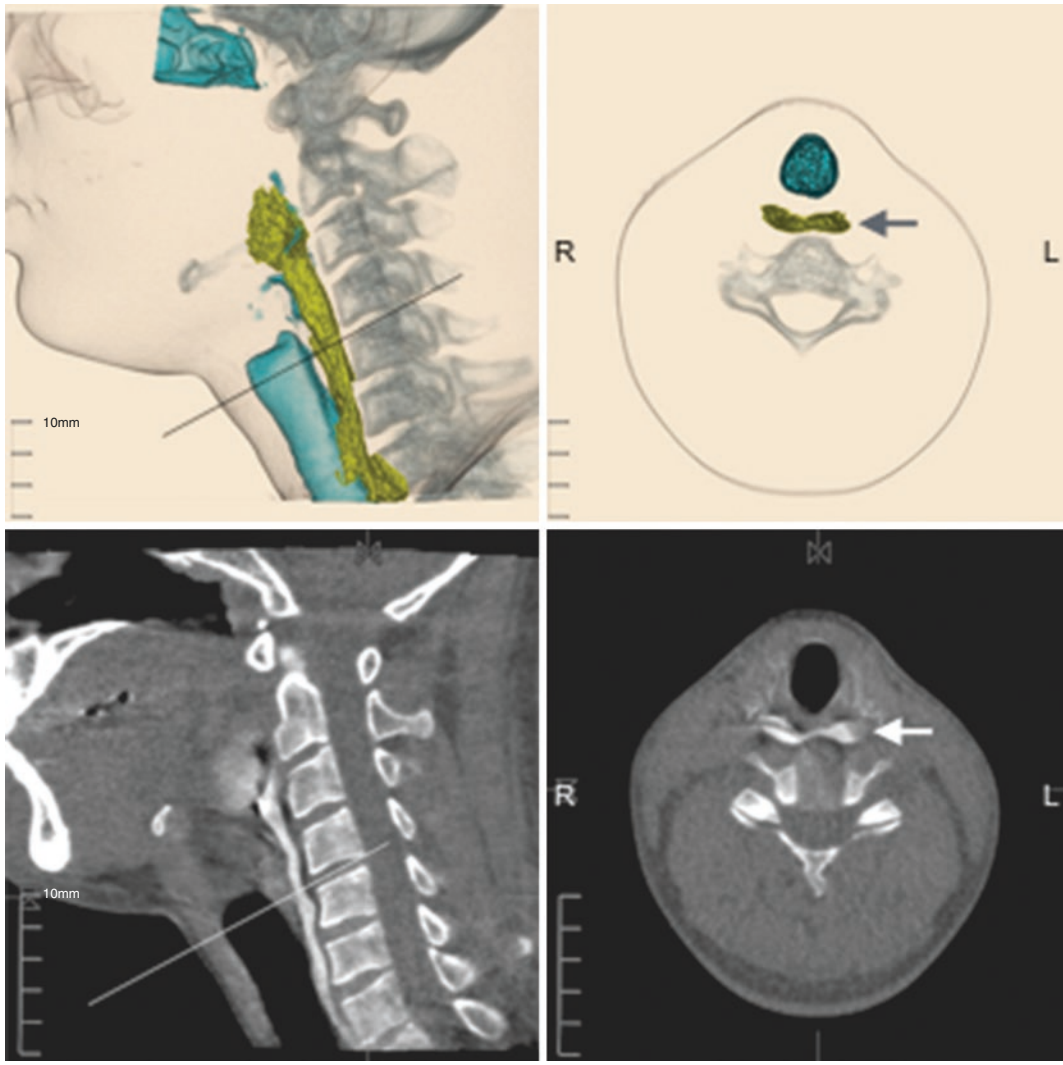

Fig. 6 Visualization of UES cross section. *Upper*: lateral view (*right*) and superior view (*left*) of 3D CT images. *Lower*: midsagittal (*right*) and axial images at UES level (*left*). Arrows indicate the UES

C) Volume Measurement: Pharynx

During swallowing, the pharyngeal walls constrict to facilitate bolus transport. Using VF images, the pharyngeal constriction ratio (PCR) has been used to estimate the degree of pharyngeal constriction; it is calculated as the ratio of the two-dimensional area of the pharynx before swallowing and the area of maximum constriction of the pharyngeal cavity during swallowing (Okada et al. 2013a; Loenard et al. 2004). Typically minimum air space is observed and the PCR approximates zero during the swallow in healthy adults. With 320-ADCT, it is possible to calculate the 3D volume of the pharynx (pharyngolaryngeal space) as well as the volume of the bolus in pharynx (Iida et al. n.d.). 320-ADCT displays how pharyngeal constriction relates to bolus flow and elucidates the mechanisms underlying pharyngeal residue (Fig. 7) (Table 3).

D) Length of Origin and Insertion of Muscles

In general, soft tissue is not well visualized by CT; however, the dynamic changes in muscle activity can be simulated by measuring changes in the distance between muscular origins and insertions of the muscles (Kendall and Leonard 2001). These measurements can indicate the coordinated pattern of muscle shortening involved in swallowing (Fig. 8).

These measurements provide essential benchmarks for understanding both physiology and pathophysiology. In the clinical setting, this tool can delineate signs of dysphagia

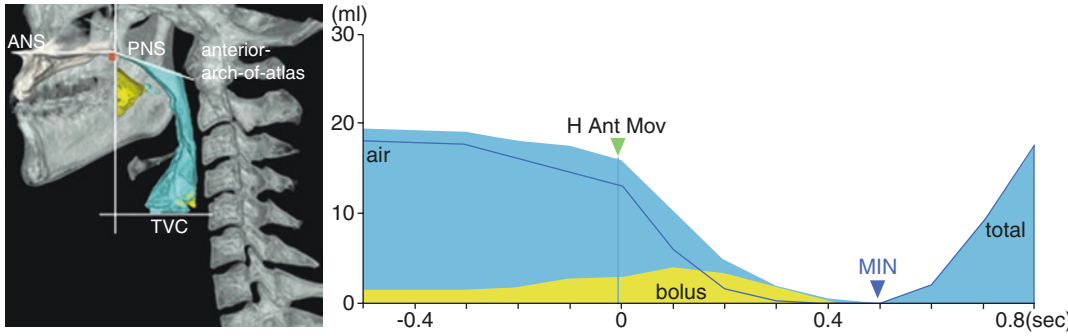

Fig. 7 Measurement of pharyngeal volume and bolus volume in the pharyngeal cavity. *Left*: 3D images show the pharyngeal cavity according to the definition in Table 3. *Right*: Change in air and bolus volumes in the pharyngeal cavity during swallowing with onset of anterosuperior hyoid movement as time zero in one healthy subject (38-year-old woman swallowing 4 mL of thick nectar liquid). *Blue line*: volume of air, *yellow space*: volume of bolus, *blue space*: total volume (air + bolus). After anterosuperior hyoid movement, the volume decreased rapidly and reached zero (minimum volume) at 0.5 s, then increased to the volume seen before swallowing. *H Ant Mov* hyoid anterosuperior movement, *MIN* minimum

Table 3 Definition of pharyngeal cavity

Top	Through the anterior and posterior nasal spine (ANS-PNS), and parallel to the infraorbital line
	Through the PNS and inferior border of anterior arch of atlas
Front	Perpendicular to the top plane and passes through PNS
Bottom	Superior surface of true vocal cord (TVC) and inferior edge of pyriform sinus

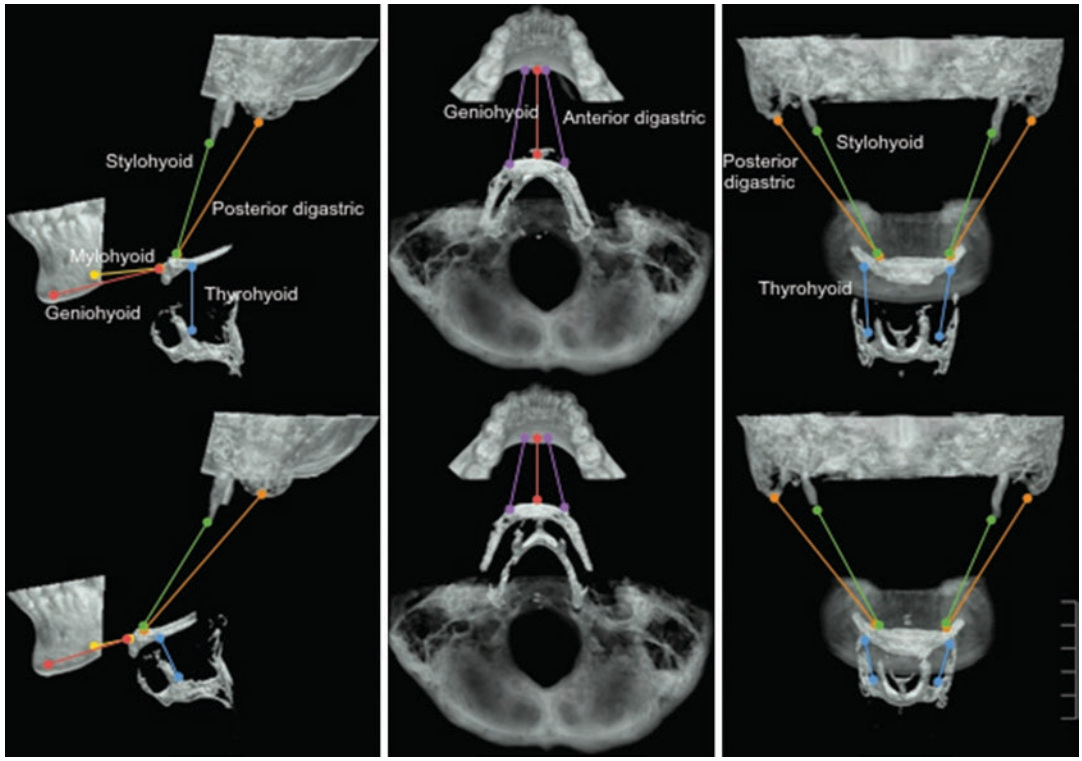

Fig. 8 Measurement of muscle length (distance between muscle origin and insertion). Lateral, superior, and anterior views of mandibular bone, hyoid bone, thyroid cartilage, and cranial bone are illustrated. Upper: first frame of scanning, lower: time at maximum hyoid displacement

signs and provides information for analyzing the mechanisms of aspiration and residue. The effects of exercise and selection of appropriate swallowing maneuvers can also be assessed on swallowing CT.

3 New Findings from 320-ADCT

3.1 Static Image Analysis

Static 3D images acquired by a single-phase volume scanning are used for morphological analysis. The 3D anatomy of the oropharyngeal and laryngeal structures, the volume of the pyriform sinus with head rotation, and the volume of pharyngeal residue have been studied.

3.1.1 Anatomy of Larynx and Pharynx

To understand the morphological characteristics of the larynx and pharynx, cadaveric and stereo-endoscopic measurement methods have been employed extensively. Cadaveric measurements, however, cannot be directly related to dynamic swallowing movements in living subjects due to natural muscle tone and fixation of tissues. The

Stereoendoscopic method is limited by insufficient field of view and quantitative measurements. Due to these imitations of available measurement techniques, the 3D anatomy remains incompletely understood, and normative reference standard has not been established. 320-ADCT enables the quantitative measurement of structures in vivo.

The pharynx and larynx of 54 healthy volunteers (30 male, 24 female) aged 41 ± 15 year old, and measuring 170 ± 5 cm (male) and 156 ± 5 cm (female) in height, were assessed by 320-ADCT to establish the normative reference values with respect to age, gender, and height (Inamoto et al. 2015). Bivariate statistics revealed that the length and the volume of pharynx and larynx were significantly greater in men than in women ($p < 0.05$) and increased proportionally with height ($p < 0.05$). Multiple regression analysis indicated that gender, height, and age each had significant effects on certain values and suggested that age, gender, and height have independent and interacting effects on the morphology of the pharynx and larynx. After adjusting for height, mean demonstrated a greater distance between the base of valleculae and the vocal cords as well as longer vocal cords. Age had a relatively small effect, with reduced laryngeal and hypopharyngeal volumes in women with aging.

3.1.2 Volume of Pyriform Sinus by Head Rotation

The purpose of postural techniques during swallowing is to eliminate aspiration and pharyngeal residue by utilizing gravity and/or manipulating spaces in order to change the speed and direction of bolus flow. Head rotation is a postural technique often used in the clinical setting. In one study with VF, head rotation to the weaker side resulted in liquid bolus transported to the opposite (unrotated) side of the pyriform sinus in patients with dysphagia (Logemann et al. 1989). While this type of change in the bolus path during head rotation may involve changes in the morphology of the pyriform sinus, 2D imaging modalities cannot accurately represent these morphological changes. However, a study using 320-ADCT was the first to 3D morphological changes to the pyriform sinuses during head rotation, accounting for lateral neck bending, flexion, and extension (Nakayama et al. 2013). The volume, cross-sectional area, and depth of both sided pyriform sinuses were calculated with the head rotated at 0, 30, 45, and 60°. As the rotational angle increased, the volume and cross-sectional area were significantly decreased on the rotated side and the volume, cross-sectional area, and depth significantly increased on the opposite side (Fig. 9). These changes were less likely to be influenced by the degree of lateral bending or

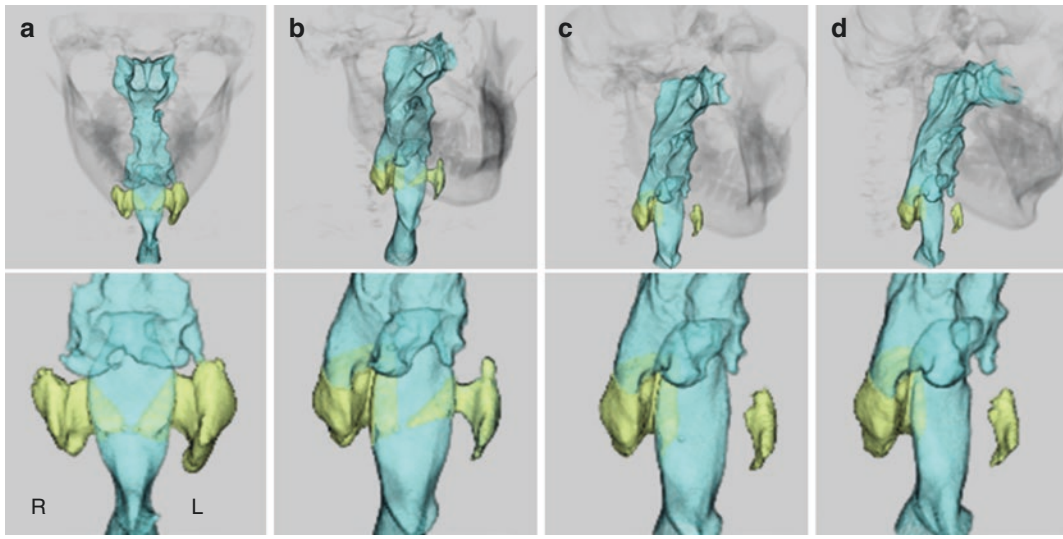

Fig. 9 3D CT images of pyriform sinus during head rotation. Head rotated to (**a**) 0°, (**b**) 30°, (**c**) 45°, and (**d**) 60°. Yellow space: pyriform sinus

flexion/extension of the head and neck accompanying head rotation, and instead resulted mainly from the increase in head rotation angle.

3.2 Dynamic Analysis

3.2.1 Effects of Age, Bolus Consistency, Bolus Volume

During normal swallowing, precise coordination between bolus transport and movement of the involved structures facilitates the complete bolus transport through the pharynx and UES and protection of the airway to prevent aspiration. An understanding of this coordination is extremely important to diagnose abnormal conditions and to provide effective adjustments in dysphagia rehabilitation. Although coordination of laryngeal kinematics and bolus transport is essential to maintain airway protection, the mechanism of laryngeal closure is not fully understood, because of limited visualization of TVC, one of the critical components of laryngeal closure. Temporal measurements of swallowing events on CT studies under differnt bolus conditions (e.g., consistency, size) can reveal how the motor control of structures adapts to prevent aspiration. Temporal measures can also identify ege-related differences in swallowing.

1. Age

   A study of 10 mL honey-thick liquid swallow showed that the duration of velopharyngeal closure and laryngeal closure (including epiglottis inversion, laryngeal vestibule closure, and TVC closure) was significantly different between three aged groups (older, middle-aged, and younger). The durations were longer in older adults than in middle-aged and younger adults. The pharyngeal phase was longer, velopharyngeal closure started earlier and velopharyngeal closure and laryngeal closure continued after complete UES opening (Inamoto et al. 2012b). This difference may have occurred due to a protective mechanism compensating for age-related pharyngeal constrictor changes. UES opening was constant among the three age groups.

2. Bolus consistency

   A study comparing swallows of honey-thick liquid and thin liquid in ten healthy subjects (6 male, 4 female) aged 45 ± 12 year showed that temporal relationships between swallowing movements varied by bolus consistency (Inamoto et al. 2013). With thin liquids, TVC closure started significantly earlier and lasted longer than with thick liquids ($p < 0.05$); this difference was associated with the rapid pharyngeal transport of thin liquids. The timing of the other two components of laryngeal closure (closure of laryngeal vestibule and epiglottis inversion) was constant between the two liquid consistencies (Figs. 10 and 11).

3. Bolus volume

   A study comparing swallows of different bolus volumes (3, 10, and 20 mL) of honey-thick liquids revealed that the overall temporal relationship of events did not differ across the three volumes; however, larger bolus volumes significantly changed the onset and offset of swallowing events (Shibata et al. 2017). The onset of UES opening was significantly earlier with increased volume ($p < 0.05$); this was associated with the earlier pharyngeal transport in the pharynx. The duration of bolus passage through the UES was significantly longer for the 10- and 20-mL volumes than 3-mL volume ($p < 0.05$). Another study comparing swallows of different bolus volumes (3, 10, and 20 mL) revealed different temporal adjustments for thin and honey thick liquids. In association with earlier pharyngeal transport with increasing volume, the authors observed significantly earlier UES opening, TVC closure, and velopharyngeal closure ($p < 0.05$) (Inamoto et al. 2014).

These findings suggest that aging, bolus viscosity, and bolus volume alter the temporal characteristics of swallowing, particularly closure of the TVC (Table 4). These changes may promote swallowing safety by preventing aspiration, suggesting that swallowing adapts to bolus properties and age-related changes.

Given that TVC closure was the only one of the three components of laryngeal closure that varied between the bolus consistencies, the TVCs appear to have an independent mechanism of control that allows for adaptation during swallowing.

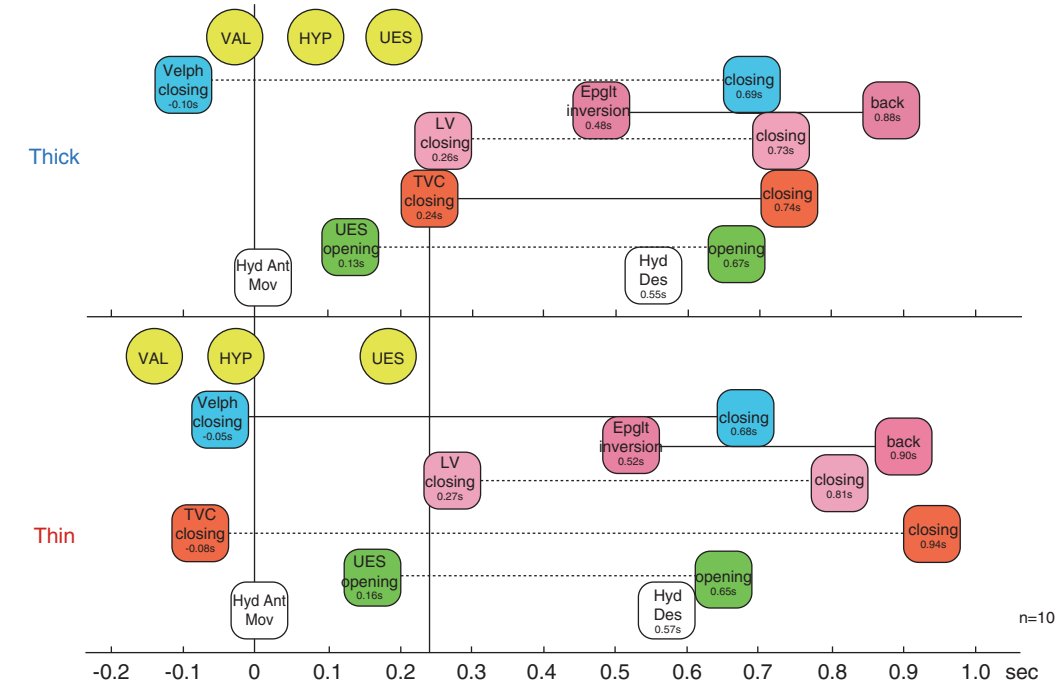

Fig. 10 Average timeline of events correlated with the onset of anterosuperior hyoid movement as time zero in ten healthy subjects. *Velph* velopharynx, *Epglt* epiglottis, *LV* laryngeal vestibule, *TVC* true vocal cords, *H Ant Mov* hyoid anterosuperior movement

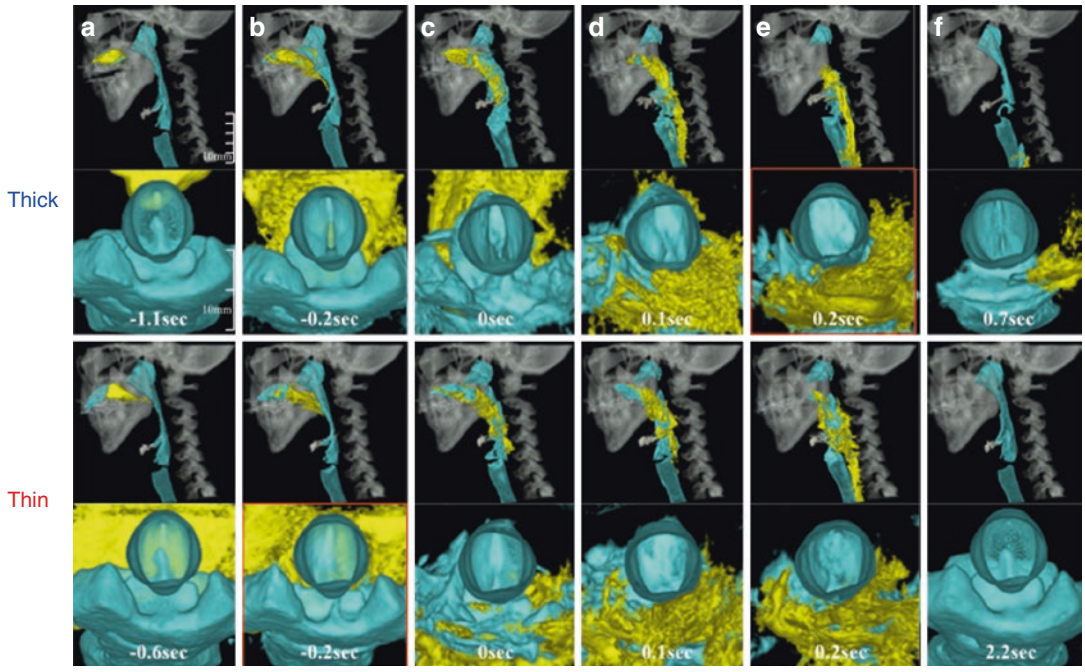

Fig. 11 3D CT images of one healthy volunteer's swallow taken the first frame (**a**); tongue down (**b**); onset of hyoid anterosuperior movement (**c**); onset of UES opening (thick (**d**), thin (**e**)); onset of TVC closure (thick (**e**), thin (**b**)); and termination of TVC closure (**f**). Timeline correlated with the onset of hyoid anterosuperior movement as zero. *Upper*: thick liquid, *lower*: thin liquid. *TVC* true vocal cord

Table 4 Changes in structures' movement in swallowing of different conditions

Variable	Bolus	Bolus transport	Onset and duration of structures' movement	
Age	Thick 10 mL	No change	Velopharyngeal closure	Earlier onset and prolongation in elderly group
			Laryngeal closure	Prolongation in elderly group
Consistency	Thick 10 mL, thin 10 mL	Faster in thin	TVC closure	Earlier onset and prolongation in 10, 20 mL
	Thick 3, 10, 20 mL	Faster in 10 and 20 mL	UES opening	Earlier onset in 20 mL
Volume	Thin 3, 10, 20 mL	Faster in 10 and 20 mL	Velopharyngeal closure	Earlier onset in larger volume
			TVC closure	
			UES opening	

3.2.2 Distance of Hyoid and Laryngeal Movement and Cross-Sectional Area of UES Opening

An analysis of honey thick liquid swallows in 26 healthy subjects showed that the average superior movement of the hyoid bone was 16.5 ± 9.2 mm and that the average anterior movement was 12.8 ± 5.0 mm (1) (Kendall and Leonard 2001). The superior movement of the thyroid cartilage was 23 mm and the anterior movement was 11 mm.

A novel finding of UES was the shape of the UES. It was observed to be oblong overall and concave in the middle, not round, as previously reported. The anteroposterior midline diameter, maximum anterior parasagittal diameter, transverse diameter, and cross-sectional area were 9 mm, 7 mm, 21 mm, and 139 mm^2, respectively. With reference to thyroid cartilage, the UES elevated 1.93 ± 0.77 mm during swallowing. The anterior displacements of the hyoid bone and the laryngeal prominence movement were correlated with the midline diameter of the UES (r = 0.477 and 0.433, respectively) (Okada et al. 2013b).

3.2.3 Pattern of Volume Change in Pharyngolaryngeal Space

The pharyngolaryngeal space during swallowing of 3, 10, and 20 mL of honey thick liquid was measured in ten healthy subjects (Iida et al. 2017). The total pharyngolaryngeal space increased with tongue loading and was maximal as the bolus was transported to the pharynx. The space then gradually decreased with pharyngeal contraction, which occurred simultaneously with the arrival of the bolus in the pharynx. After the onset of anterosuperior hyoid movement, the space rapidly decreased in volume. As the UES opened and the bolus flowed into the esophagus, the volume reached its minimum (nearly zero). Most of the air was disappeared in the pharyngolaryngeal space before the bolus was transported to the esophagus.

3.2.4 Pattern of Hyoid Muscle Shortening

The association between hyolaryngeal movement and shortening of the hyoid muscles (stylohyoid, posterior digastric, mylohyoid, geniohyoid, and thyrohyoid muscles) was studied during swallowing in healthy volunteers (Kendall and Leonard 2001). First, the stylohyoid, posterior digastric, and mylohyoid muscles began to shorten simultaneously, during the superior hyoid movement. Next, the geniohyoid, thyrohyoid, and anterior digastric muscles shortened concurrently with anterior hyoid movement. This serial shortening of the hyoid muscles influenced the anterosuperior trajectory of the hyoid bone. A significant correlation was observed between the shortened muscle lengths of the stylohyoid (r = 0.652), posterior digastric (r = 0.452), and mylohyoid (r = 0.625) muscles and the superior movement of the hyoid bone (Fig. 12).

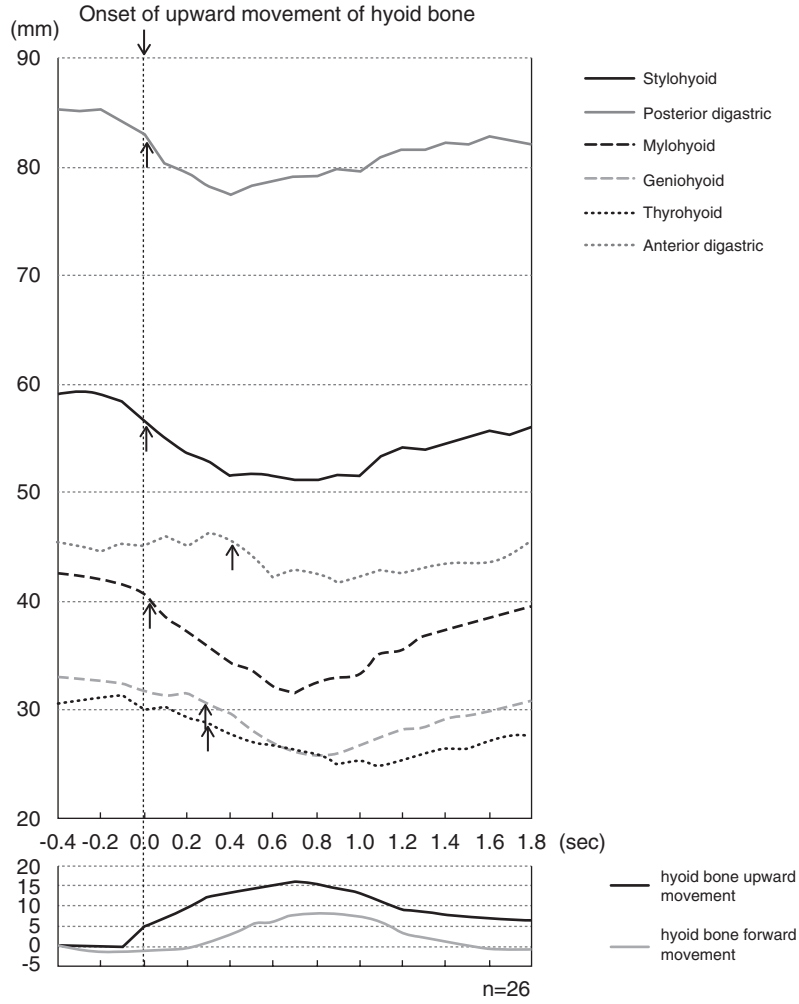

Fig. 12 Changes in muscle length and the trajectory of hyoid bone movement during swallowing of a 10 mL honey-thick liquid. Onset of the upward movement of the hyoid bone was set as 0 s. The graphs are averaged data from 26 subjects. An arrow indicates the point when a shortened muscle length became <95% of the maximal shortened length at which the muscle is considered to be as actively shortened. Positive value indicates the upward and forward directions in the graph below

4 Clinical Application: Evaluation of Pathophysiology

Quantification of the pharyngeal volume and UES opening elucidates the understanding of the mechanism of pharyngeal residue.

A case of a 62-year-old woman with right lateral medullary infarction after dissection of an aneurysm in the right vertebral artery was evaluated by VF and 320-ADCT. After 4ml of nectar thick liquid on VF study, significant pharyngeal residue was present and was not cleared out after several swallows. The mechanism of pharyngeal residue became clear in a frame-by-frame analysis using swallowing CT. 3D–CT images revealed that the pharyngeal cavity on the affected side remained opened when the bolus passed through the UES (Fig. 13). Measurement of the pharyngeal volume showed that the minimum volume was 13.0 mL (Fig. 14). Given the fact that the minimum volume normally approaches zero, pharyngeal wall on the affected side did not sufficiently contract. Additionally, the bolus did not pass through the affected side of the UES. The duration of UES opening was 0.3 s and the maximum cross-sectional area of the UES was 69.2 mm^2 (Figs. 15 and 16). Both values were lower than average. The anterior and superior hyoid displacements were 10.8 mm and 5.0 mm, respectively (Fig. 17), and the anterior and superior laryngeal displacments were 14.8 mm and 0.3 mm, respectively. The anterior displacement of both

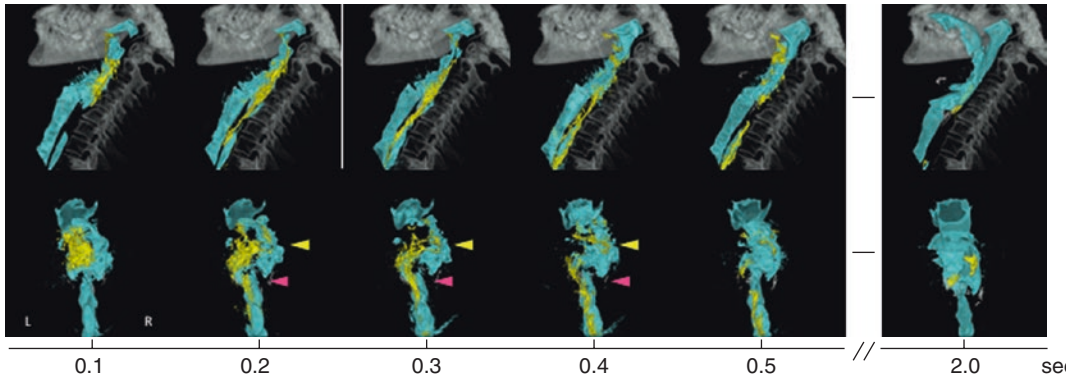

Fig. 13 3D CT images from a 62-year-old female patient with dysphagia swallowing of 4 mL of nectar thick liquid. Time is correlated with the onset of hyoid anterosuperior movement as time zero. Upper: lateral view, lower: posterior view. *Yellow arrows* show the remaining right pharyngeal cavity (affected side). *Pink arrows* show no bolus transport through the right UES (affected side). L: *left*, R: *right*

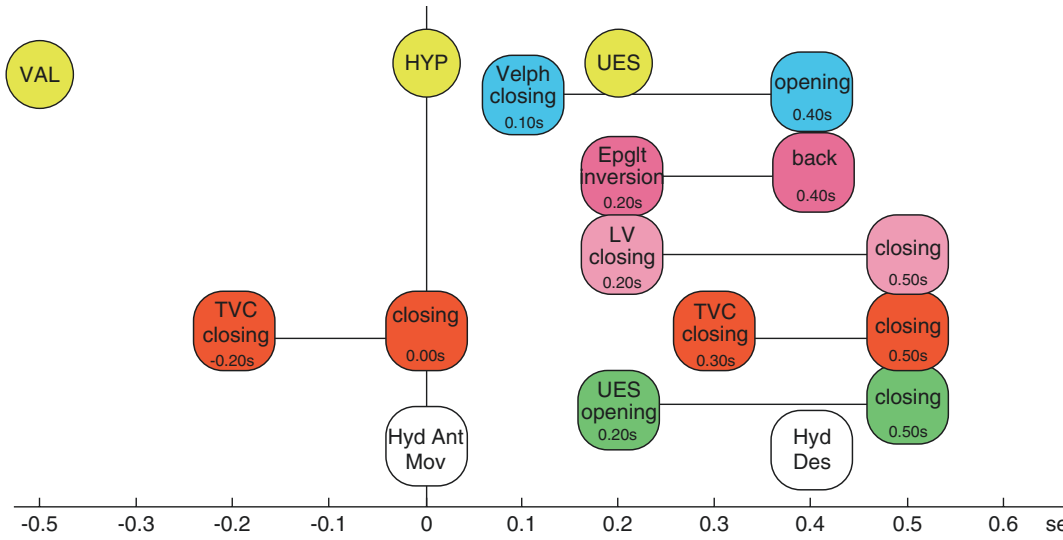

Fig. 14 Timeline of events correlated with the onset of hyoid anterosuperior movement as time zero. *Velph* velopharynx, *Epglt* Epiglottis, *LV* laryngeal vestibule, *TVC* true vocal cords, *H Ant Mov* Hyoid anterosuperior movement

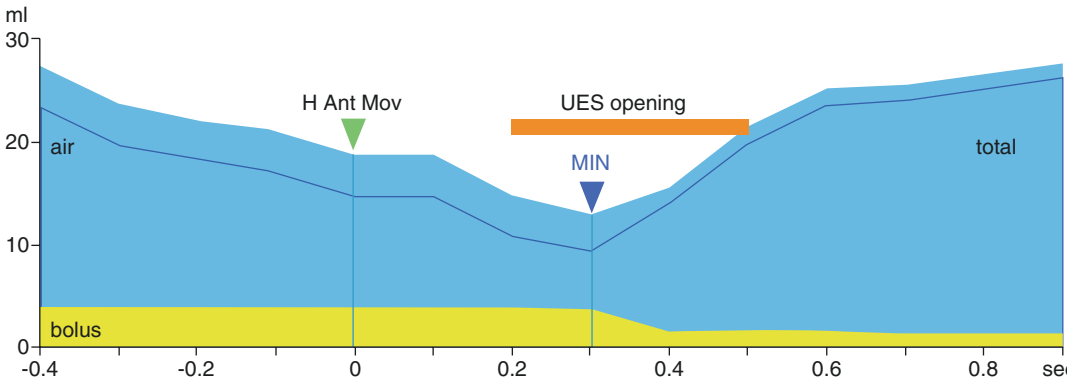

Fig. 15 Pharyngeal volume change. This graph shows the changes in the air and bolus volumes in the pharyngeal cavity during swallowing. *H Ant Mov* Hyoid anterosuperior movement, *MIN* minimum

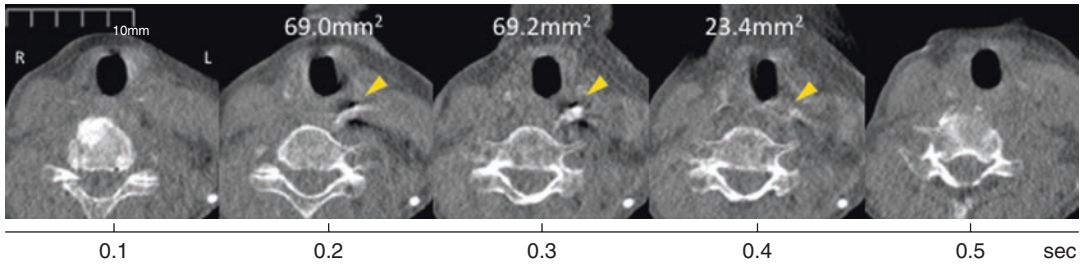

Fig. 16 Cross section of the UES opening. Axial images at the level of UES from one frame before UES opening to one frame after UES opening. The UES is opened for 0.3 s. Yellow arrows show UES opening. L: *left*, R: *right*

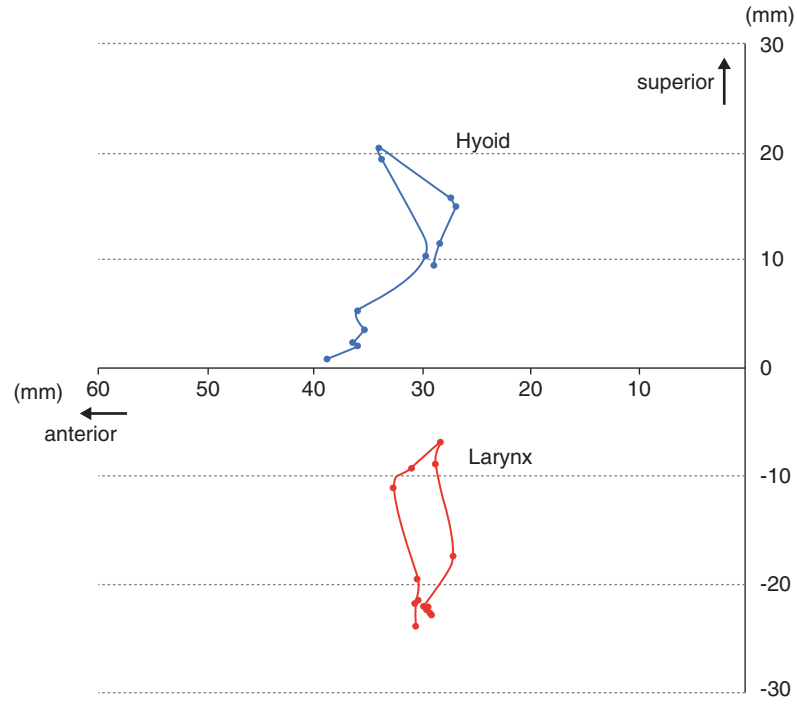

Fig. 17 Hyoid and larynx trajectory. The *y*-axis was defined as a plane made by the anterior-inferior corner of the second cervical vertebra and anterior-superior corner of the fourth cervical vertebra. Zero point (0, 0) is the fourth cervical vertebra. *Blue* is the hyoid and red is the larynx trajectory

the hyoid and larynx was minimal. The volume of pharyngeal residue was 1.8 mL (45% residue rate). In summary, the pharyngeal residue was likely caused by poor pharyngeal contraction and reduced duration and area of UES opening. One of the factors affecting UES opening was reduced hyolaryngeal displacement. 3D images with temporal and spatial kinematic analysis revealed the significant causes of the pharyngeal residue. These detailed analyses allowed for accurate selection of effective swallowing exercises. For example, exercises to strengthen pharyngeal contraction and hyolaryngeal movement were recommended for this patient. Thus, 320-ADCT realizes the treatment-oriented evaluation with more precise and quantitative manner than VF or VE and it will be beneficial to unveil underlining pathophysiology in complicated dysphagia cases.

Acknowledgment This chapter would not be possible without the gracious support of all the members of the Fujita radiological team and Fujita swallowing team. We would like to express our deep appreciation and sincerest thanks to Professor Jeffrey B. Palmer for his significant contributions and to Dr. Marlis Gonzalez and Dr. Rachel Mulheren for editorial assistance. And we must thanks to the subjects and patients, who generously participated in some of the imaging studies presented in this text.

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Pharyngeal Morphology

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Contents

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Abstract

This chapter discusses the radiographic findings of structural abnormalities of the pharynx.

1 Introduction

There is no dividing line between morphologic and functional disorders of the pharynx. Structural abnormalities frequently cause abnormal pharyngeal motility. Motility disorders often are manifested by abnormal pharyngeal structure. Therefore, examination of the pharynx requires a dynamic examination of motility in combination with static images of morphology. The radiologist tailors the dynamic (videofluoroscopy) and morphologic (spot image) examination to the patient's clinical history, symptoms, and initial fluoroscopic findings (Rubesin and Glick 1988; Rubesin and Stiles 1997). This chapter discusses morphologic disorders of the pharynx.

2 Surface Anatomy Pertinent to Roentgen Interpretation

The principles of interpreting roentgen images of the pharynx are the same as in the evaluation of the remainder of the gastrointestinal tract (Rubesin and Laufer 1991). The shape of the

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pharynx is determined by the tongue, laryngeal cartilages (epiglottic, thyroid, cricoid, and arytenoid cartilages), pharyngeal musculature, and supporting skeleton. The normal surface of distended pharyngeal mucosa is smooth (Fig. 1), except in the regions of the palatine and lingual tonsils. The normal surface of the palatine and lingual tonsils is slightly nodular because of the underlying lymphoid tissue (Figs. 2 and 3) (Gromet et al. 1982). When the pharynx is slightly collapsed, barium-coated striations may be seen (Fig. 4a) (Rubesin et al. 1987a). These lines reflect the underlying vertically oriented inner longitudinal muscle layer of the pharynx: the fibers and aponeurosis of the salpingopharyngeal, stylopharyngeal, and palatopharyngeal muscles (Fig. 4b). Transversely oriented lines are seen in the lower hypopharynx and reflect redundant epithelium overlying the muscular processes of the arytenoid cartilages and cricoid cartilage. Thus, any nodularity or focal barium collection that disrupts the smooth mucosal surface of the lateral or posterior pharyngeal wall is suspicious for an inflammatory or a neoplastic process.

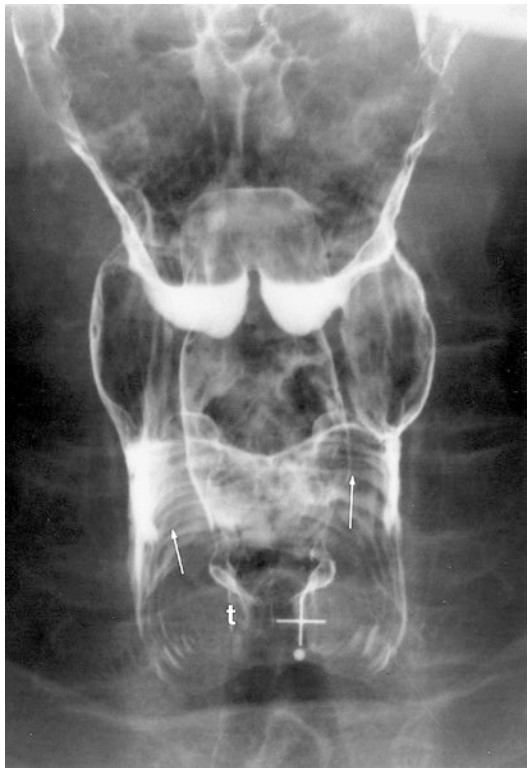


Fig. 1 Arcuate lines in hypopharynx. After the patient aspirated a small amount of barium, this spot radiograph of the pharynx shows the relationship of the barium-coated larynx (right true vocal cord identified with *t*) to the hypopharynx. The larynx acts as an extrinsic mass impression upon the lower hypopharynx. Arcuate lines (*arrows*) reflect redundant mucosa in the hypopharynx. As long as the arcuate lines are smooth and thin, no tumor or inflammatory process should be considered (reproduced with permission from Rubesin and Glick 1988, Fig. 11a)

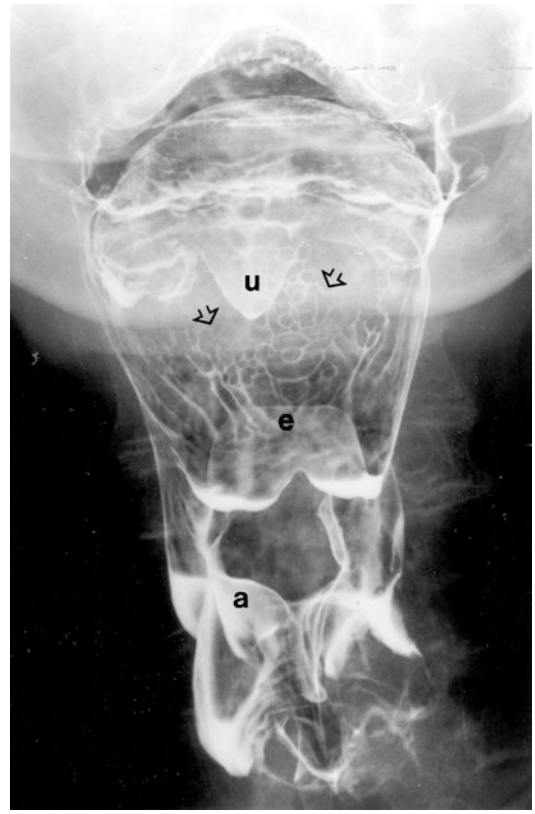


Fig. 2 Mucosal surface base of tongue. Spot radiograph of the pharynx demonstrating a reticular pattern (representative area identified by *open arrows*) reflecting barium filling the interstices of the fine nodular surface of the base of the tongue. The reticular surface reflects the underlying lingual tonsil. Disruption of the normal, relatively flat reticular surface of the tongue is abnormal. Also identified are the uvula (*u*) and epiglottic tip (*e*). The mucosa overlying the muscular processes of the arytenoid cartilages (right arytenoid cartilage identified by *a*) is elevated owing to radiation-induced edema. The left hypopharynx, the site of a previously radiated cancer, is contracted

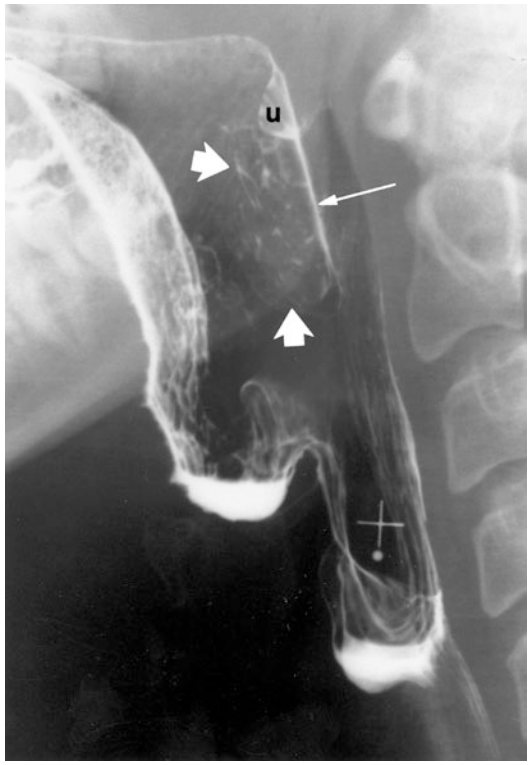


Fig. 3 Normal mucosal surface of the palatine tonsils. Spot radiograph of the pharynx showing barium filling the interstices of the normal lymphoid tissue of the palatine tonsil (*thick arrows*). Also note the uvular tip (*u*) of the soft palate and the palatopharyngeal fold (*long arrow*) (reproduced with permission from Rubesin et al. 1987b, Fig. 2b)

During pharyngography, the mucosa behind the cricoid cartilage appears undulating (Fig. 5a). Although this prominent postcricoid mucosa was thought to reflect a venous plexus (Pitman and Fraser 1965), redundant squamous epithelium and submucosa explain the radiographic findings (Fig. 5b) (Rubesin et al. 1987a). As long as the postcricoid mucosa changes size and shape during swallowing, a postcricoid tumor need not be considered.

3 Pouches and Diverticula

Pouches are transient protrusions at sites of anatomic weakness of the pharyngeal wall, whereas diverticula are persistent protrusions of pharyngeal mucosa and submucosa at these same sites (Perrot 1962).

3.1 Lateral Pharyngeal Pouches and Diverticula

The lateral pharyngeal wall most frequently protrudes in the region of the thyrohyoid membrane (Fig. 6), an area bounded superiorly by the greater cornu of the hyoid bone, inferiorly by the ala of the thyroid cartilage, anteriorly by the posterior border of the thyrohyoid muscle, and posteriorly by the superior cornu of the thyroid cartilage and the insertion of the stylopharyngeal muscle (Fig. 7) (DuBrul 1980). The unsupported portion of thyrohyoid membrane is perforated by the superior laryngeal artery and vein and the internal laryngeal branch of the superior laryngeal nerve (Pernkopf 1989). It is not known what happens to this space during swallowing, when the hyoid bone and thyroid cartilage are brought together by contraction of the thyrohyoid muscle.

Lateral pharyngeal pouches are extremely common, the incidence increasing with patient age. Only a small percentage (about 5%) of patients with lateral pharyngeal pouches are symptomatic, complaining of dysphagia, choking, or regurgitation of undigested food (Curtis et al. 1988; Lindbichler et al. 1998).

During swallowing, in the frontal view, lateral pharyngeal pouches are manifested as transient saclike protrusions (Fig. 8) of the lateral wall above the notch in the lateral pharyngeal wall that denotes the junction of the ala of the thyroid cartilage and the thyrohyoid membrane. The neck of the sac changes size during swallowing when the thyroid cartilage is raised to appose the hyoid bone. On the lateral view, pouches are manifested as barium-filled sacs on the anterior hypopharyngeal wall just below the hyoid bone at the level of the valleculae. Barium retained in the pouches is spilled into the lateral swallowing channels just after the bolus passes.

Lateral pharyngeal diverticula are persistent protrusions at the level of the thyrohyoid mem-

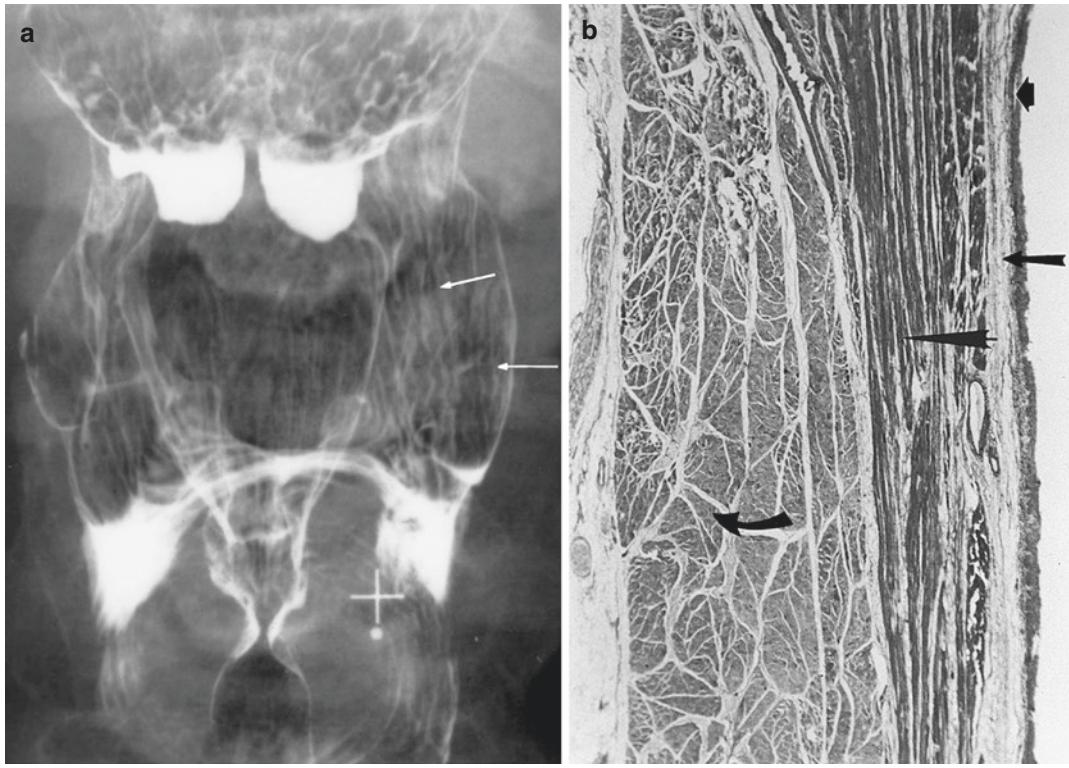


Fig. 4 Lines of the pharynx. (**a**) Spot radiograph showing vertically oriented striations (*arrows*) in the lateral and posterior surface of the hypopharynx. These lines reflect the underlying longitudinal muscle layer. (**b**) Low-power photomicrograph of the lateral pharyngeal wall showing close apposition of the squamous epithelium (*short arrow*) to the longitudinal muscle layer (*long arrowhead*). Only a thin tunica propria (*long straight arrow*) separates the squamous epithelium from the longitudinal muscle layer. The constrictor muscle layer is identified by a curved arrow (reproduced with permission from Rubesin and Glick 1988, Figs. 5a and 6)

brane. These diverticula are barium-filled sacs which usually fill via a narrow neck. In contrast to lateral pharyngeal pouches, lateral pharyngeal diverticula are often unilateral (Fig. 9).

3.2 Branchial Cleft Cysts and Fistulas

Branchial clefts are grooves of ectodermal origin that develop on both sides of the neck in a 4-week-old embryo (Hyams et al. 1988; Maran and Buchanan 1978). The branchial pouches are four pharyngeal outpouchings of endodermal origin that meet the branchial clefts. The first branchial cleft forms the external auditory meatus. The second branchial cleft forms the middle ear, eustachian tube, and floor of the tonsillar fossa. The third and fourth branchial pouches form the piriform sinuses. Persistence of either a branchial cleft or a branchial pouch may result in a sinus tract or cyst.

The most common branchial vestige is a cyst arising from the second branchial cleft. Small second branchial cleft cysts lie anterior to the sternocleidomastoid muscle. Larger cysts may extend below the sternocleidomastoid muscle between the internal and external carotid arteries. These cysts only rarely communicate with the pharynx (Bachman et al. 1968).

Branchial pouch sinuses end blindly in the soft tissue of the neck. Branchial pouch fistulas extend to the skin. Branchial pouch sinuses and fistulas arise from the tonsillar fossa (second pouch), the upper anterolateral wall of the piriform sinus (third pouch), and the lower anterolat-

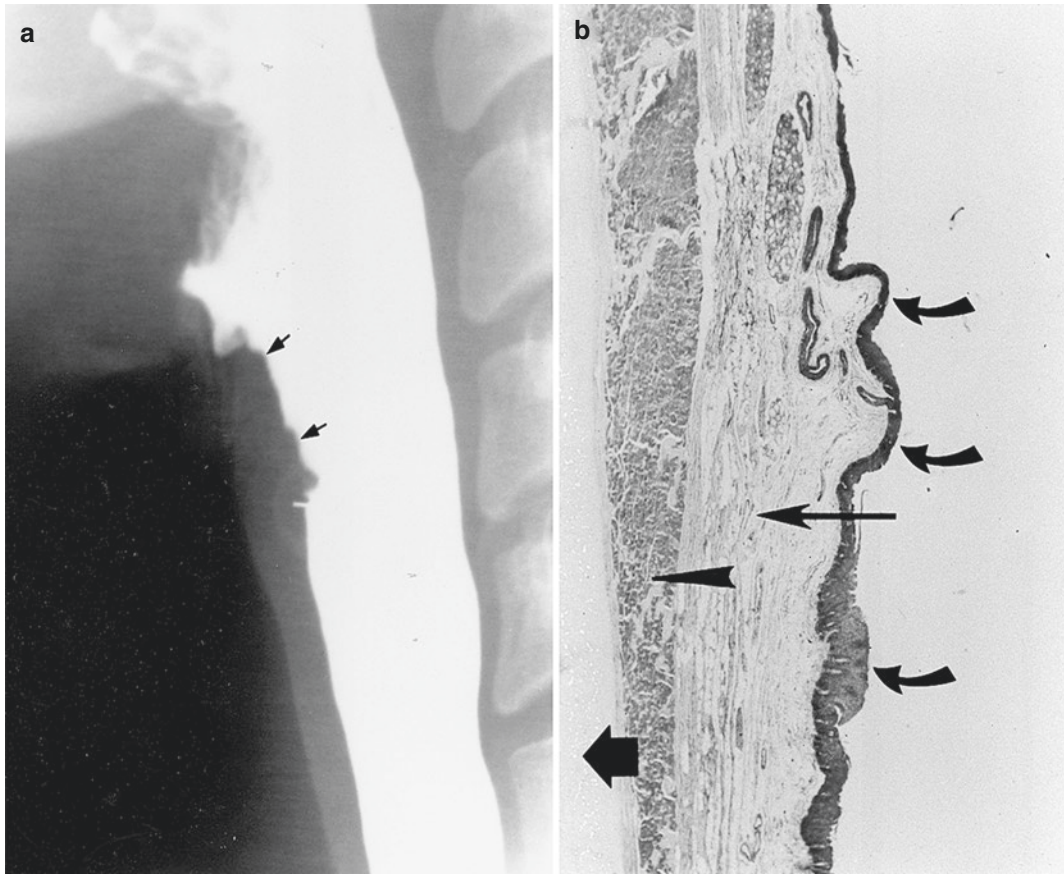


Fig. 5 Postcricoid mucosa. (**a**) Spot radiograph of the pharynx obtained while the bolus was passing through the pharyngoesophageal segment showing undulating mucosa (*arrows*) just behind the cricoid cartilage. (**b**) Low-power photomicrograph obtained at the level of the cricoid cartilage (*thick arrow*) showing a sinuous squamous epithelium (*curved arrows*) corresponding to the undulating mucosa seen in (**a**). The submucosa (*long arrow*) is very thick at this level, reflecting the need for this area to move easily. Compare the thickness of the submucosa here with the thickness of the tunica propria in Fig. 4b. The cricoarytenoid muscle (*arrowhead*) lies posterior to the cricoid cartilage. (**a** reproduced with permission from Rubesin 2000a, Fig. 47a; **b** reproduced with permission from Rubesin and Glick 1988, Fig. 8)

eral wall of the piriform sinus (fourth pouch). Although most of these sinuses and pouches are present at birth, sinus tracts are occasionally detected for the first time in adults (Fig. 10).

3.3 Zenker's Diverticulum

Zenker's diverticulum (posterior pharyngeal diverticulum) is an acquired mucosal herniation through Killian's dehiscence, a gap in the region of the cricopharyngeal muscle, found in about one-third of individuals on autopsy (Zaino et al. 1970). There is considerable variation in the anatomy of the thyropharyngeal muscle and the cricopharyngeal muscle. Thus, Killian's dehiscence has been described as arising either between the thyropharyngeal muscle and the cricopharyngeal muscle or between the oblique and transverse fibers of the cricopharyngeal muscle (Perrot 1962; Zaino et al. 1967, 1970).

The relationship between Zenker's diverticulum and function of the cricopharyngeal muscle is not known. In some studies, upper esophageal sphincter (UES) pressure is normal (there is no spasm), the muscle relaxes completely during

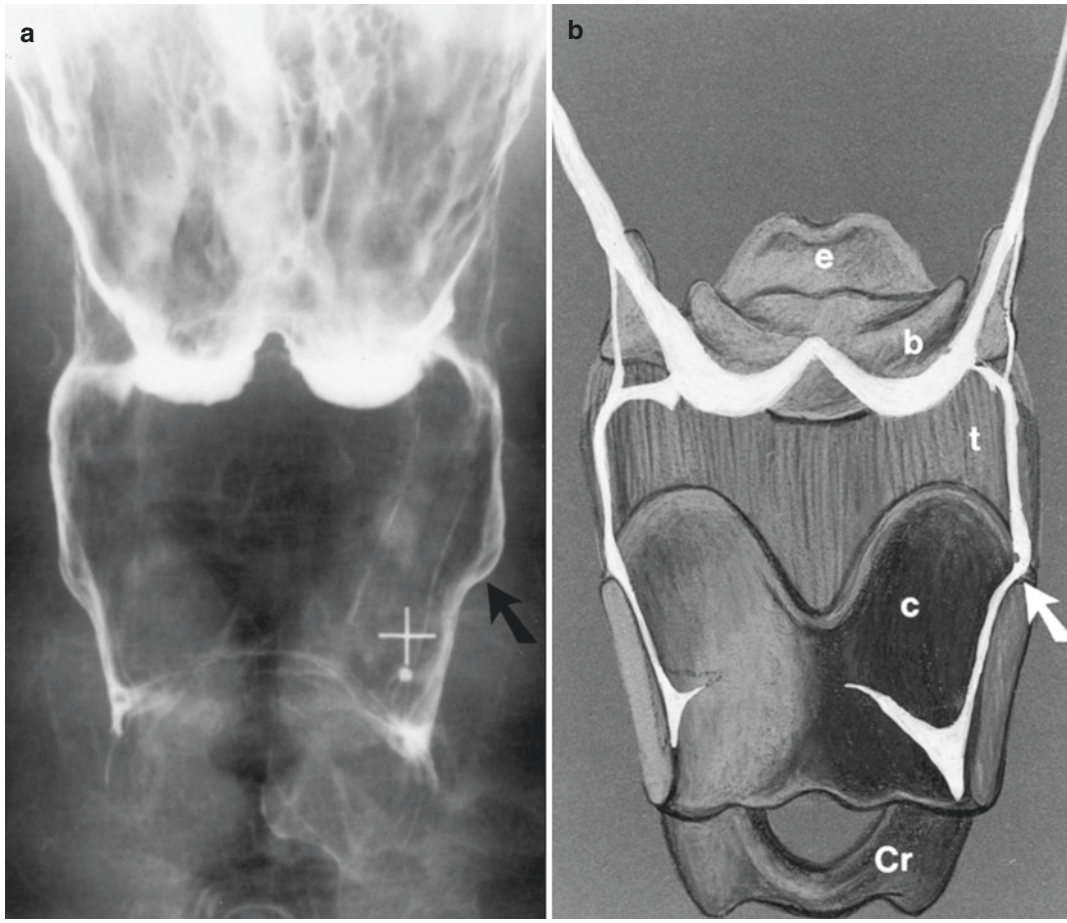


Fig. 6 The thyrohyoid membrane. (**a**) Spot radiograph of the pharynx showing focal indentation of the contour of the lateral hypopharyngeal wall (*arrow*). This marks the transition between the hypopharynx that lies above the ala of the thyroid cartilage and the portion of hypopharynx confined by the thyroid cartilage. (**b**) Corresponding line drawing demonstrating the point where the anterolateral hypopharyngeal wall becomes confined by the thyroid cartilage (*arrow*). The thyrohyoid membrane (*t*) bridges the space between the hyoid bone (*b*) and the thyroid cartilage (*c*). Also note the epiglottic cartilage (*e*) and cricoid cartilage (*Cr*) (reproduced with permission from Rubesin et al. 1987a, Fig. 10a and b)

swallowing (there is no achalasia), and there is normal coordination between pharyngeal contraction and UES relaxation (Knuff et al. 1982; Frieling et al. 1988). Other studies have suggested that there is either abnormal relaxation of the UES or incoordination of pharyngeal contraction. It is also not known whether chronic gastroesophageal reflux predisposes to the development of Zenker's diverticulum. Clearly, between 65 and 95% of patients with Zenker's diverticulum have gastroesophageal reflux (Smiley et al. 1970; Delahunty et al. 1971; Rubesin and Levine 2001).

Zenker's diverticulum is usually first detected in elderly patients who complain of dysphagia, halitosis, choking, hoarseness, or regurgitation of undigested food. Zenker's diverticulum is not infrequently found in asymptomatic individuals or patients being studied for symptoms of gastroesophageal reflux disease. Change in the character of dysphagia or bloody discharge in a patient with a known Zenker's diverticulum suggests development of a complication such as ulceration, fistula formation, or carcinoma (Nanson 1976; Shirazi et al. 1977).

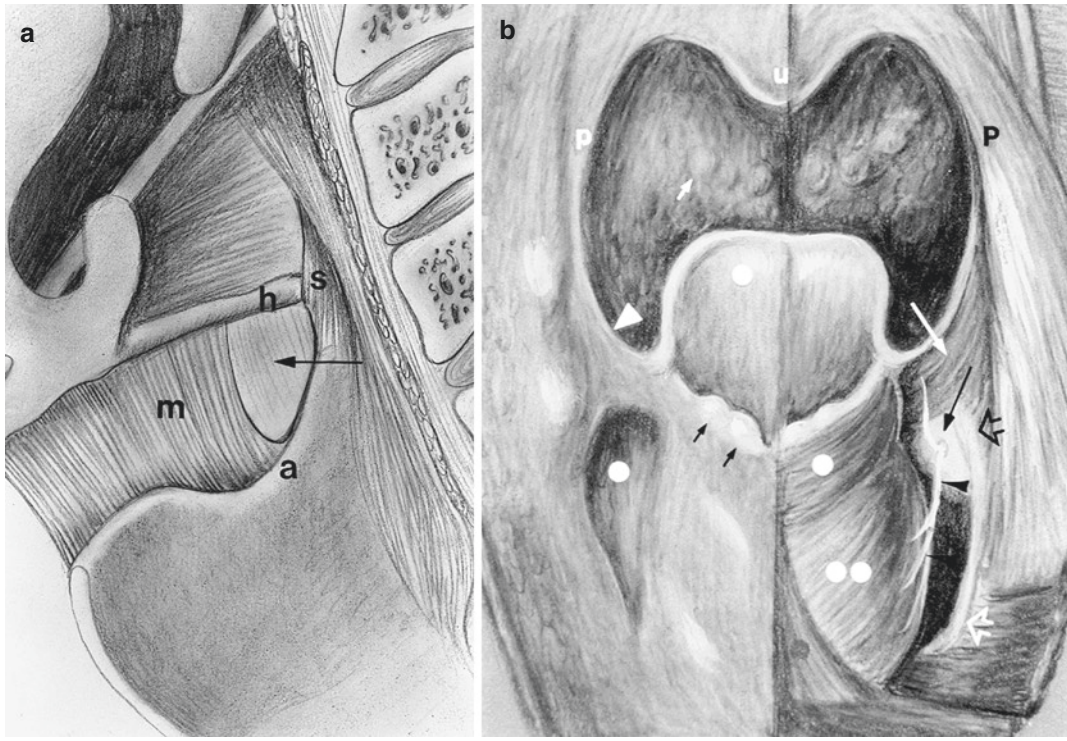


Fig. 7 Location of lateral pharyngeal pouches. (**a**) Line drawing performed in the lateral view showing the location of the unsupported portion of the thyrohyoid membrane (*arrow*): posterior to the thyrohyoid muscle (*m*) and membrane, anterior to the superior cornu of the thyroid cartilage and inserting fibers of the stylopharyngeal muscle (*s*), inferior to the hyoid bone (*h*), and superior to the ala of the thyroid cartilage (*a*). (**b**) Dissection of the pharynx viewed from behind showing the unsupported portion of the thyrohyoid membrane (*black arrow*) and the internal branch of the superior laryngeal nerve (*black arrowheads*). The thyroid cartilage is identified by *open arrows*. Also identified are the palatopharyngeal fold (*white P*) and its corresponding palatopharyngeal muscle (*black P*), the uvula (*u*), the circumvallate papillae (*tiny white arrow*), the left pharyngoepiglottic fold (*arrowhead*), the left piriform sinus (*one white dot on the left*), the mucosa overlying the cuneiform and corniculate cartilages (*tiny black arrows*), the right arytenoid muscle (*one white dot on the right*), and the cricoarytenoid muscle (*two white dots on the right*) (reproduced with permission from Rubesin et al. 1987a, Figs. 8b and 11c)

Radiographically, in the frontal view, Zenker's diverticulum appears as a barium-filled sac midline below the tips of the piriform sinuses (Figs. 11 and 12). In the lateral view, Zenker's diverticulum appears as a barium-filled sac posterior to a prominent pharyngoesophageal segment and the upper cervical esophagus (see Fig. 12). During swallowing, Zenker's diverticulum appears as a protrusion of the lower hypopharyngeal wall posterior to the expected luminal contour, the neck of the diverticulum originating above a "prominent" pharyngoesophageal segment. The opening of the diverticulum may be very large during swallowing, almost 2 cm in height (Fig. 13). After the swallow has passed, barium regurgitates back into the hypopharynx, in rare cases, resulting in overflow aspiration. Any irregularity of the contour of the diverticulum suggests development of an ulcer or a carcinoma (Wychulis et al. 1969).

Zenker's diverticulum should not be confused with a "pseudo-Zenker's diverticulum," barium trapped above a cricopharyngeal bar that has either opened incompletely or closed early (Fig. 14). Some pseudo-Zenker's diverticula are pouches arising at Killian's dehiscence. It is not known whether a Zenker's diverticulum can develop from a pseudo-Zenker's diverticulum. This author believes that many pseudo-Zenker's

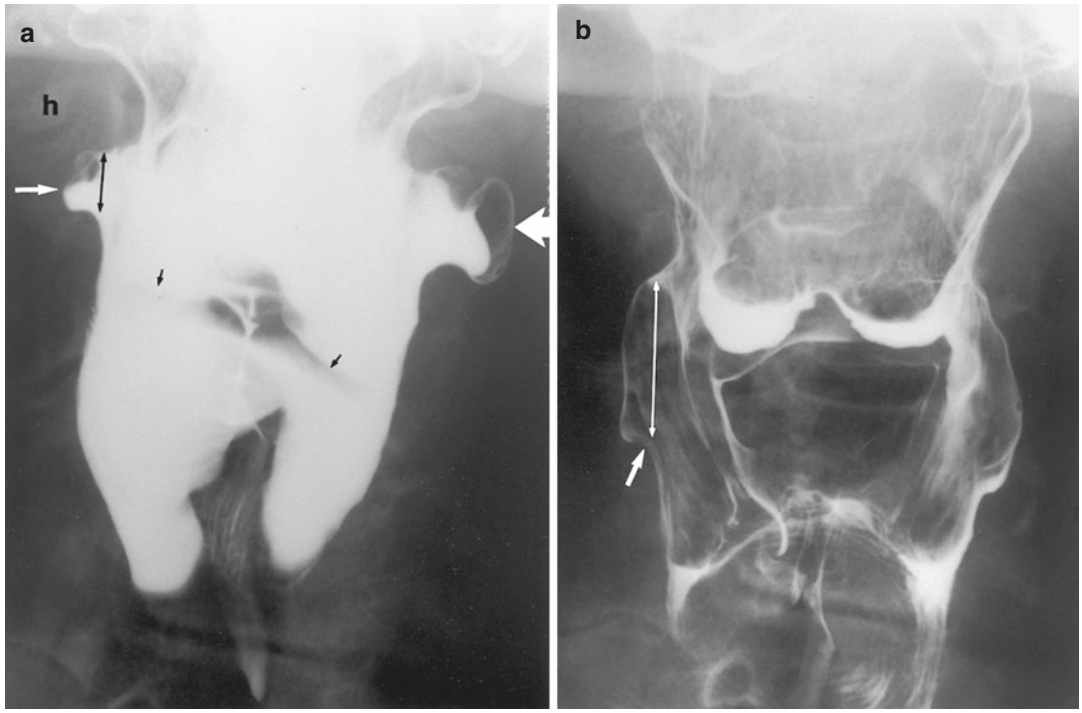


Fig. 8 Lateral pharyngeal pouches. (**a**) Spot radiograph obtained during drinking showing a small right (*small white arrow*) and larger left (*large white arrow*) lateral pharyngeal pouch. Note the relationship with the hyoid bone (*h*). The epiglottis (*small black arrows*) is tilting asymmetrically. Note the height of the right lateral pharyngeal pouch (*double arrow*) while the patient drinks the bolus. (**b**) Spot radiograph obtained just after the swallow in (**a**) showing that the pharynx has descended to its normal resting position. The notch identifying the superior border of the thyroid cartilage is identified (*white arrow*). Note the difference in height of the thyrohyoid membrane during swallowing (*double arrow* in **a**) and at rest (*double arrow* in **b**)

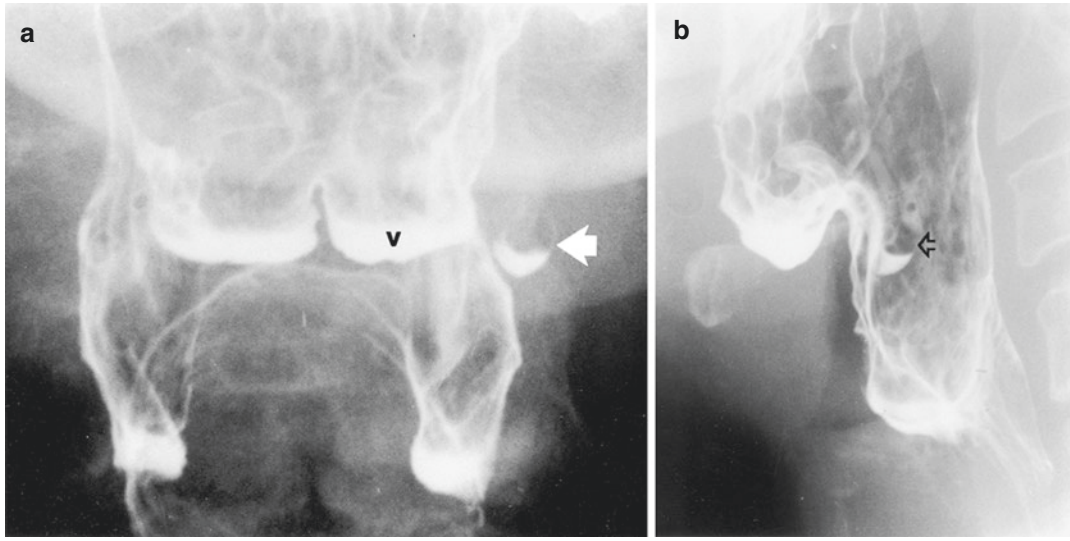


Fig. 9 Lateral pharyngeal diverticulum. (**a**) Spot radiograph obtained with the patient in the frontal position showing a 5 mm ovoid sac (*arrow*), partially filled with barium. Note that the diverticulum protruding from the left lateral upper hypopharyngeal wall is about at the level of the valleculae (left vallecula identified with *v*). (**b**) Spot radiograph obtained with the patient in the lateral position showing that the ovoid diverticulum (*arrow*) arises from the anterior portion of the lateral hypopharyngeal wall

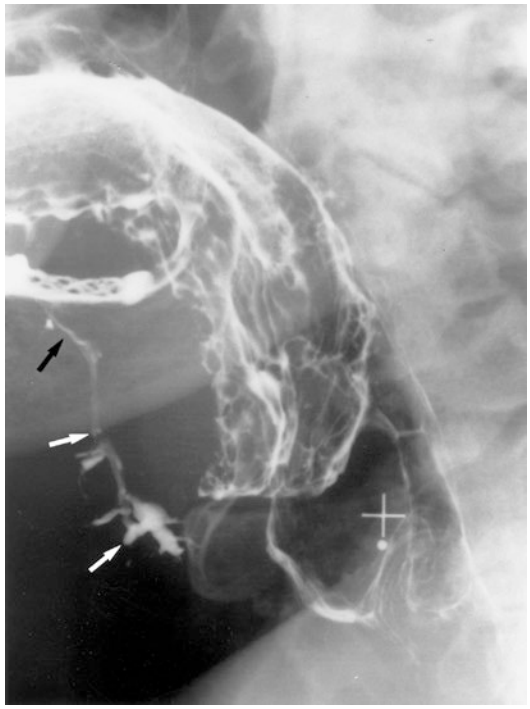


Fig. 10 Second branchial pouch sinus. Spot radiograph obtained with the patient in a steep right posterior oblique position showing an irregular barium-filled track (*arrows*) arising from the region of the right palatine fossa (reproduced with permission from Rubesin and Glick 1988, Fig. 23b)

diverticula result from cricopharyngeal response to gastroesophageal reflux (Brady et al. 1995).

3.4 Killian-Jamieson Pouches and Diverticula

Killian-Jamieson diverticula protrude through the Killian-Jamieson space, a gap in the muscle of the proximal cervical esophagus. This gap is bounded superiorly by the inferior margin of the cricopharyngeal muscle, anteriorly by the inferior margin of the cricoid cartilage, and inferomedially by the suspensory ligament of the esophagus just below its origin on the posterior lamina of the cricoid cartilage (Killian 1908). These diverticula are also known as "proximal lateral cervical esophageal diverticula" or "lateral diverticula from the pharyngoesophageal junction area" (Ekberg and Nylander 1983a). Patients with Killian-Jamieson diverticula are usually asymptomatic or have symptoms caused by abnormal pharyngeal motility (Rubesin and Levine 2001).

During pharyngography, the opening of the Killian-Jamieson diverticulum lies just below the cricopharyngeal muscle (Fig. 15). The opening of the sac changes size and shape with elevation of the cervical esophagus during swallowing (see Fig. 15). The sac of the diverticulum lies lateral to the proximal cervical esophagus on frontal views and overlaps the cervical esophagus on lateral views. Killian-Jamieson diverticula are more frequently unilateral than bilateral and are usually left sided (Fig. 16) (Rubesin and Levine 2001). Bilateral diverticula are seen in about one-quarter of patients. Killian-Jamieson diverticula are smaller than Zenker's diverticula, averaging about 1.4 cm (Rubesin and Levine 2001). Regurgitation of barium from the sac into the hypopharynx is uncommon because regurgitation is prevented by the cricopharyngeal muscle. Occasionally, Killian-Jamieson diverticula and a Zenker's diverticulum are seen in the same patient (Fig. 17).

Pouches are also frequently detected at the Killian-Jamieson space. These pouches may be related to early closure of the upper cervical esophagus, a finding associated with gastroesophageal reflux. On the frontal view, pouches appear as shallow, broad-based protrusions of the lateral proximal cervical esophageal wall; these pouches are effaced during swallowing (Ekberg and Nylander 1983a).

4 Inflammatory and Other Lesions

4.1 Lymphoid Hyperplasia

The normal surface of the base of the tongue has a reticular pattern created by the underlying lingual tonsil, an aggregate of 30–100 follicles extending from the circumvallate papillae to the root of the epiglottis (see Fig. 2) (Gromet et al. 1982). Hypertrophy of the lingual tonsils may occur after puberty, as a compensatory response to tonsillectomy/adenoidectomy, or as nonspecific response to allergy or repeated infection.

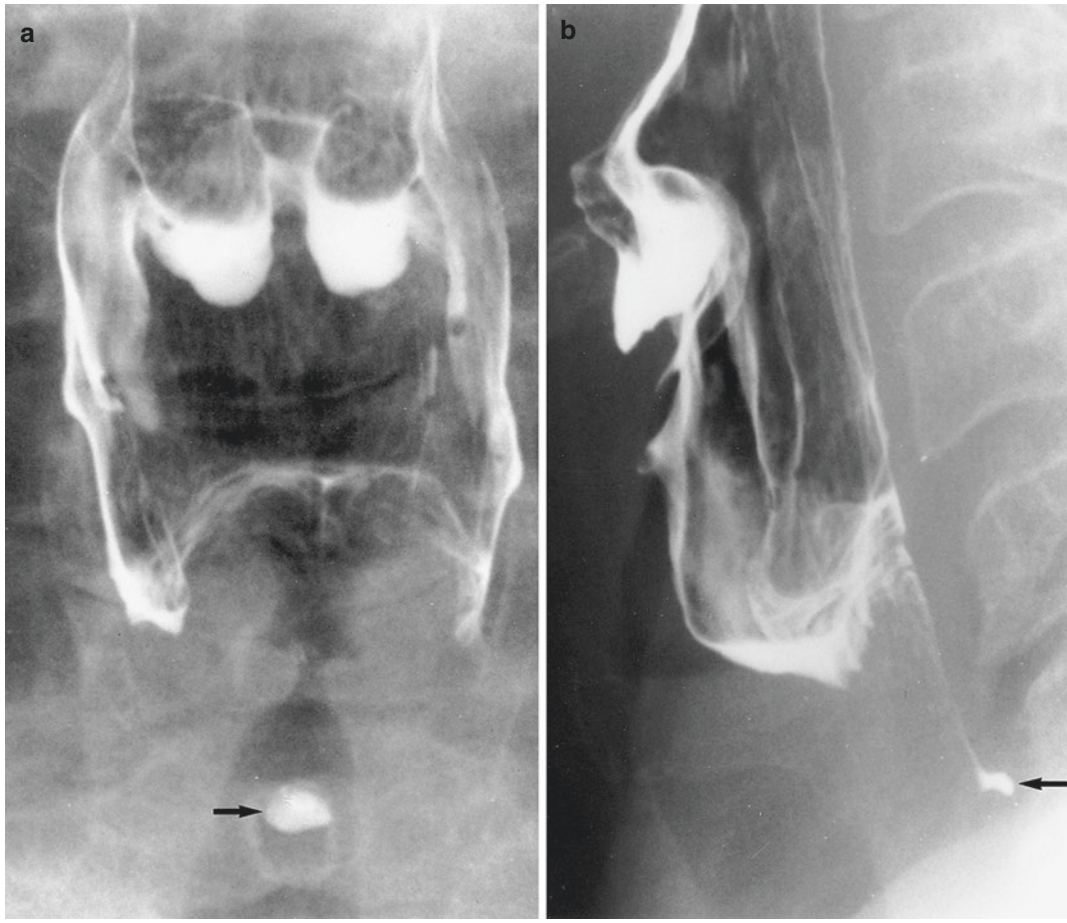


Fig. 11 Small Zenker's diverticulum. (**a**) Spot radiograph obtained with the patient in the frontal position showing a 5 mm ovoid barium-filled sac (*arrow*) midline below the tips of the piriform sinuses. (**b**) Spot radiograph obtained with the patient in the lateral position showing a 4 mm barium-filled sac (*arrow*) posterior to the expected lumen of the pharyngoesophageal segment. Note that this tiny diverticulum persists after swallowing but does not extend posterior to the pharyngoesophageal segment

Hypertrophy of the lingual tonsils disrupts the normal reticular surface pattern. There are no radiographic criteria, however, to differentiate nodularity of the base of the tongue attributed to the normal lingual tonsil from that of lymphoid hyperplasia. On frontal views in patients with lymphoid hyperplasia, there are large 5–7 mm, smooth-surfaced nodules carpeting the vertical surface of the tongue (Figs. 18 and 19a). On the lateral view, these nodules protrude posteriorly (Fig. 19b). With severe lymphoid hyperplasia, nodules may be detected in the valleculae, on the lingual surface of the epiglottis, and in the upper hypopharynx. Although lymphoid hyperplasia can appear coarsely nodular, asymmetrically distributed, or masslike, if any asymmetric or masslike nodularity is demonstrated radiographically, carcinoma or lymphoma should be excluded via ENT examination and/or MRI.

4.2 Acute Pharyngitis

Acute epiglottitis usually affects children between 3 and 6 years of age, but may also be seen in adults (Harris et al. 1970). Plain-film diagnosis is important, as manipulation of the tongue/pharynx or barium studies may exacer-

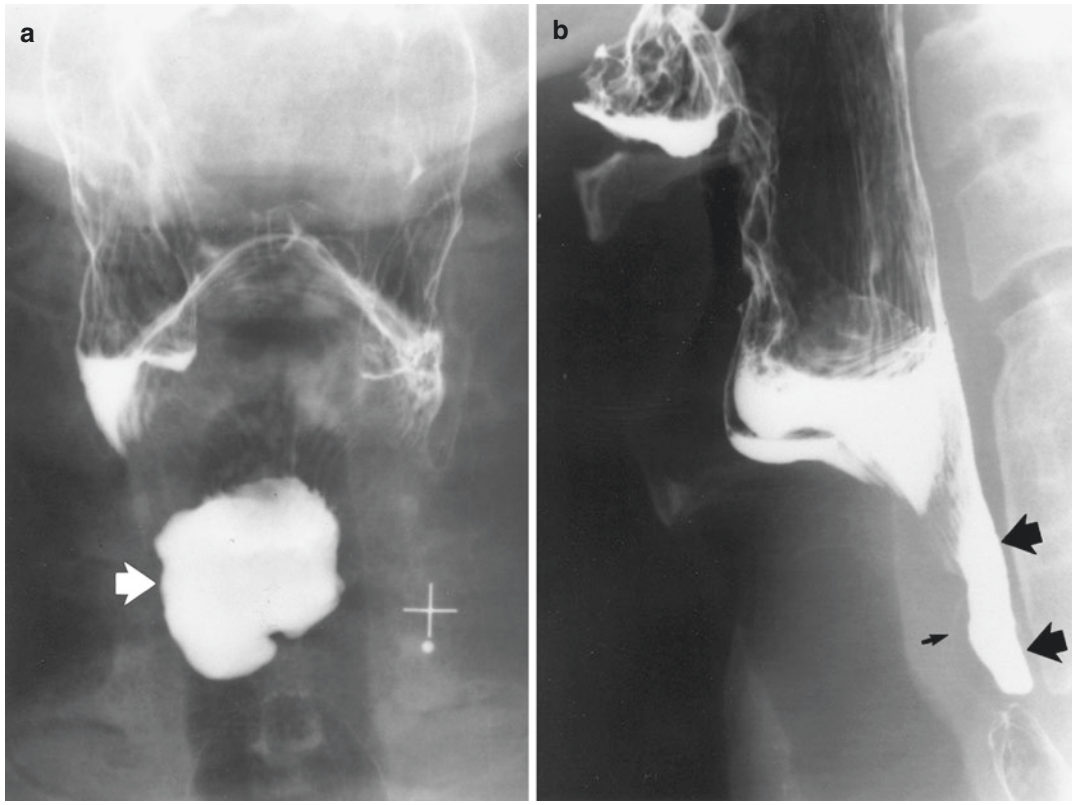


Fig. 12 Moderately large Zenker's diverticulum. (**a**) Spot radiograph obtained with the patient in the frontal position showing a 3 cm barium-filled sac (*arrow*) midline below the tips of the piriform sinuses. (**b**) Spot radiograph obtained with the patient in the lateral position showing a relatively flat, but long barium-filled sac (*large arrows*) posterior to the pharyngoesophageal segment and upper cervical esophagus (*small arrow*)

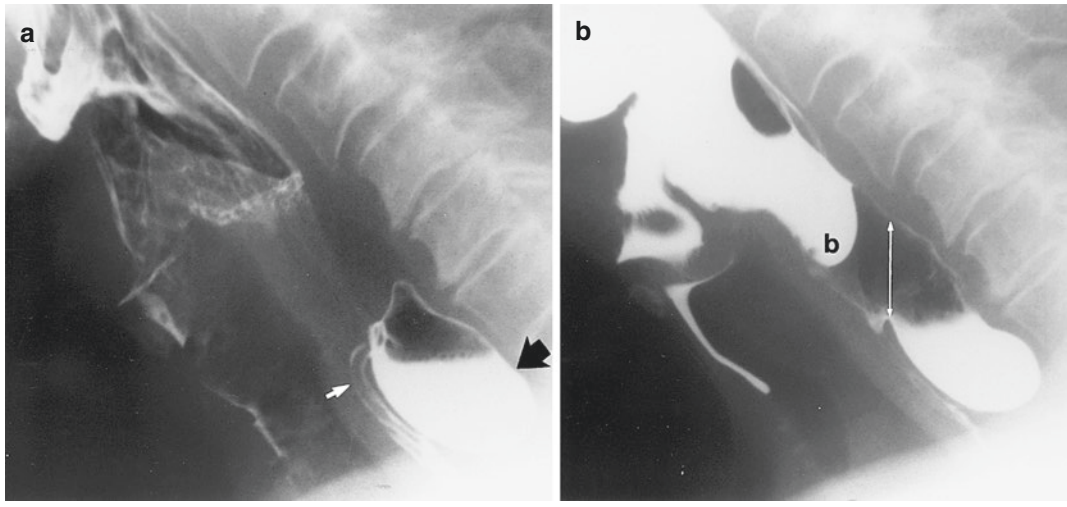


Fig. 13 Opening of a moderately large Zenker's diverticulum. (**a**) Spot radiograph obtained with the patient at rest and in the lateral position showing a 2 cm × 3 cm sac (*large arrow*) posterior to the pharyngoesophageal segment (*small arrow*) and upper cervical esophagus. (**b**) Spot radiograph obtained just as the bolus (*b*) had approached the pharyngoesophageal segment showing that the opening (*double arrow*) of the Zenker's diverticulum is very high, at least the height of one vertebral body. Barium entering the laryngeal vestibule was due to abnormal timing between the oral and pharyngeal phases of swallowing (**b** reproduced with permission from Rubesin 1991, Fig. 5c)

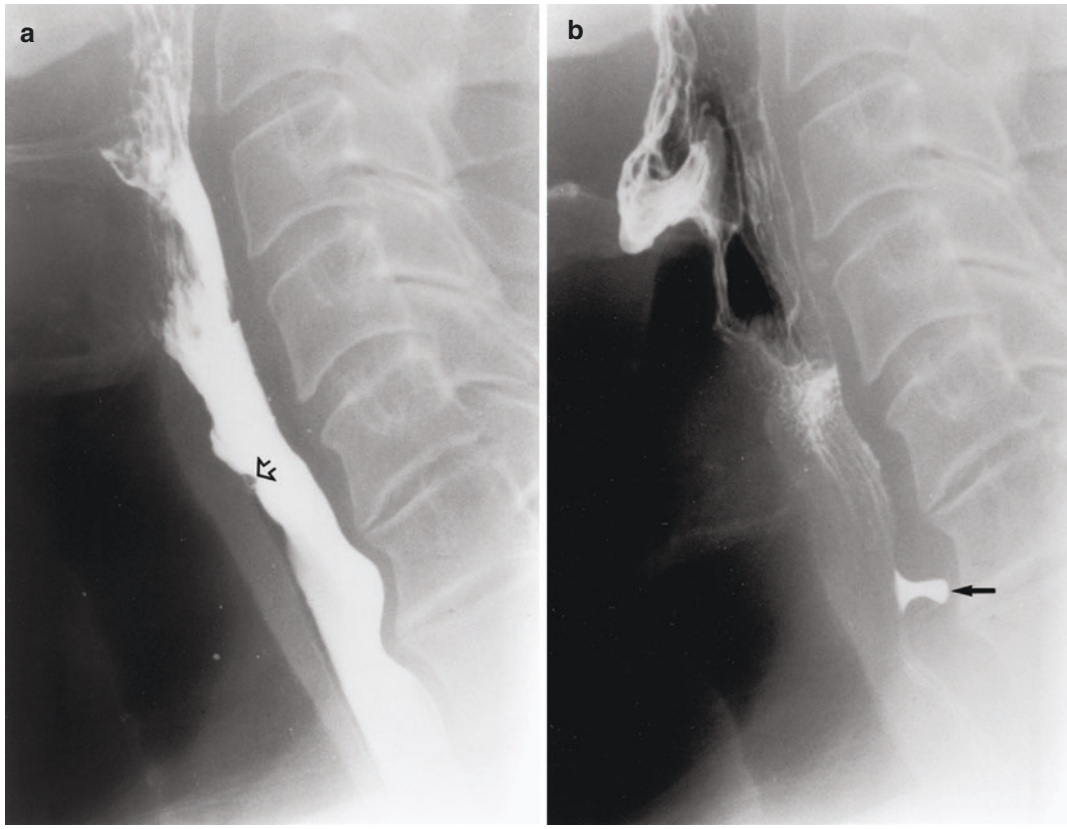
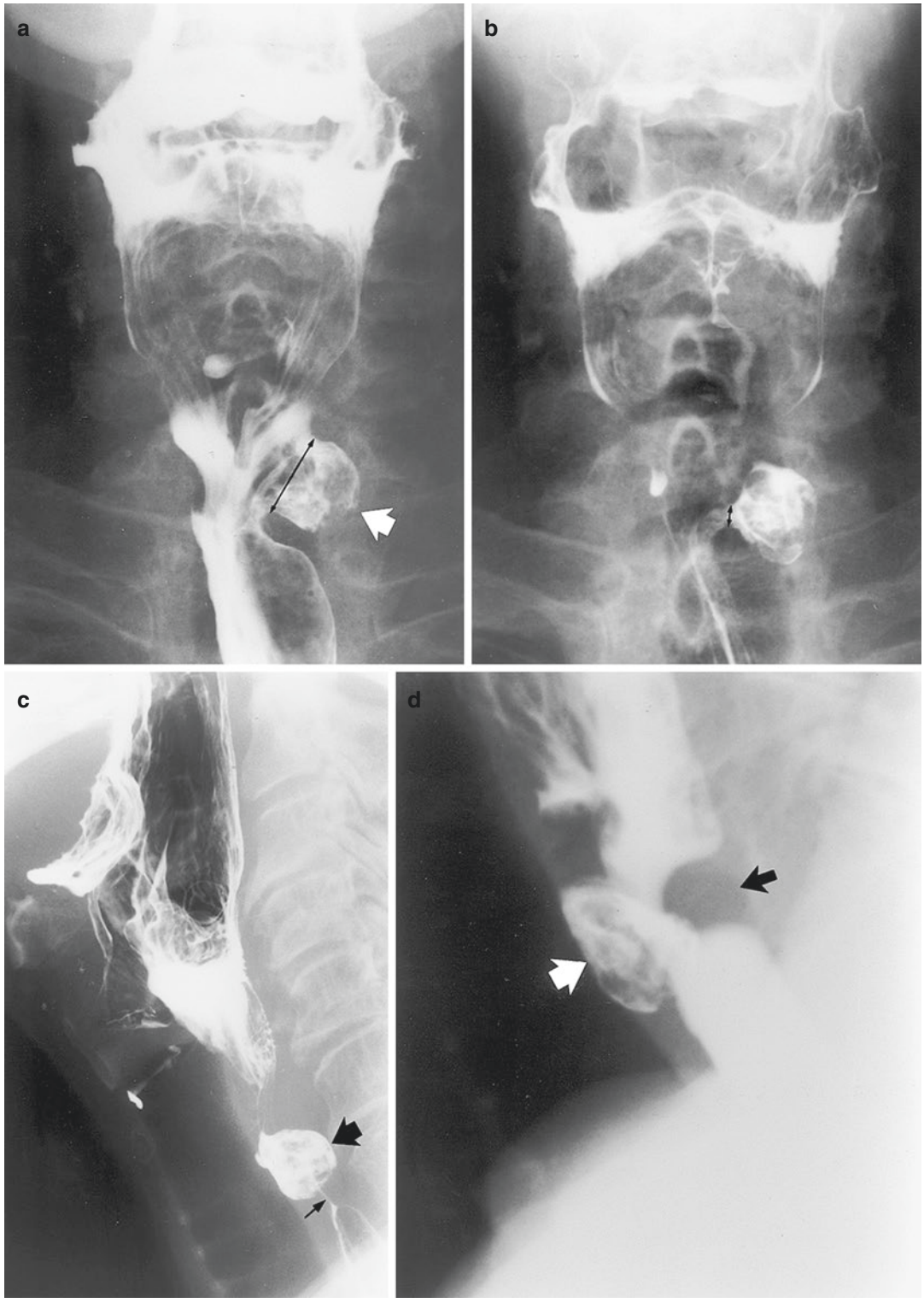


Fig. 14 Pseudo-Zenker's diverticulum. (**a**) Spot image obtained during swallowing showing no evidence of a diverticulum at the level of the cricoid cartilage, as identified by redundant postcricoid mucosa (*open arrow*). (**b**) Spot image obtained just after the swallow had passed showing barium trapped (*arrow*) above a cricopharyngeal bar that had closed early. Seconds later the pseudo-Zenker's diverticulum disappeared when the collection of barium entered the cervical esophagus

Fig. 15 Killian-Jamieson diverticula. (**a**) Spot radiograph obtained at the end of the swallow showing a 1.3 cm diverticulum (*thick arrow*) arising from the left lateral wall just below the level of the cricopharyngeal muscle. The neck (*double arrow*) of the diverticulum is broad during swallowing. (**b**) Spot radiograph obtained just after the bolus had passed showing a narrower neck (*double arrow*) of the diverticulum. (**c**) Spot radiograph obtained with the patient in the lateral position showing a 1.3 cm diverticulum (*large arrow*) below the level of the cricopharyngeal muscle. Part of the diverticulum lies anterior to the expected course of the pharyngoesophageal segment and upper cervical esophagus (*small arrow*). Barium in the laryngeal vestibule and proximal trachea was related to a pharyngeal motor disorder. (**d**) Spot radiograph obtained during swallowing demonstrating that part of the diverticulum (*white arrow*) lies anterior to the pharyngoesophageal segment. The presence of a prominent cricopharyngeal muscle (*black arrow*) demonstrates that the diverticulum lies below the cricopharyngeal muscle (reproduced with permission from Rubesin and Levine 2001, Fig. 1)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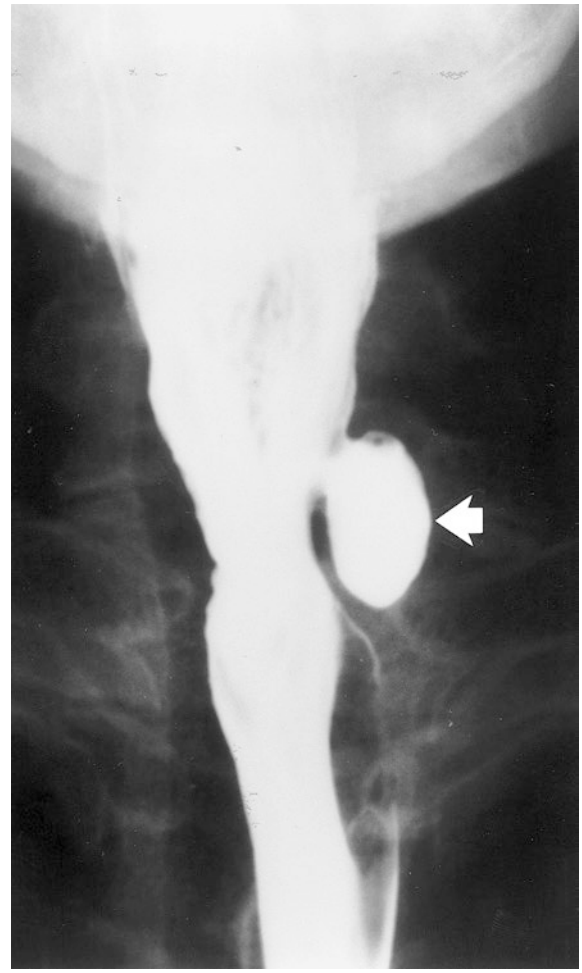

Fig. 16 Killian-Jamieson diverticulum. Spot radiograph obtained during swallowing showing a 1.5 cm barium-filled sac (*arrow*) arising from the left lateral wall near the pharyngoesophageal segment. After swallowing the orifice of the diverticulum was shown to be below the cricopharyngeal muscle (reproduced with permission from Rubesin and Levine 2001, Fig. 2)

bate edema and trigger acute respiratory arrest (Balfe and Heiken 1986). Smooth enlargement of the epiglottis and aryepiglottic folds allows plain-film diagnosis of severe epiglottitis.

Barium studies are usually not performed in immunocompetent patients with acute sore throat. In immunocompromised patients, barium studies are used to demonstrate the presence, type, and severity of esophagitis. Thus, in patients with AIDS, a double-contrast examination may demonstrate the small ulcers of herpetic pharyngitis or the plaques of *Candida* pharyngitis (Fig. 20) (Rubesin and Glick 1988). Acute inflammatory disorders may cause laryngeal penetration due to abnormal pharyngeal elevation, epiglottic tilt, or laryngeal closure.

Videopharyngography may be performed, however, on patients with acute odynophagia or dysphagia after trauma or suspected iatrogenic trauma. A nonionic water-soluble contrast agent is given first, followed by an ionic, water-soluble contrast agent if no laryngeal penetration is seen (Fig. 21). When no perforation is demonstrated with a water-soluble contrast agent, this author prefers to give high-density barium, as this form of barium sticks to the mucosal surface and is easier to detect in the extraluminal soft tissues than thin barium.

4.3 Chronic Inflammatory Conditions

In patients with acute corrosive ingestion, water-soluble contrast agent studies may be utilized to exclude perforation of the pharynx, esophagus,

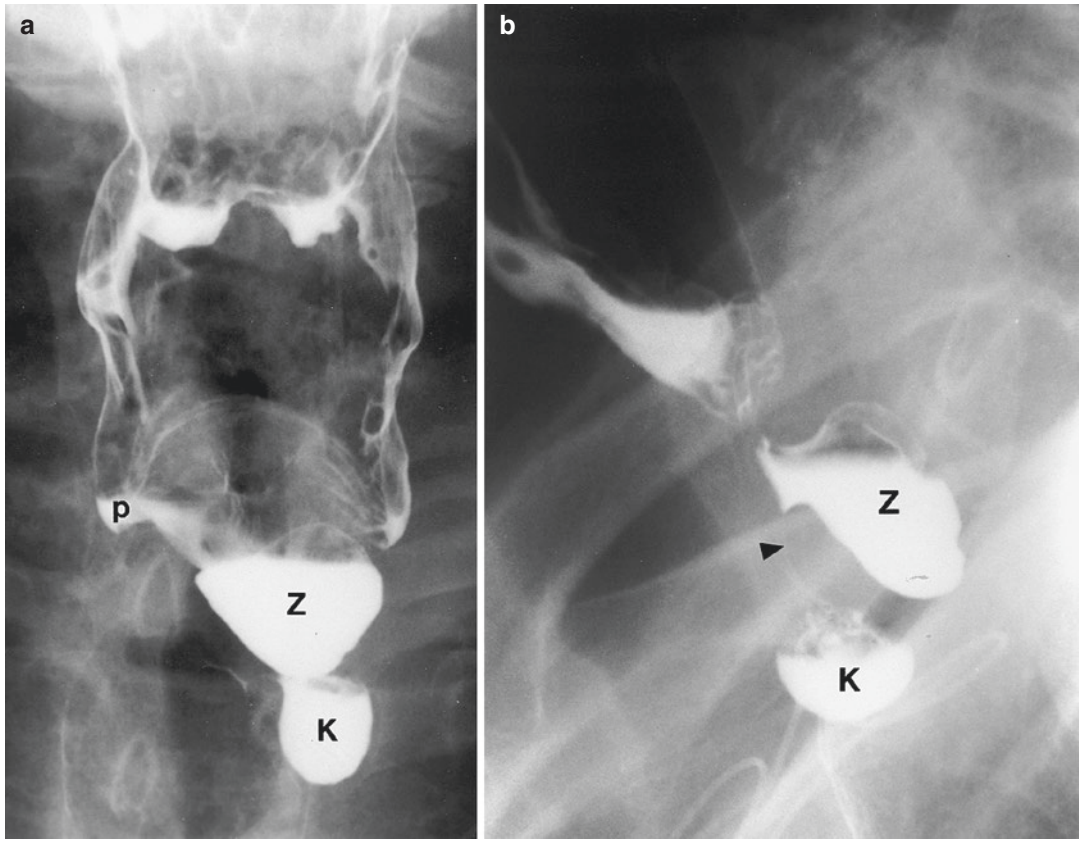

Fig. 17 Zenker's diverticulum and left lateral Killian-Jamieson diverticulum arising in the same patient. (**a**) Spot radiograph obtained with the patient in the frontal position demonstrating a 3 cm barium-filled Zenker's diverticulum (*Z*) positioned slightly to the left of the midline. Barium in the right piriform sinus (*p*) results from reflux of barium from the Zenker's diverticulum back into the hypopharynx. A 1.6 cm left lateral, barium-filled Killian-Jamieson diverticulum (*K*) lies below and to the left of the Zenker's diverticulum. (**b**) Spot radiograph obtained with the patient in a steep right posterior oblique position showing that the Zenker's diverticulum (*Z*) extends posterior to the pharyngoesophageal segment (*arrowhead*). Part of the Killian-Jamieson diverticulum (*K*) lies anterior to the course of the proximal cervical esophagus (reproduced with permission from Rubesin and Levine 2001, Fig. 3)

or stomach. Corrosive ingestion can result in amputation of the uvula and epiglottis and diffuse ulceration. With healing and scarring, epiglottic and pharyngeal wall deformity results in pharyngeal dysmotility (Fig. 22).

Aphthous stomatitis and oropharyngeal ulceration with subsequent scarring may be seen in Behçet's syndrome, bullous pemphigoid, epidermolysis bullosa, Reiter's syndrome, and Stevens-Johnson syndrome (Bosma et al. 1968; Kabakian and Dahmash 1978). Amputation of the uvula and tip of the epiglottis may be detected radiographically (Bosma et al. 1968).

4.4 Webs

Webs are thin folds of epithelium and lamina propria most frequently found on the anterior wall of the lower hypopharynx and proximal cervical esophagus (Clements et al. 1974). Pharyngeal and cervical esophageal webs are seen in 3–8% of patients undergoing an upper gastrointestinal examination and in up to 16% of patients on autopsy (Seaman 1967; Clements et al. 1974; Nosher et al. 1975; Ekberg 1981; Ekberg and Nylander 1983b). Some webs are the result of diseases that cause chronic inflamma-

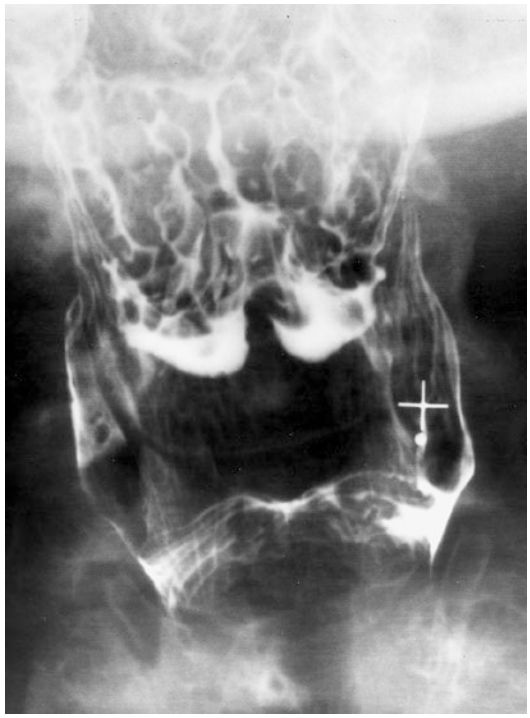

Fig. 18 Lymphoid hyperplasia, base of tongue. Frontal view showing many large, 5–7 mm nodules carpeting the surface of the base of the tongue (reproduced with permission from Rubesin et al. 1987a, Fig. 9c)

tion and scarring, such as epidermolysis bullosa and benign mucous membrane pemphigoid. Webs in the valleculae or piriform sinuses may be normal variants (Ekberg et al. 1986). This author believes that some cervical esophageal webs are related to chronic gastroesophageal reflux, similar to the association of distal esophageal webs and gastroesophageal reflux disease (Weaver et al. 1984). The association of cervical esophageal webs, iron-deficiency anemia, and pharyngeal or esophageal carcinoma—the Plummer–Vinson or Patterson–Kelly syndrome—is controversial (Waldenstrom and Kjellberg 1939; Mcnab-Jones 1961).

Webs are manifested radiographically as 1–2 mm in height, shelflike radiolucent filling defects on the anterior wall of the pharyngoesophageal segment or proximal cervical esophagus. Larger webs may protrude deeply into the lumen or extend circumferentially around the wall of the cervical esophagus (Fig. 23). Dilatation of the pharynx or cervical esophagus proximal to the web or a stream of barium spurting through the web (the "jet phenomenon") is a sign of partial obstruction and is usually seen in symptomatic patients (Shauffer et al. 1977; Taylor et al. 1990). Webs should not be confused with redundant mucosa just posterior to the cricoid cartilage or a prominent cricopharyngeal muscle (Fig. 24).

5 Tumors

5.1 Benign Tumors

A wide variety of benign tumors originate in the pharynx (Hyams et al. 1988; Bachman 1978). Retention cysts are lined by squamous epithelium and filled with desquamated debris. These cysts are the most common benign tumors of the base of the tongue (Fig. 25) and aryepiglottic folds (Fig. 26) (Bachman 1978). Ectopic thyroid tissue, thyroglossal duct cysts, granular cell tumors, and benign tumors of minor mucoserous salivary gland origin also arise in the base of the tongue. Saccular cysts of the aryepiglottic folds are the mucus-filled variant of internal laryngoceles, arising from mucous-secreting glands of the appendix of the laryngeal ventricle. Lipomas, neurofibromas, granular cell tumors, and oncocytomas rarely also are seen in the aryepiglottic folds (Mannsson et al. 1978; Patterson et al. 1981; Hyams et al. 1988). Tumors related to neurofibromatosis (von Recklinghausen's disease) typically occur in the aryepiglottic folds (Fig. 27) and arytenoid cartilages (Chang-Lo 1977). Chondromas may originate in the posterior lamina of the cricoid cartilage (Hyams and Rabuzzi 1970).

Benign pharyngeal tumors are usually sessile submucosal masses, appearing radiographically *en face* as smooth, round, sharply circumscribed protrusions (see Fig. 26) and in profile as hemispheric lines with abrupt angulation to the luminal contour (see Fig. 25) (Balfe and Heiken 1986). Pedunculated tumors such as lipoma, papilloma, and fibrovascular polyp are uncommon.

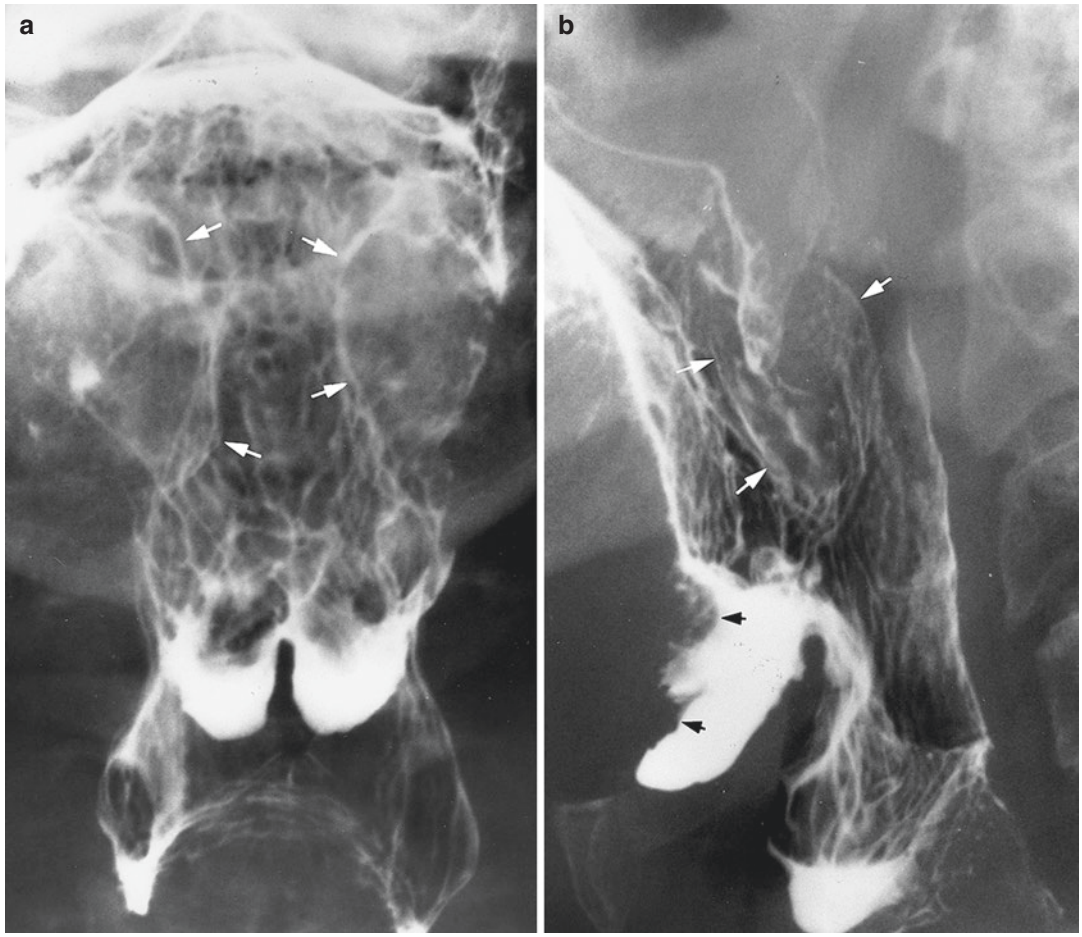

Fig. 19 Lymphoid hyperplasia of palatine tonsils and the base of the tongue. (**a**) Frontal view demonstrating large left and right palatine tonsils (*arrows*) protruding into the oropharynx. The reticular surface of the base of the tongue is slightly prominent and the nodules are slightly enlarged. (**b**) Lateral view obtained while the patient sang "Eeee …" showing a slightly nodular mass (*white arrows*) in the tonsillar fossa. Several nodules (*black arrows*) protrude into the barium pooling in the valleculae (reproduced with permission from Rubesin 1994, Fig. 17.12)

5.2 Squamous Cell Carcinoma

Squamous cell carcinomas constitute 90% of malignant pharyngeal lesions (Hyams et al. 1988; Cunningham and Catlin 1967). Multiple primary sites of squamous carcinoma are found in the oral cavity, pharynx, larynx, esophagus, and lung in more than 20% of patients (Carpenter et al. 1976). Between 1 and 20% of patients with a head and neck squamous cell carcinoma will subsequently develop an esophageal squamous cell carcinoma (Goldstein and Zornoza 1978; Thompson et al. 1978).

Squamous cell carcinoma may be initially detected in patients undergoing pharyngoesophagography for pharyngeal symptoms or a palpable neck mass. The symptoms are usually of short duration and include sore throat, dysphagia, odynophagia, choking, or coughing. Hoarseness occurs in patients with laryngeal carcinoma, supraglottic cancers, or tumors infiltrating the arytenoid cartilage and medial pharyngeal wall. Most patients are 50–70 years of age and almost all abuse alcohol and tobacco. Some tumors may be caused by human papilloma virus infection.

In patients with known pharyngeal carcinoma, pharyngoesophagography assists in planning

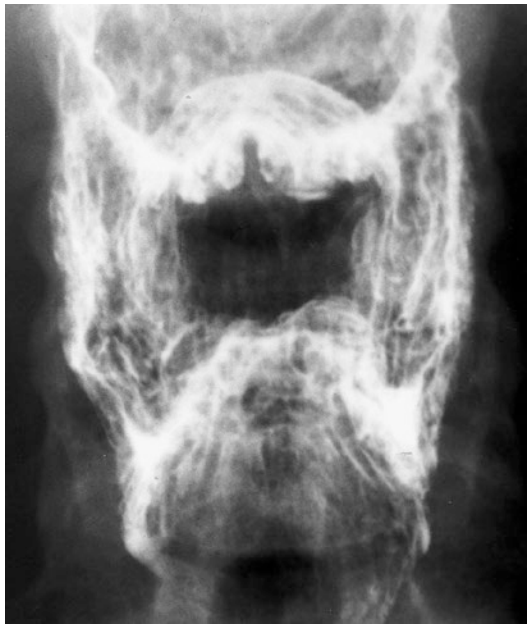

Fig. 20 *Candida* pharyngitis. Frontal view of the pharynx showing numerous small nodules etched in white by barium. The nodules carpet the pharynx (reproduced with permission from Rubesin 2000c, Fig. 15.14)

patient workup and therapy. A pharyngogram establishes baseline motility and helps define the size, extent, and inferior border of the tumor. Barium examination can exclude a synchronous esophageal tumor or a structural disorder (Zenker's diverticulum) that may change the way endoscopy is performed or the patient is treated. Pharyngography cannot be used to screen for pharyngeal cancer, as small, flat tumors can be missed in the region of the palatine tonsils or the base of the tongue, areas of normal mucosal nodularity. Below the pharyngoesophageal fold, however, barium studies detect 95% of structural abnormalities (Semenkovich et al. 1985). Barium studies are especially valuable in the deep valleculae, lower hypopharynx, and pharyngoesophageal segment, areas that are difficult to visualize on endoscopy (Fig. 28).

The radiographic findings of pharyngeal cancer are similar to those for tumors elsewhere in the gastrointestinal tract (Rubesin and Glick 1988). A mass protruding intraluminally may be manifested as loss of the normal expected contour, a focal area of increased radiodensity replacing the original air of the lumen, extra barium-coated lines protruding into the pharyngeal air column (Fig. 29), or a radiolucent filling defect in the barium pool (Fig. 30) (Jing 1970; Balfe and Heiken 1986; Rubesin 2000a; Rubesin and Laufer 1991). Mucosal ulceration is manifested as shallow pools of barium. Surface irregularity is manifested as a granular, finely nodular, or lobulated surface texture (Fig. 31). Asymmetric motion may result from fixation of structures due to infiltrating tumor (Fig. 32). Asymmetric distensibility may result from an extrinsic mass impinging on the pharynx. In some patients with pharyngeal carcinoma, a focal area of mucosal nodularity is the only radiographic finding (Figs. 33 and 34).

The palatine tonsil is the most frequent site of pharyngeal squamous cell carcinoma. Exophytic tumors are easily seen in barium studies. Small infiltrative or ulcerative tumors may be missed in the normally nodular surface of the palatine tonsils. Tonsillar tumors spread to the soft palate, base of the tongue, and posterior pharyngeal wall. Cervical nodal metastases are found in half of patients (Balfe and Heiken 1986).

Squamous cell cancers of the base of the tongue often present as deeply infiltrative, advanced lesions with nodal metastases (Frazell and Lucas 1962; Strong 1979). Lymph node metastases are detected ipsilaterally or bilaterally in more than 70% of patients. Exophytic lesions protrude into the oropharyngeal air space (Jimenez 1970; Apter et al. 1984). Ulcerated lesions appear as irregular barium collections extending deep to the expected contour of the base of the tongue. Tumor spreads to the palatine tonsil, valleculae, or pharyngoepiglottic fold. Small plaquelike or ulcerative lesions may be hidden in the valleculae or in the recess between the tongue and tonsil.

Supraglottic carcinomas are tumors that arise in the epiglottis (see Fig. 30), aryepiglottic folds, mucosa overlying the muscular processes of the arytenoid cartilages (see Fig. 32), false vocal cords, and laryngeal ventricles. Supraglottic carcinomas spread rapidly through the rich lymphatic network of the supraglottic space. Ulcerative lesions penetrate the tongue, vallecu-

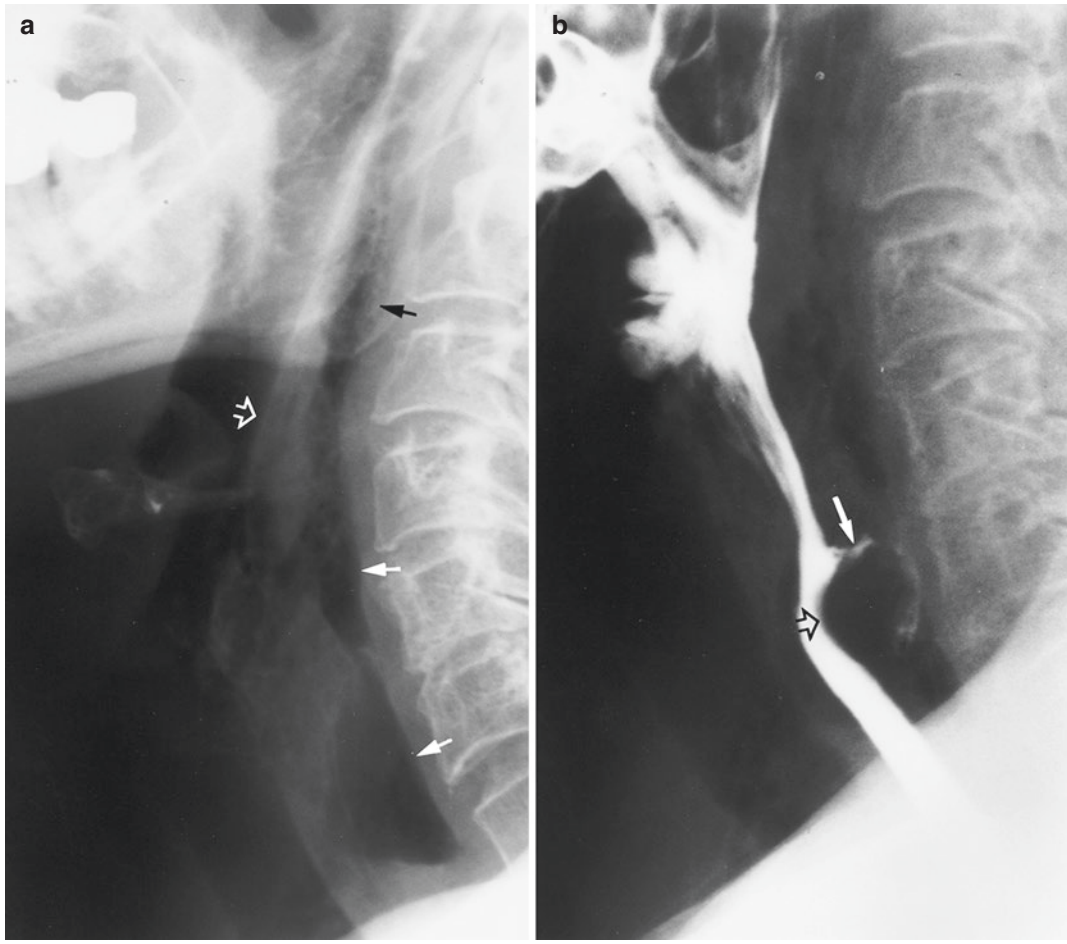

Fig. 21 Acute perforation during endoscopy. (**a**) Scout radiograph showing a large amount of air (arrows) in the retropharyngeal space. The posterior wall of the pharynx (*open arrow*) is deviated anteriorly. (**b**) Spot radiograph obtained while the patient swallowed water-soluble contrast agent showing a small spurt of contrast agent (*arrow*) just above the cricopharyngeal muscle (*open arrow*). The contrast agent spreads in the retropharyngeal space

lae, pre-epiglottic space, pharyngoepiglottic folds, and lateral pharyngeal walls (Seaman 1974). A paucity of lymphatics near the true vocal cords limits the spread of supraglottic tumors through the laryngeal ventricles into the true vocal folds. Cervical lymph node metastases are found in 30–50% of patients (Balfe and Heiken 1986; Kirchner and Owen 1977).

Piriform sinus carcinomas are bulky, exophytic lesions that spread quickly and metastasize widely. Medial wall tumors spread to the aryepiglottic fold, arytenoid and cricoid cartilages, and paraglottic space (Jing 1970; Johnson et al. 1995). Lateral wall tumors (see Fig. 33) may invade the thyrohyoid membrane, thyroid cartilage, and soft tissues of the neck, including the carotid sheath (Zbaren and Egger 1997). Lymph node metastases are found in 70–80% of patients (Balfe and Heiken 1986; Silver 1977).

Carcinomas of the posterior pharyngeal wall are typically long fungating lesions that may spread vertically into the nasopharynx or cervical esophagus. Jugular or retropharyngeal lymphatic metastases are found in 50% of patients (Carpenter et al. 1976).

Postcricoid squamous cell carcinomas are uncommon, annular, infiltrating lesions that may extend into the hypopharynx or cervical esopha-

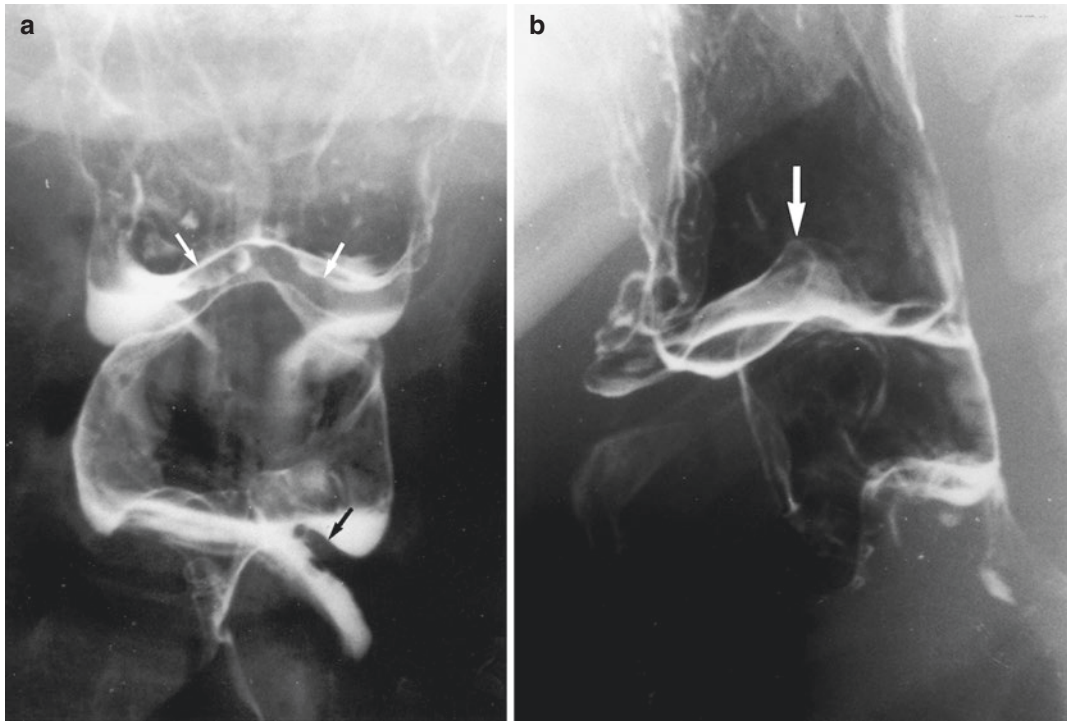

Fig. 22 Sequelae of corrosive ingestion. Twenty years prior to this examination, the patient had ingested lye. (**a**) Frontal view demonstrating a low and easily seen epiglottis (*white arrows*). The right piriform sinus is contracted; the left piriform sinus has a radiolucent band representing a scar (*black arrow*) crossing its lower portion. (**b**) Lateral view showing that the truncated epiglottis (*arrow*) is displaced posteriorly. A small amount of barium coats the anterior wall of the laryngeal vestibule (reproduced with permission from Rubesin 2000a, Fig. 4.20)

gus (see Fig. 28). In Scandinavia, these are the tumors that have been associated with Plummer–Vinson syndrome.

5.3 Lymphoma

Lymphomas constitute about 10% of pharyngeal malignancies (Banfi et al. 1970). Almost all pharyngeal lymphomas are non-Hodgkin's lymphoma, arising in the palatine or lingual tonsils or the adenoids. Pharyngeal involvement in Hodgkin's disease occurs in only 1–2% of patients, despite the fact that Hodgkin's disease often begins in cervical lymph nodes (Todd and Michaels 1974).

Lymphoma of the pharynx occurs in the palatine tonsils in 40–60% of patients, the nasopharynx in 18–28% of patients, and the base of the tongue in 10% of patients (Hyams et al. 1988; Al-Saleem et al. 1970). Multiple sites of involvement are seen in 25% of patients. Fifteen percent of patients have bilateral palatine tonsillar involvement (Banfi et al. 1970). Lymphomas only rarely arise in the hypopharynx. At the time of initial diagnosis, the cervical lymph nodes are involved in 60% of patients, and 10% of patients have extranodal involvement.

Pharyngeal lymphomas typically appear as large, lobulated masses involving the nasopharynx, palatine tonsil (Fig. 35), base of the tongue, or a combination of these locations (Fig. 36) (Hyams et al. 1988; Rubesin 2000b, c). The bulging submucosal masses obliterate the normal lymphoid follicular pattern of the base of the tongue or palatine tonsil (Rubesin 2000c).

5.4 Other Malignant Tumors

The minor mucoserous salivary glands scattered deep to the epithelial layer of the pharynx give

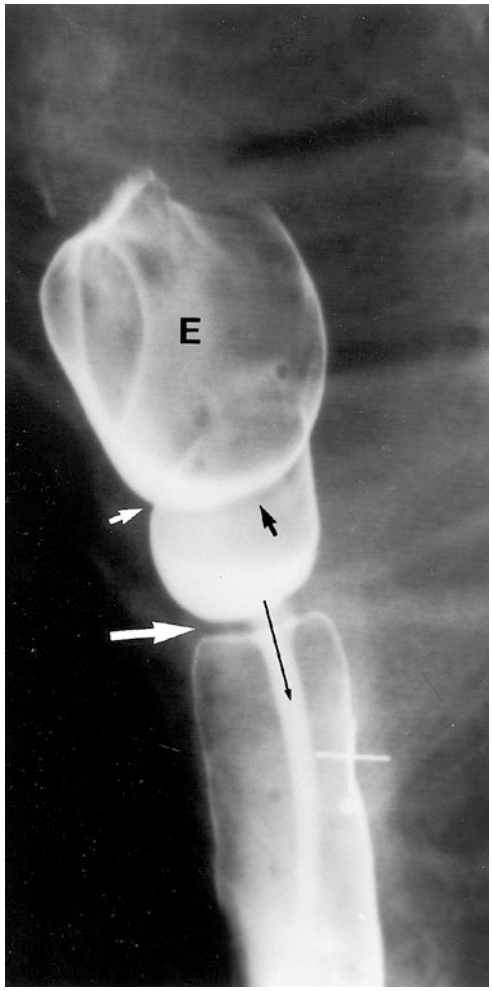

Fig. 23 Cervical esophageal webs. Spot radiograph obtained with the patient in an erect slightly right posterior oblique position showing two circumferential webs in the cervical esophagus. The upper web (*short white and black arrows*) is circumferential and only mildly compromises the lumen. The lower web (*large white arrow*) is also circumferential, but occludes more than two-thirds of the luminal diameter. Partial obstruction is manifested by dilatation of the proximal cervical esophagus (*E*) and the "jet phenomenon," barium spurting (*long black arrow*) through the web (reproduced with permission from Rubesin 1995, Fig. 1)

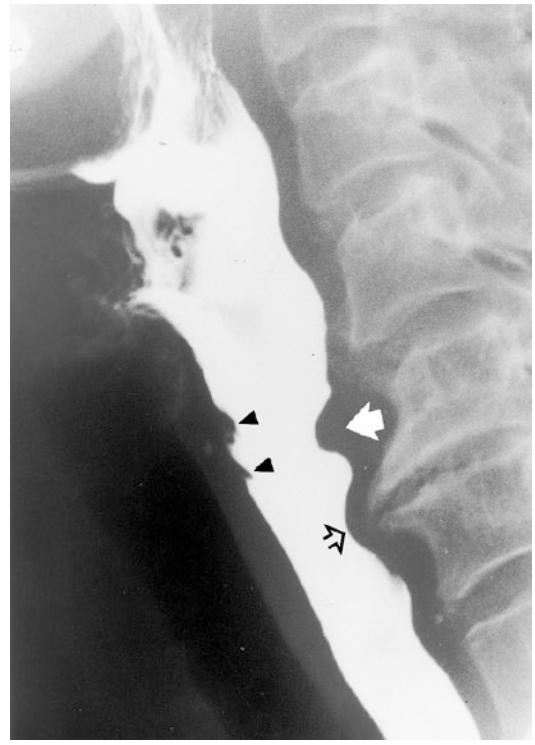

Fig. 24 Postcricoid mucosa, prominent cricopharyngeal muscle, and cervical osteophyte impression. Spot radiograph obtained while the patient was drinking demonstrating osteophytes mildly impressing the upper cervical esophagus (*open black arrow*). Also note a mildly prominent cricopharyngeal muscle (*white arrow*) and redundant mucosa posterior to the cricoid cartilage (*arrowheads*). None of these entities should be confused with cervical esophageal webs (reproduced with permission from Rubesin 1995, Fig. 7)

rise to tumors of diverse histologic characteristics and clinical course. Most (65–88%) minor salivary gland tumors are malignant (Spiro et al. 1973; Conley and Dingman 1974). The most frequent malignant minor salivary tumors are adenoid cystic carcinoma (35%), solid adenocarcinoma (22%) (Fig. 37), and mucoepidermoid carcinoma (16%) (Spiro et al. 1973). Most pharyngeal minor salivary tumors arise in the soft palate. Palatal salivary gland tumors spread directly to the tongue, submandibular gland, mandible, and lingual and hypoglossal nerves. Adenoid cystic carcinoma typically spreads via a perineural route. Cervical metastases are infrequent, occurring in 23% of patients with malignant minor salivary tumors.

Synovial sarcomas of the pharynx are extremely rare (Krugman et al. 1973). These lesions are large, bulky tumors involving the larynx, pharynx, and soft tissues of the neck (Gatti et al. 1975).

Kaposi sarcoma may be detected in the pharynx in patients with AIDS. Kaposi sarcoma has a wide range of radiographic appearances, including small nodules, plaquelike lesions, small sub-

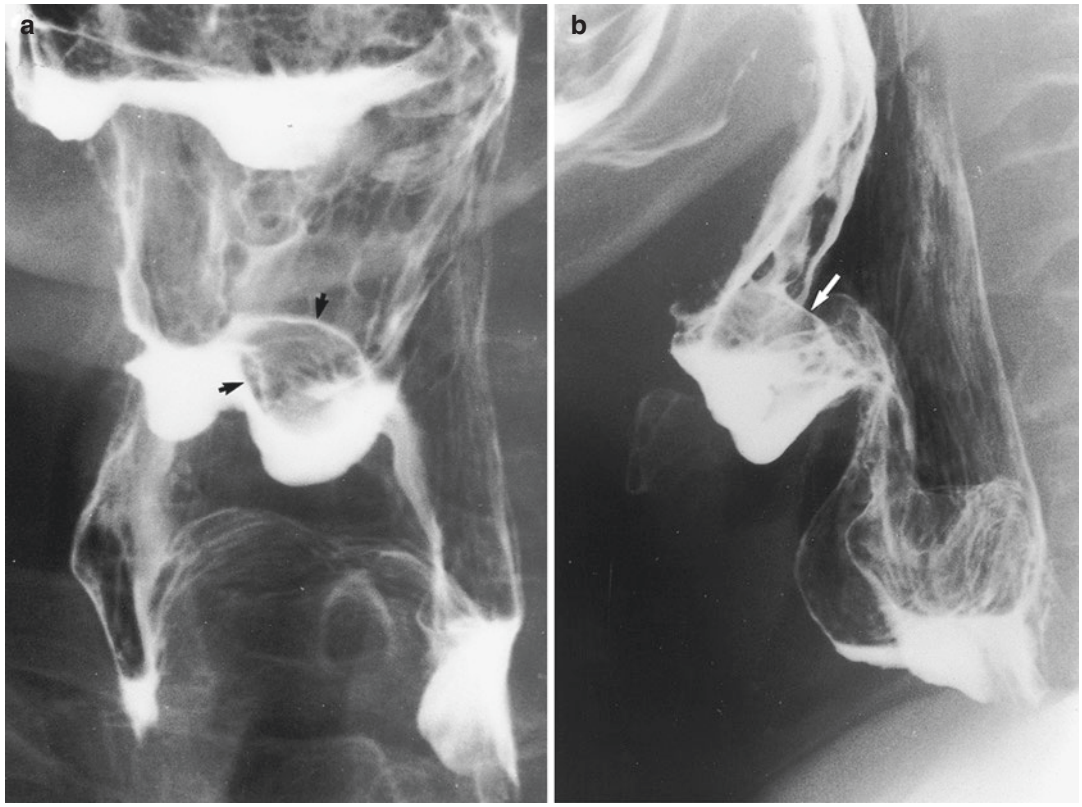

Fig. 25 Retention cyst, left vallecula. (**a**) Spot radiograph obtained with the patient in a slightly right posterior oblique position showing an ovoid, 1.5 m radiolucent filling defect (*arrows*) in the barium pool of the left vallecula. (**b**) Lateral view showing an ovoid area of increased radiodensity (*arrow*) etched by barium

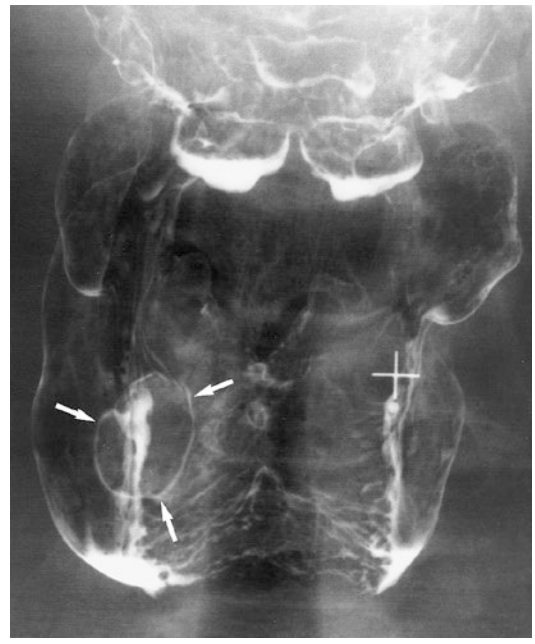

Fig. 26 Retention cyst arising in mucosa overlying the muscular process of the right arytenoid cartilage. A ring shadow (*arrows*) surrounding a 1.7 cm smooth-surfaced area of increased radiodensity is seen. This lesion had been missed on two previous endoscopies (reproduced with permission from Rubesin and Glick 1988, Fig. 25a)

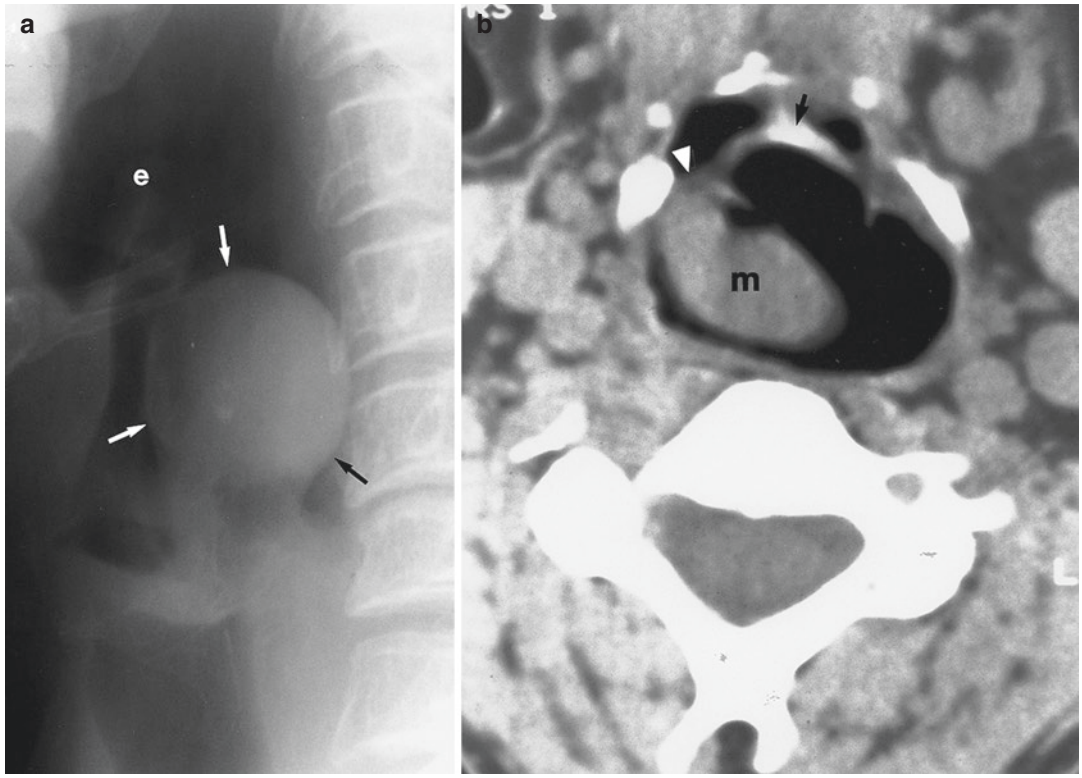

Fig. 27 Neurofibroma in 27-year-old-man with known neurofibromatosis and stridor. (**a**) Plain radiograph of the neck obtained with the patient in the lateral position showing a large, round soft-tissue mass (*arrows*) near the aryepiglottic folds. The epiglottic tip (*e*) is identified. (**b**) Axial image from CT scan showing a soft-tissue mass (*m*) arising from the right aryepiglottic fold (*arrowhead*). The tip of the epiglottis (*small arrow*) is calcified (**a** reproduced with permission from Rubesin 1991, Fig. 1a; **b** reproduced with permission from Rubesin 1994, Fig. 17.17b)

mucosal masses with or without central ulceration, and larger polypoid masses (Fig. 38) (Emery et al. 1986).

The pharynx may be invaded by a variety of tumors arising in the laryngeal cartilages, most frequently the cricoid cartilage. These cartilaginous tumors include chondroma, osteochondroma, and chondrosarcoma (Huizenga and Balogh 1970). Radiographically, the lower hypopharynx and pharyngoesophageal segment is compressed by a smooth-surfaced mass arising in the posterior lamina of the cricoid cartilage. In more than 80% of patients, stippled calcification is detected centrally or peripherally (Hyams et al. 1988).

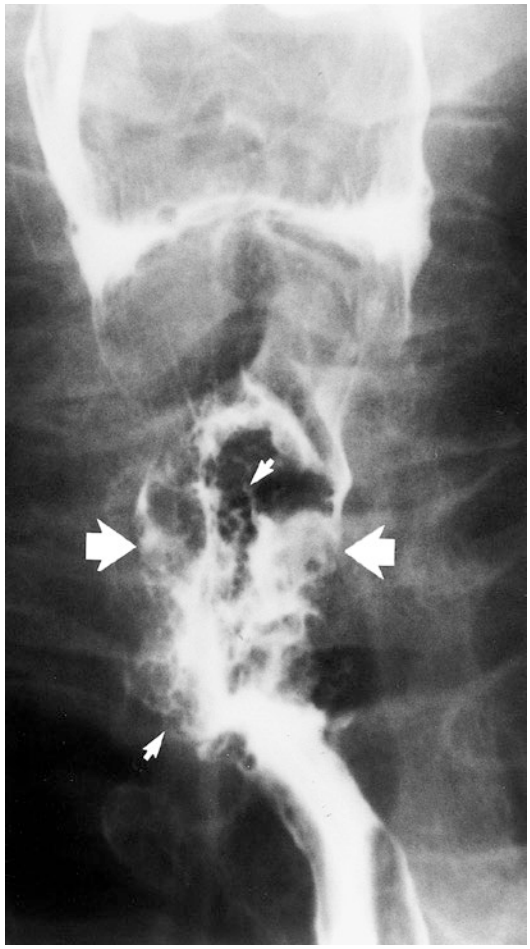

Fig. 28 Carcinoma of the pharyngoesophageal segment missed on ENT endoscopy. Spot radiograph showing mucosal nodularity (representative areas of nodularity identified by *small arrows*) involving the distal hypopharynx, pharyngoesophageal segment, and upper cervical esophagus. The pharyngoesophageal segment is expanded (*large arrows*) by tumor. This patient had two ENT endoscopies within 6 months of the pharyngoesophagram

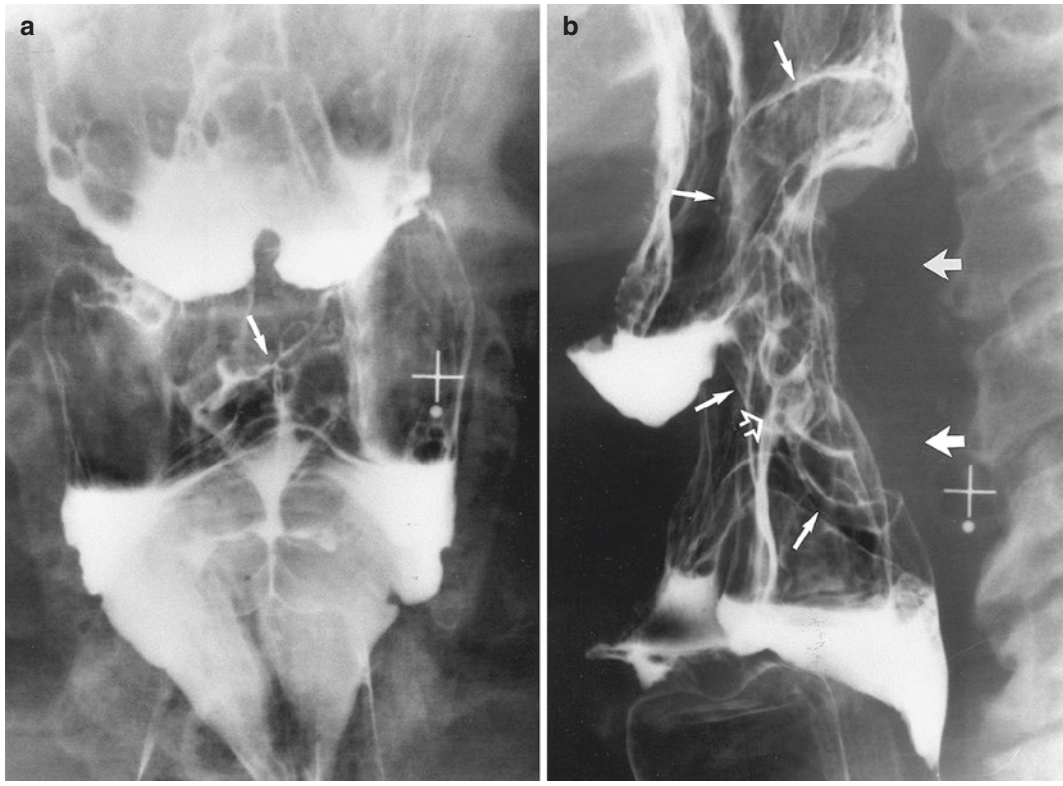

Fig. 29 Radiographic findings of pharyngeal cancer and the value of obtaining multiple projections. (**a**) Frontal view of the pharynx showing a few barium-etched nodules in the upper hypopharynx (*arrow*). Aspirated barium coats the false and true vocal cords. There is moderate stasis in the hypopharynx. (**b**) Lateral view demonstrating a large mass arising from the posterior pharyngeal wall as the explanation for the subtle mucosal nodularity seen on the frontal view. The mass is manifested as loss of the normal contour and soft-tissue density partially replacing the air shadow of the lower oropharynx and upper hypopharynx (*large arrows*), barium-etched lines within the lumen (*thin arrows*), and focal mucosal nodularity (*open arrow*). Barium coating the laryngeal vestibule and upper trachea and stasis in the lower hypopharynx is the result of pharyngeal dysmotility (reproduced with permission from Rubesin and Glick 1988, Fig. 30a, b)

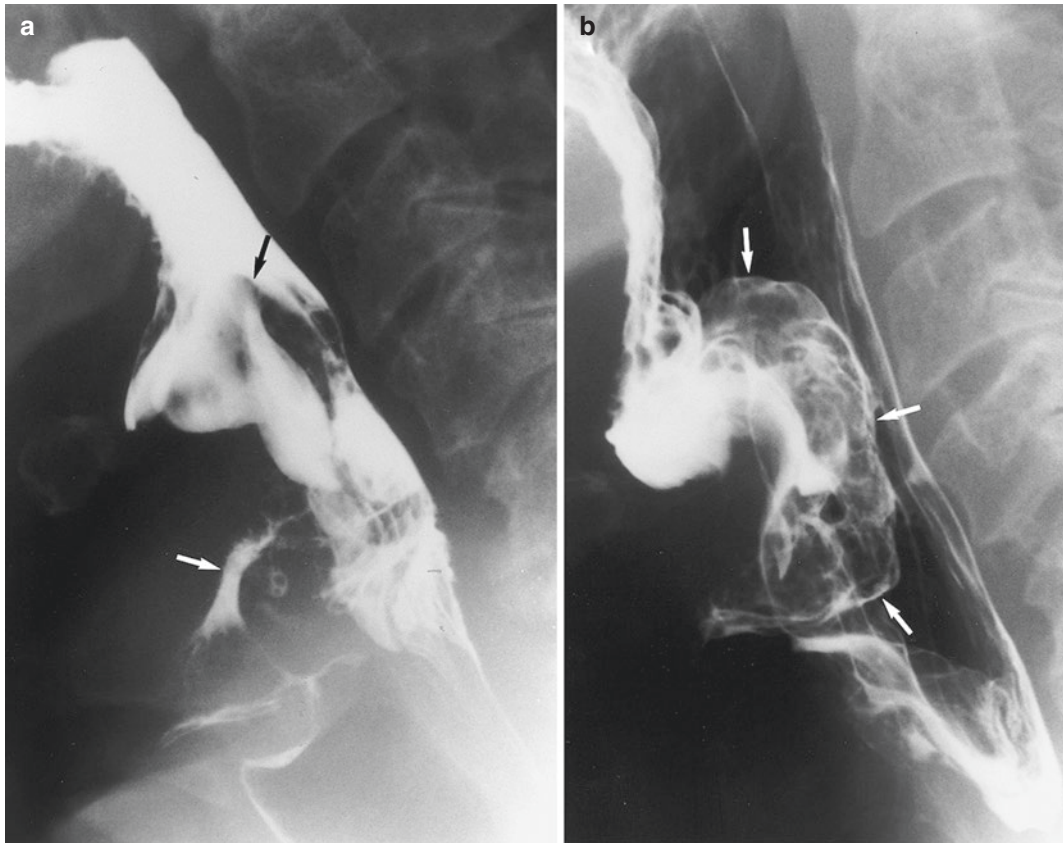

Fig. 30 Spot radiographs versus dynamic imaging in a patient with large supraglottic carcinoma. (**a**) Image obtained during dynamic imaging showing lack of epiglottic tilt (*black arrow*) and probable epiglottic enlargement. Barium enters the laryngeal vestibule (*white arrow*) during swallowing, with subsequent coating of the laryngeal ventricle and trachea. (**b**) Spot radiograph demonstrating massive enlargement of the epiglottis (*arrows*). The epiglottic mucosa is markedly nodular. These images show how spot radiographs demonstrate morphology better than dynamic images, but dynamic images demonstrate motility (reproduced with permission from Rubesin 1991, Fig. 11c, d)

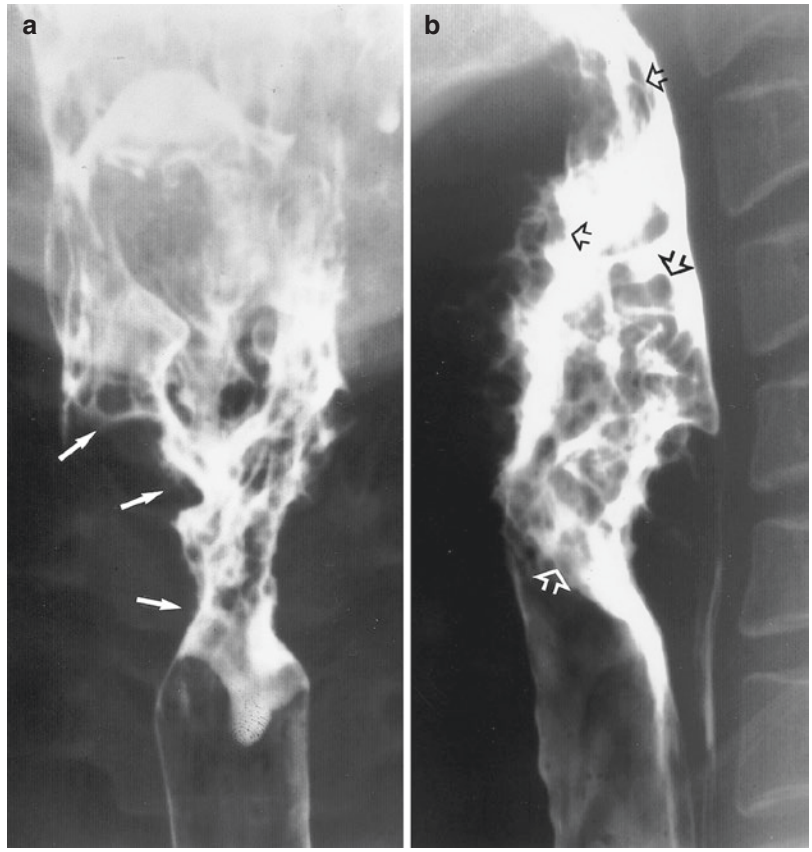

Fig. 31 Mucosal nodularity as a sign of cancer. (**a**) Frontal view showing diffuse narrowing of the lumen (*arrows*) of the lower hypopharynx, pharyngoesophageal segment, and upper cervical esophagus. The normal tips of the piriform sinuses are obliterated. (**b**) Lateral view obtained while the patient was drinking showing numerous radiolucent nodules (representative nodules identified by *arrows*) in the barium bolus. The tumor involves the base of the tongue, the anterior wall of the laryngeal vestibule, the entire glottis, and the anterior wall of the lower hypopharynx

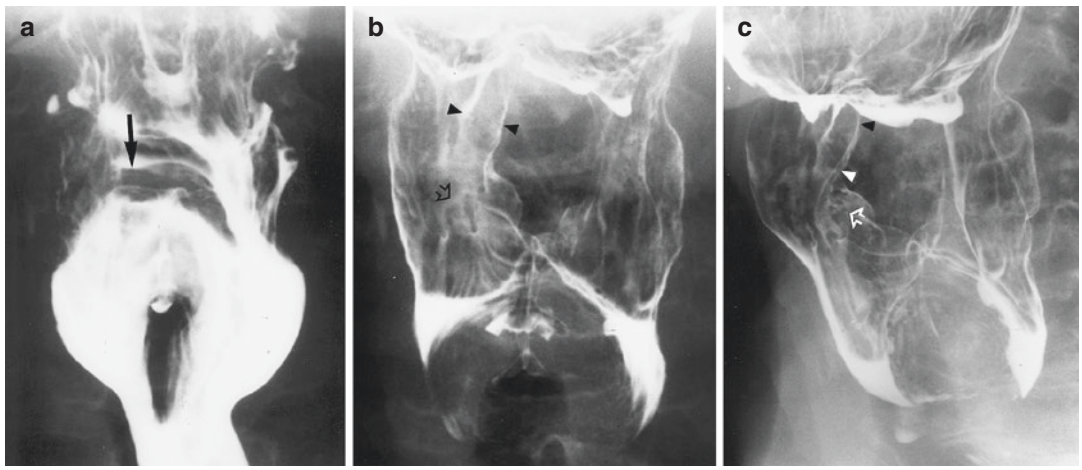

Fig. 32 Value of spot radiographs. (**a**) Frontal view obtained at the end of bolus passage through the pharynx showing diminished epiglottic tilt on the right (*arrow*). (**b**, **c**) Spot radiographs obtained in frontal (**b**) and slight right posterior oblique (**c**) positions showing moderate thickening of the right aryepiglottic fold (*arrowheads*), mild enlargement, and tumor nodularity involving the mucosa overlying the muscular process of the right arytenoid cartilage (*open arrow*) (reproduced with permission from Rubesin 1991, Fig. 12a–c)

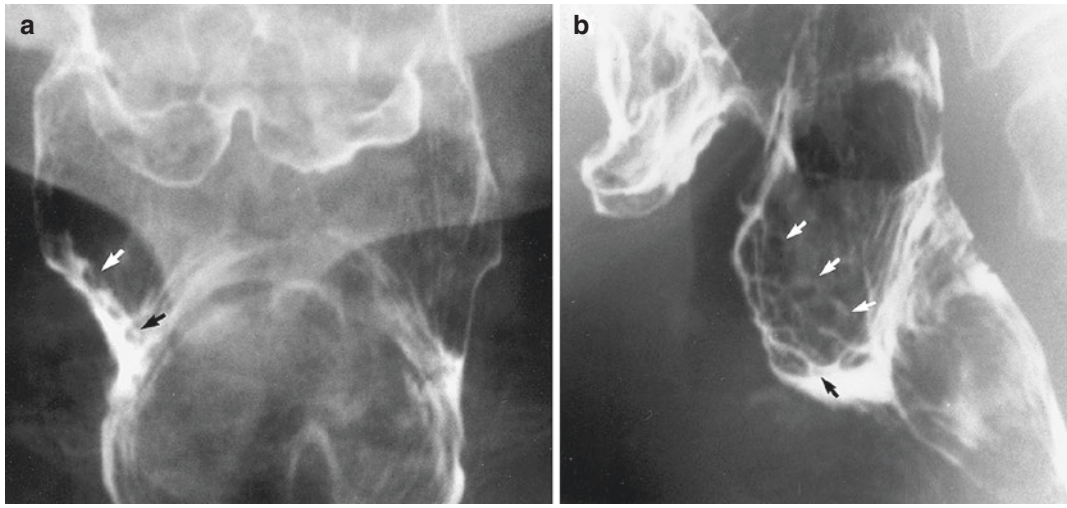

Fig. 33 Early squamous cell carcinoma manifested as tumor nodularity. (**a**) Frontal view showing subtle, focal nodularity (*arrows*) in the lower right piriform sinus. (**b**) Lateral view demonstrating a focal area of nodularity along the anterior wall of the hypopharynx (*arrows*). This 64-year-old woman had a tip of the tongue squamous cell carcinoma and was being studied to exclude an esophageal carcinoma prior to surgery (reproduced with permission from Levine Levine and Rubesin 1990a, Fig. 4)

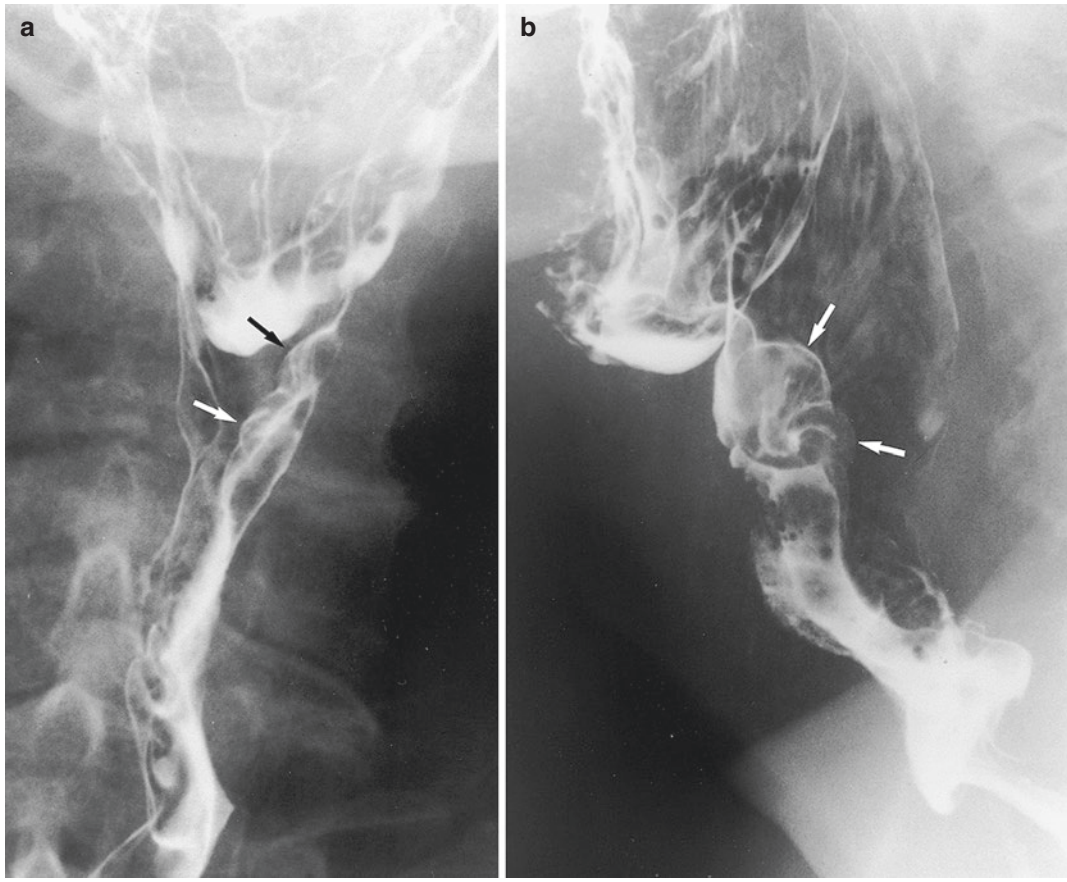

Fig. 34 Recurrent squamous cell carcinoma 2 years after total laryngectomy and radiation therapy. (**a**) Frontal view showing large nodules (*arrows*) altering the normally smooth contour of the neopharyngeal tube. (**b**) Lateral view showing a mass (*arrows*) etched in white by barium just below the level of the neovalleculae. The posterior neopharyngeal wall is poorly coated by barium

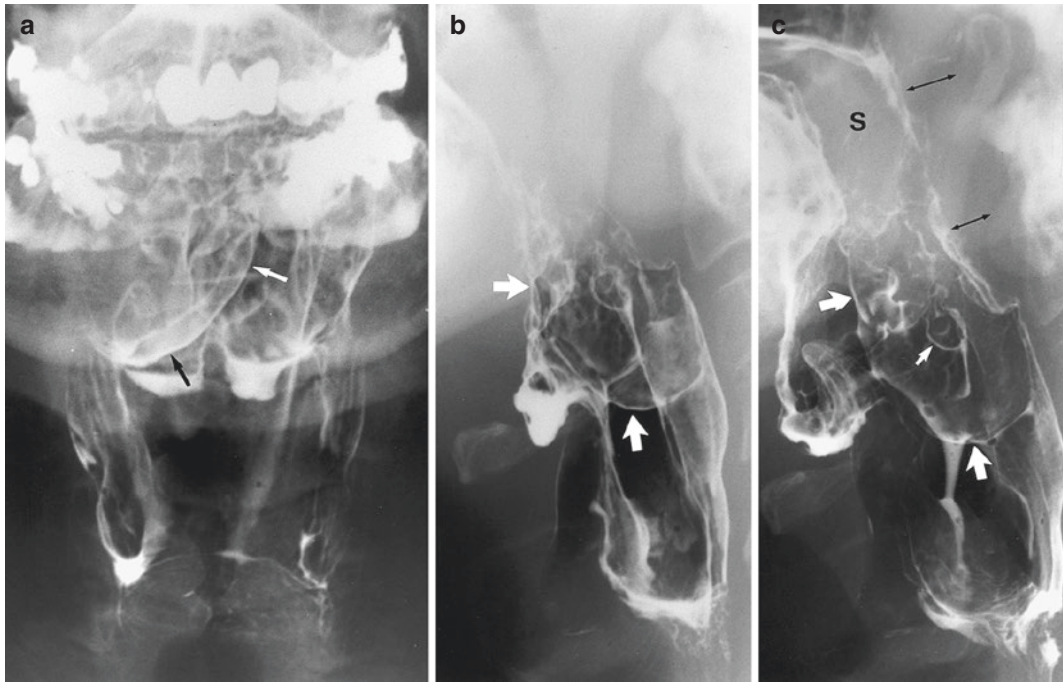

Fig. 35 Lymphoma of pharynx and the value of phonation. (**a**) Frontal view showing a soft-tissue mass (*arrows*) obliterating the right oropharyngeal wall. (**b**) Lateral view showing a soft-tissue mass (*arrows*) in the oropharynx. (**c**) Lateral view obtained after instillation of 1 ml barium into each naris and having the patient phonate "Eeee…." The mass (*large arrows*) has a smooth surface inferiorly and a central ring (*small arrow*) demarcating an empty ulcer. The mass is clearly separated from the base of the tongue by the patient's phonation. Tumor extension into the soft palate and posterior pharyngeal wall is manifested as enlargement and nodularity of the soft palate (*s*) and enlargement of the retropharyngeal space and nodularity of its surface (*double arrows*) (reproduced with permission from Levine and Rubesin 1990b)

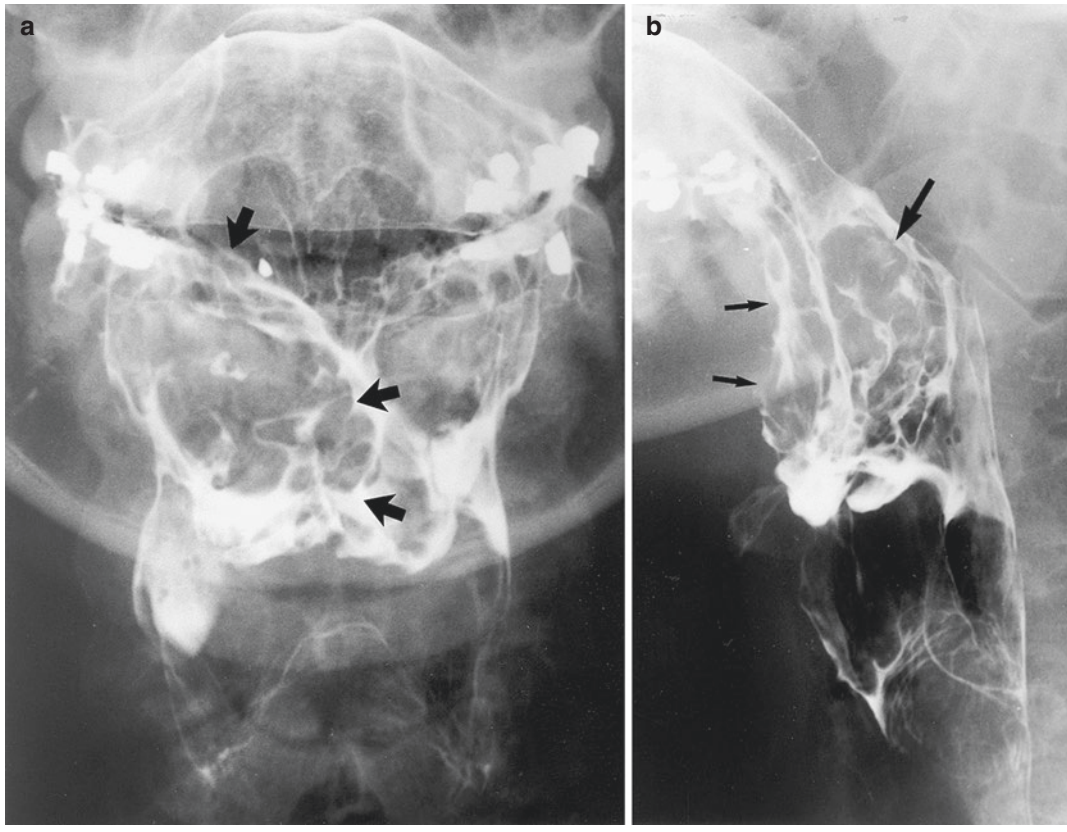

Fig. 36 Lymphoma of tongue and right palatine tonsil. (**a**) Frontal view showing a mass (*arrows*) manifested by increased soft-tissue density and tumor nodularity. (**b**) Right posterior oblique view showing tumor nodularity *en face* involving the right palatine fossa (*small arrows*) and the base of the tongue (*large arrow*)

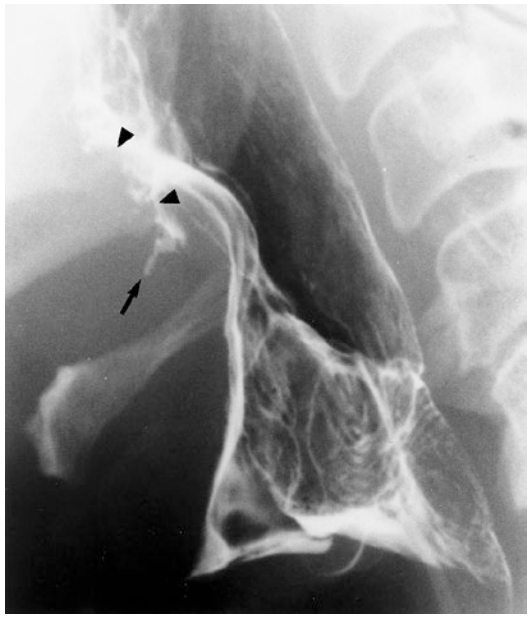

Fig. 37 Adenocarcinoma of the base of the tongue. Lateral view showing obliteration of the valleculae (*arrow*) and nodularity of the base of the tongue (*arrowheads*). Barium coating the laryngeal vestibule and ventricle resulted from absent epiglottic tilt. The tumor presumptively arose in submucosal glands in the base of the tongue (reproduced with permission from Rubesin 1994, Fig. 17.37)

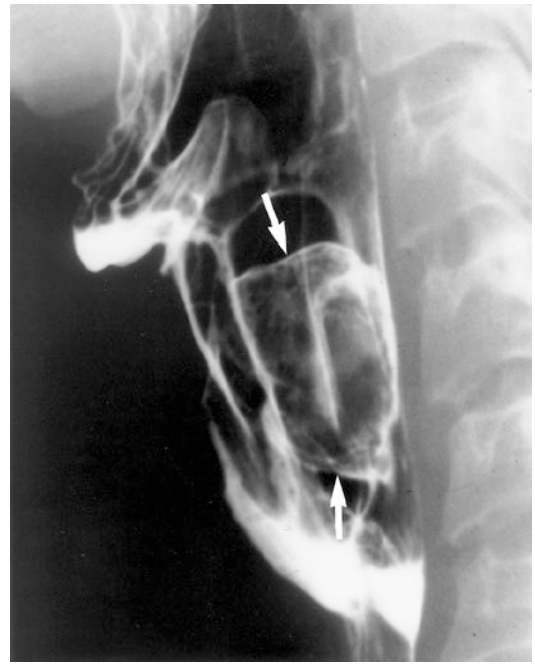

Fig. 38 Kaposi sarcoma. Lateral view showing a relatively smooth-surfaced mass (*arrows*) in the air space of the upper hypopharynx (courtesy of Dean D.T. Maglinte, University of Indiana)

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Morphology of the Esophagus

Marc S. Levine

Contents

Abstract

Barium esophagography is an invaluable radiologic technique for detecting a host of morphologic abnormalities in the esophagus. Double-contrast barium studies are particularly well suited for diagnosing reflux esophagitis and its complications, including peptic strictures and Barrett's esophagus. Double-contrast esophagography is also useful for detecting infectious esophagitis and for differentiating the underlying causes, including *Candida albicans*, the herpes simplex virus, cytomegalovirus, and human immunodeficiency virus. Barium studies can also facilitate the diagnosis of drug-induced esophagitis, eosinophilic esophagitis, and other less common forms of esophagitis. In patients with dysphagia, barium esophagography is a sensitive test for detecting the two common malignant tumors of the esophagus—squamous cell carcinoma and adenocarcinoma. Finally, esophagography can be used to diagnose other morphologic abnormalities in the esophagus, including webs, rings, diverticula, varices, foreign body impactions, fistulas, and perforation. All of these conditions are discussed in this chapter.

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1 Inflammatory Conditions

1.1 Reflux Esophagitis

Reflux esophagitis is by far the most common inflammatory disease of the esophagus. The severity of reflux esophagitis depends not only on the frequency and duration of reflux episodes, but also on the content of the refluxed material and the resistance of the esophageal mucosa (Ekberg 2012; Pope 1994). Gastroesophageal reflux can be detected on barium studies, scintigraphy, and pH-monitoring techniques, but reflux esophagitis can only be diagnosed using esophagography or endoscopy.

Reflux esophagitis may be manifested on single-contrast barium studies by thickened folds, decreased distensibility, and marginal ulceration. However, these findings are detected only in patients with advanced disease. In contrast, double-contrast barium studies have a sensitivity approaching 90% for the diagnosis of reflux esophagitis because of the ability to detect mucosal granularity, superficial ulceration, and other findings that cannot be visualized on single-contrast studies (Creteur et al. 1983b). Conversely, prone single-contrast views permit optimal distention of the distal esophagus for demonstration of hernias, rings, or strictures that are sometimes missed on upright double-contrast views (Chen et al. 1985).

Early reflux esophagitis may be manifested on double-contrast studies by a finely nodular or granular appearance in the distal esophagus due to mucosal inflammation and edema (Fig. 1, Kressel et al. 1981). In almost all cases, this nodularity or granularity extends proximally from the gastroesophageal junction as a continuous area of disease. As the disease progresses, other patients may develop shallow ulcers and erosions that are seen as streaks or dots of barium in the distal esophagus (Fig. 2, Laufer 1982). These ulcers are sometimes associated with radiating folds or surrounding halos of edematous mucosa. Occasionally, the ulcers may be more widespread. However, ulceration in reflux esophagitis almost always involves the distal esophagus, so the presence of one or more ulcers that are confined to the upper or midesophagus should suggest another cause for the patient's disease. Others with reflux esophagitis may have a single dominant ulcer, most commonly on the posterior wall of the distal esophagus (Hu et al. 1997). It has been hypothesized that these ulcers are located posteriorly because of prolonged exposure to refluxed acid that pools posteriorly when patients sleep in the supine position (Hu et al. 1997).

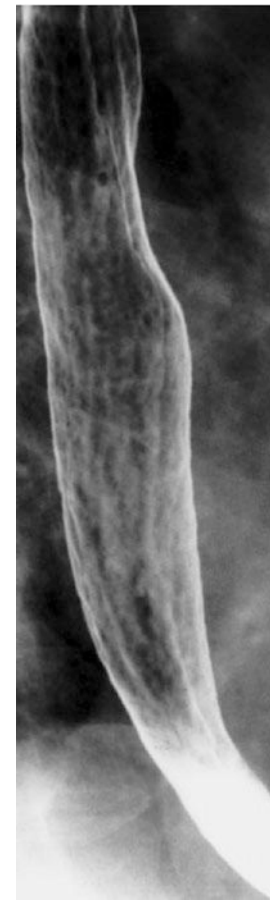

Fig. 1 Reflux esophagitis. Double-contrast view shows fine nodularity or granularity of the mucosa in the *lower* half of the thoracic esophagus. Note how this granularity extends proximally from the gastroesophageal junction as a continuous area of disease

Reflux esophagitis may also be manifested by thickened longitudinal folds due to inflammation and edema extending into the submucosa. These folds may have a smooth or lobulated contour, occasionally mimicking the appearance of esophageal varices. Other patients with chronic reflux

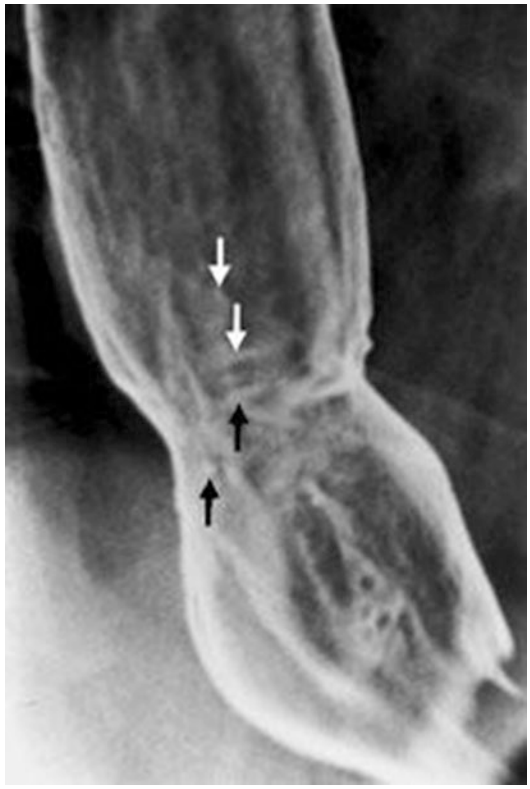

Fig. 2 Reflux esophagitis. Double-contrast view shows superficial, punctate, and linear ulcers (*arrows*) in the distal esophagus above a hiatal hernia

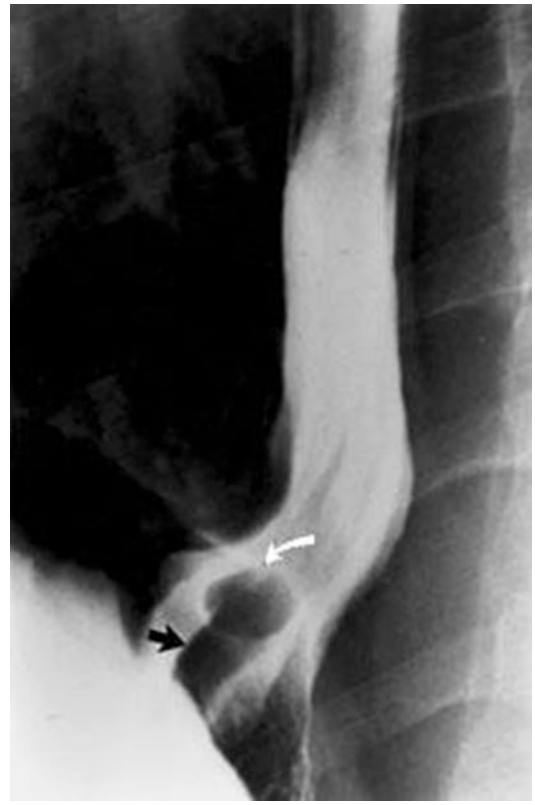

Fig. 3 Inflammatory esophagogastric polyp. Single-contrast view shows a prominent fold (*straight arrow*) that arises at the gastric cardia and terminates in the distal esophagus as a smooth polypoid protuberance (*curved arrow*)

esophagitis have a single prominent fold that arises in the gastric fundus and extends upward into the distal esophagus as a smooth, polypoid protuberance, also known as an *inflammatory esophagogastric polyp* (Fig. 3, Bleshman et al. 1978). Because these lesions have no malignant potential, endoscopy is not warranted when a typical inflammatory esophagogastric polyp is found on double-contrast studies.

1.1.1 Peptic Scarring and Strictures

As esophageal ulcers heal, localized flattening or puckering of the esophageal wall may occur at the site of healing. Further scarring leads to the development of circumferential strictures, also known as *peptic strictures*, which typically appear as smooth, tapered areas of concentric narrowing in the distal esophagus above a hiatal hernia (Fig. 4). However, asymmetric scarring can lead to asymmetric narrowing with focal sacculation of the wall between areas of fibrosis. Scarring from reflux esophagitis can also lead to longitudinal shortening of the distal esophagus and the development of fixed transverse folds, producing a characteristic *stepladder* appearance due to pooling of barium between the folds (Fig. 5, Levine and Goldstein 1984). These fixed transverse folds should be differentiated from the thin transverse folds (i.e., *feline esophagus*) often seen as a transient finding due to contraction of the longitudinally oriented muscularis mucosae in patients with reflux.

1.1.2 Barrett's Esophagus

Barrett's esophagus is characterized by progressive columnar metaplasia of the distal esophagus due to long-standing gastroesophageal reflux and reflux esophagitis. Although the metaplastic

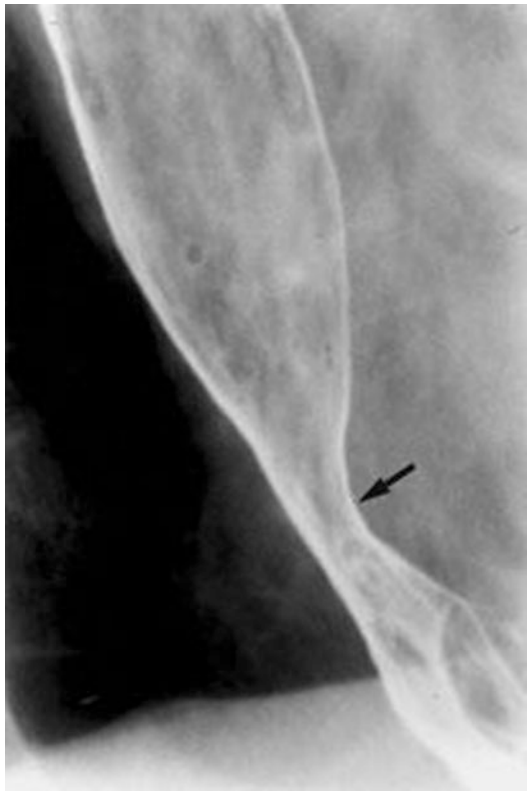

Fig. 4 Peptic stricture. Double-contrast view shows a smooth, tapered area of concentric narrowing (*arrow*) in the distal esophagus above a small hiatal hernia

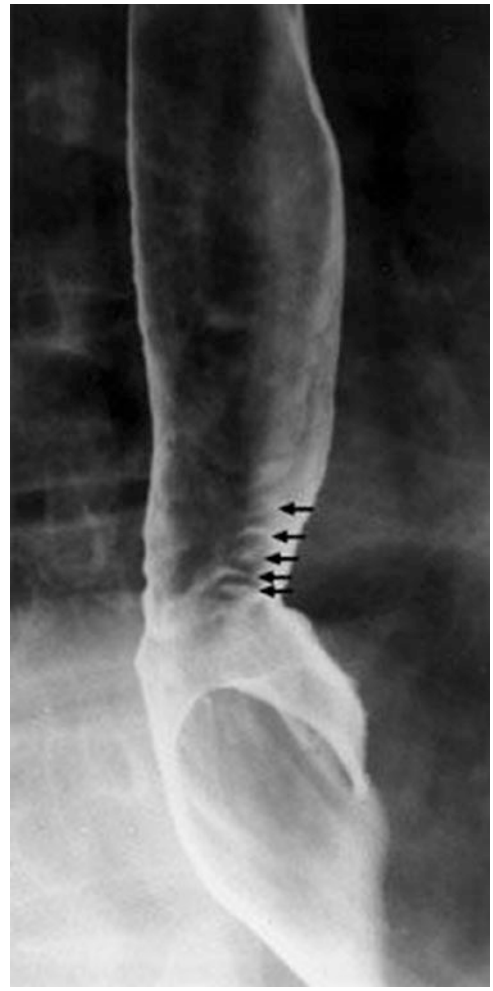

Fig. 5 Mild peptic stricture with fixed transverse folds. Double-contrast view shows a mild peptic stricture in the distal esophagus with a series of incomplete transverse folds in the region of the stricture. Note how barium traps between the folds (*arrows*), producing a characteristic *stepladder* appearance

segment in Barrett's esophagus traditionally has been thought to extend 3 cm or more above the gastroesophageal junction, short-segment Barrett's esophagus has also been described (Yamamoto et al. 2001). Barrett's esophagus is important because it is a premalignant condition associated with an increased risk of developing esophageal adenocarcinoma through a sequence of progressively severe epithelial dysplasia.

The classic radiologic signs of Barrett's esophagus consist of a high stricture or ulcer associated with a hiatal hernia and reflux (Fig. 6, Levine 1994). However, strictures are actually more common in the distal esophagus in patients with this condition, so most cases do not fit the classic description of a high stricture or ulcer (Robbins et al. 1978). Another sign of Barrett's esophagus is a distinctive reticular pattern characterized by tiny barium-filled grooves resembling the areae gastricae on double-contrast studies of the stomach (Fig. 7, Levine et al. 1983). However, this reticular pattern is also found in only a small percentage of all patients with Barrett's esophagus.

Some investigators have employed a novel approach for evaluating patients with reflux symptoms. These patients were classified at high risk for Barrett's esophagus if double-contrast radiographs revealed a high stricture or ulcer or a reticular pattern; at moderate risk if the radiographs revealed a distal stricture or reflux esophagitis; and

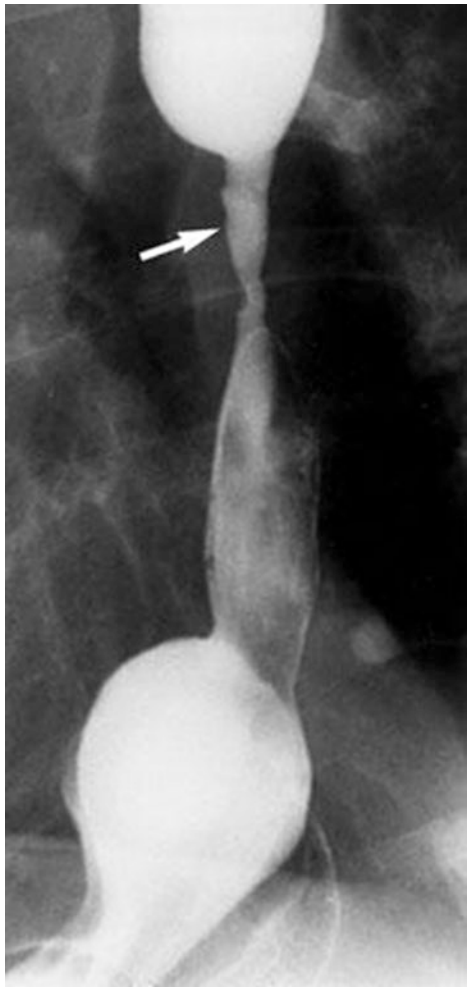

Fig. 6 Barrett's esophagus. Prone single-contrast view shows a smooth, tapered stricture (*arrow*) in the mid-esophagus above a moderately large hiatal hernia

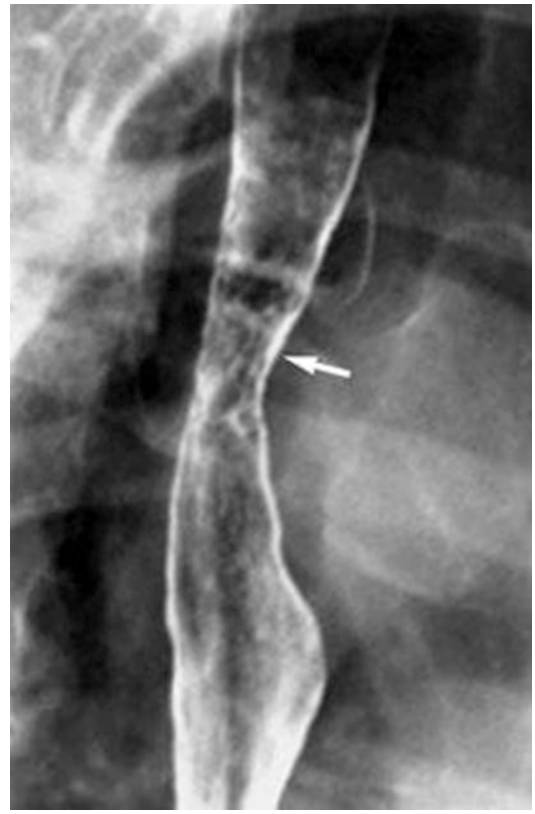

Fig. 7 Barrett's esophagus. Double-contrast view shows a tapered stricture (*arrow*) in the midesophagus. Also note a delicate reticular pattern of the mucosa in the region of the stricture in this patient with proven Barrett's esophagus

at low risk if the esophagus appeared normal (Gilchrist et al. 1988). The vast majority of those classified at high risk on double-contrast barium studies were found to have Barrett's esophagus versus only 1% classified at low risk. Thus, the major value of double-contrast esophagography in patients with reflux symptoms is its ability to stratify these individuals into various risk groups for Barrett's esophagus to determine the relative need for endoscopy and biopsy.

Other more common findings in Barrett's esophagus, such as reflux esophagitis and distal peptic strictures, often occur in patients with uncomplicated reflux disease. Thus, radiographic findings that are relatively specific for Barrett's esophagus are not sensitive, and findings that are more sensitive are not specific.

1.2 Infectious Esophagitis

1.2.1 Candida Esophagitis

Candida albicans is the most common cause of infectious esophagitis (Haulk and Sugar 1991). It most often occurs as an opportunistic infection in immunocompromised patients, particularly those with AIDS, but others may develop candidiasis as a result of local esophageal stasis due to achalasia or scleroderma (Gefter et al. 1981). It should be recognized that 50% of patients with Candida esophagitis do not have oropharyngeal candidiasis (i.e., thrush), so the

absence of oropharyngeal disease in no way excludes this diagnosis (Levine et al. 1987). Single-contrast barium studies have limited value in detecting esophageal candidiasis because of the superficial nature of the disease. In contrast, double-contrast barium studies have a sensitivity of nearly 90% in diagnosing *Candida* esophagitis, primarily because of the ability to demonstrate mucosal plaques (Levine et al. 1985).

Candida esophagitis usually is manifested on double-contrast studies by discrete plaque-like lesions corresponding to the characteristic white plaques seen on endoscopy (Levine et al. 1985). The plaques appear as linear or irregular filling defects that tend to be oriented longitudinally and are associated with normal intervening mucosa (Fig. 8). Patients with AIDS may develop a more fulminant form of *Candida* esophagitis characterized by a grossly irregular or *shaggy esophagus* due to coalescent plaques and pseudomembranes with trapping of barium between these lesions (Fig. 9, Levine et al. 1987). Some of the plaques may eventually slough, producing one or more deep ulcers on a background of diffuse plaque formation. Patients with scleroderma or achalasia may also develop a *foamy esophagus* due to innumerable bubbles layering out in the barium column (Fig. 10); this phenomenon presumably results from infection by a yeast form of candidiasis (Sam et al. 2000).

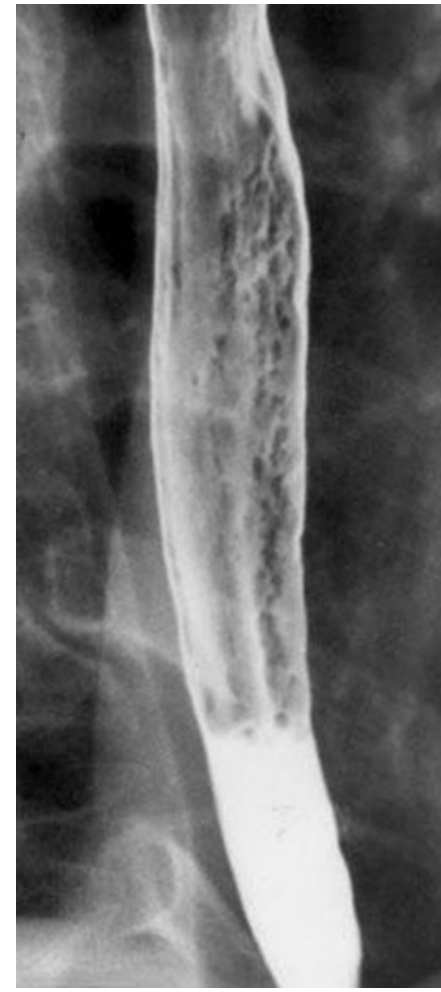

Fig. 8 *Candida* esophagitis. Double-contrast view shows multiple discrete plaque-like lesions in the midesophagus. Note how some of the plaques have a linear configuration

1.2.2 Herpes Esophagitis

The herpes simplex virus type I is the second most frequent cause of infectious esophagitis. Herpes esophagitis is most commonly seen in immunocompromised patients, but it occasionally may occur as an acute, self-limited disease in otherwise healthy patients who have no underlying immunologic problems (Shortsleeve and Levine 1992).

Herpes esophagitis is initially manifested by small vesicles that subsequently rupture to form discrete, punched-out ulcers on the mucosa (Levine et al. 1981). Affected individuals typically present with severe odynophagia. Although some patients may have herpetic lesions in the oropharynx, the majority are not found to have oropharyngeal disease. Moreover, some patients with oral herpes and odynophagia are found to have *Candida* esophagitis. The presence of herpetic lesions in the oropharynx therefore does not accurately predict herpes esophagitis in patients with odynophagia.

Herpes esophagitis is usually manifested on double-contrast studies by small, discrete ulcers in the upper or midesophagus (Fig. 11). The ulcers can have a punctate, stellate, or volcano-like appearance, often separated by normal intervening mucosa (Levine et al. 1981). Discrete ulcers are seen in up to 50% of patients with herpes

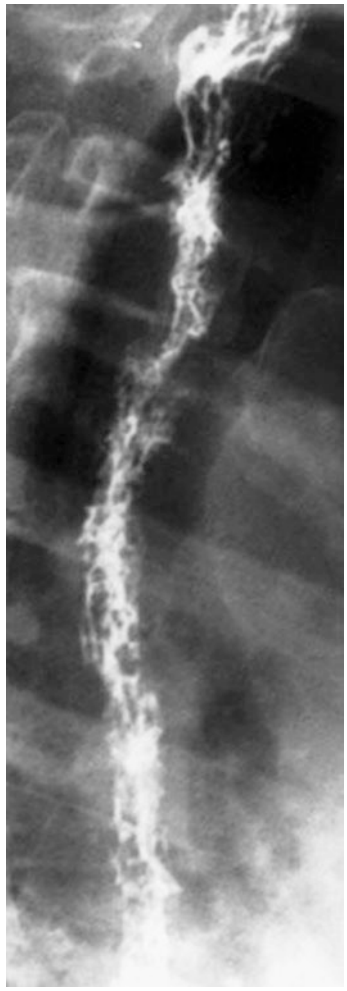

Fig. 9 Advanced *Candida* esophagitis with a *shaggy esophagus*. Double-contrast view shows a grossly irregular esophagus due to innumerable coalescent plaques and pseudomembranes with trapping of barium between the lesions. This patient had AIDS

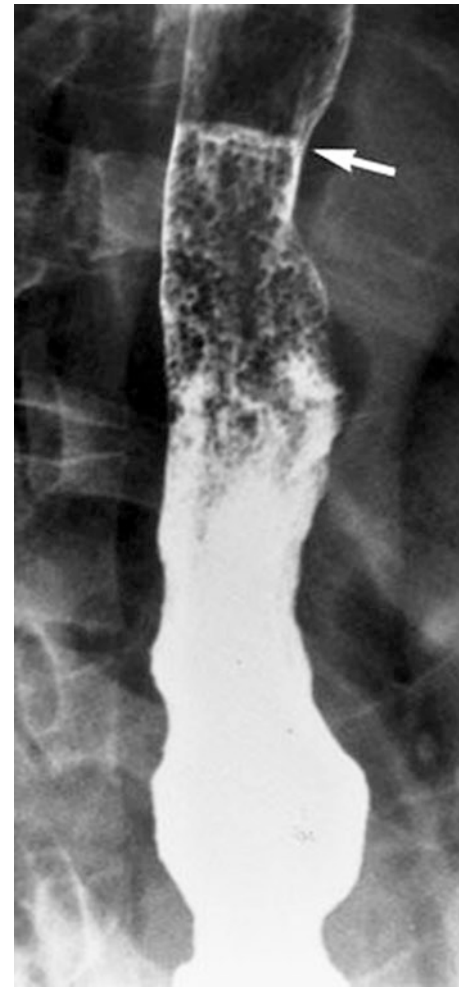

Fig. 10 *Candida* esophagitis with a *foamy esophagus*. Double-contrast view shows innumerable tiny bubbles layering out in the barium column (*arrow*) as a result of the yeast form of candidiasis. The esophagus is also dilated in this patient with underlying achalasia. It should be noted that patient did not receive an effervescent agent for this examination

esophagitis (Levine et al. 1988). Rarely, severe infection may be manifested by multiple ulcers and plaques, mimicking the findings of advanced *Candida* esophagitis. In the appropriate setting, however, it usually is possible to differentiate these infections on the basis of the radiographic findings without the need for endoscopy (Levine et al. 1987).

1.2.3 Cytomegalovirus Esophagitis

Cytomegalovirus (CMV) is another cause of infectious esophagitis associated with the development of ulcers. Affected individuals usually present with severe odynophagia and are almost always found to have AIDS. These patients may also have evidence of CMV in other organs such as the retina, liver, or colon.

CMV esophagitis is usually manifested on double-contrast barium studies by one or more giant, flat ulcers that are several centimeters or more in length (Levine et al. 1987). The ulcers may have an ovoid, elongated, or diamond-shaped configuration and are frequently surrounded

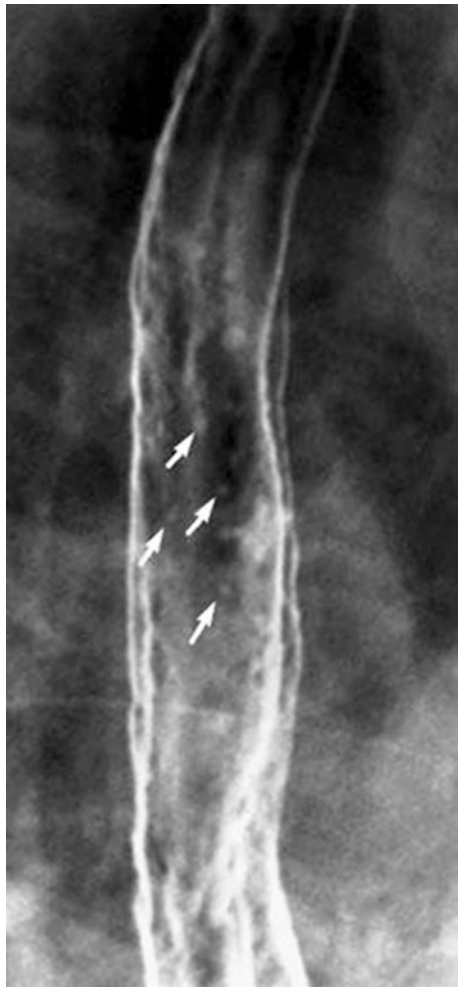

Fig. 11 Herpes esophagitis. Double-contrast view shows multiple tiny ulcers (*arrows*) in the midesophagus. Note tiny radiolucent mounds of edema surrounding the ulcers

Fig. 12 HIV esophagitis. Double-contrast view shows a large *diamond*-shaped ulcer (*black arrows*) with a cluster of small satellite ulcers (*white arrows*) in the midesophagus

by a thin radiolucent rim of edema. Because herpetic ulcers rarely become this large, the presence of one or more giant ulcers should suggest the possibility of CMV esophagitis in patients with AIDS. Nevertheless, the differential diagnosis also includes giant human immunodeficiency virus (HIV) ulcers in the esophagus (see next section). Less commonly, CMV esophagitis may be manifested by small, superficial ulcers indistinguishable from those of herpes esophagitis. CMV esophagitis is treated with potent antiviral agents such as ganciclovir that may cause bone marrow suppression. Endoscopy with biopsy specimens, brushings, and cultures from the esophagus is therefore required to confirm the presence of CMV before treating these patients.

1.2.4 Human Immunodeficiency Virus Esophagitis

HIV infection of the esophagus can lead to the development of giant ulcers indistinguishable from those caused by CMV (Levine et al. 1991b). The ulcers typically appear as ovoid or diamond-shaped collections, sometimes associated with a cluster of small satellite ulcers (Fig. 12). Affected individuals may also have palatal ulcers or a characteristic maculopapular rash on the upper half of the body. The diagnosis is confirmed by obtaining endoscopic biopsy specimens, brushings, and

cultures from the esophagus to exclude CMV. Unlike CMV ulcers, these HIV-related esophageal ulcers usually respond dramatically to treatment with oral steroids. Endoscopy is therefore required in HIV-positive patients with giant esophageal ulcers to differentiate HIV from CMV, so appropriate therapy can be instituted (Sor et al. 1995).

1.3 Drug-Induced Esophagitis

Tetracycline and doxycycline are the most frequent causes of drug-induced esophagitis, but other offending agents include aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), quinidine, potassium chloride, and alendronate. These patients typically ingest the medications with little or no water immediately before going to bed. It has therefore been postulated that prolonged contact of the esophageal mucosa with the medication causes a direct contact esophagitis. Drug-induced esophagitis usually involves the upper or middle thirds of the esophagus with sparing of the distal third (Bova et al. 1987).

The radiographic findings in drug-induced esophagitis depend on the nature of the offending medication. Tetracycline and doxycycline are associated with the development of small, superficial ulcers indistinguishable from those of herpes esophagitis (Fig. 13). In contrast, quinidine, potassium chloride, and NSAIDs may cause more severe injury, leading to the development of large ulcers and subsequent stricture formation (Creteur et al. 1983a). Alendronate may also produce extensive ulceration and strictures, but these strictures are usually confined to the distal esophagus (Ryan et al. 1998). Whatever the offending agent, a repeat esophagram usually shows marked healing of the ulcers within 7–10 days after withdrawal of the offending medication (Creteur et al. 1983a).

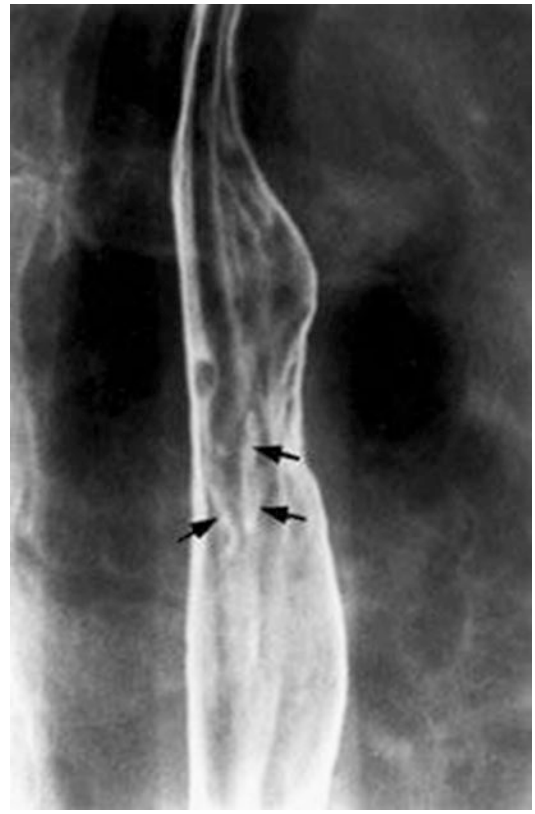

Fig. 13 Drug-induced esophagitis. Double-contrast view shows several small linear ulcers (*arrows*) in the mid-esophagus due to recent tetracycline ingestion

1.4 Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) has been recognized as an increasingly common inflammatory condition of the esophagus, occurring predominantly in young men with long-standing dysphagia and recurrent food impactions, often associated with an atopic history, asthma, and, less frequently, a peripheral eosinophilia. The diagnosis of EoE can be confirmed on endoscopic biopsy specimens showing more than 20 eosinophils per high-power field. The etiology is uncertain, but many authors believe that EoE develops as an inflammatory response to ingested food allergens in predisposed individuals. As a result, symptomatic patients often have a marked clinical response to treatment with steroids (especially inhaled steroid preparations) or elemental diets.

The diagnosis of EoE may be suggested on barium studies by the presence of segmental esophageal strictures, sometimes associated with multiple distinctive ringlike indentations, producing a *ringed esophagus* (Zimmerman et al. 2005, Fig. 14). The radiographic diagnosis can also be suggested by the development of

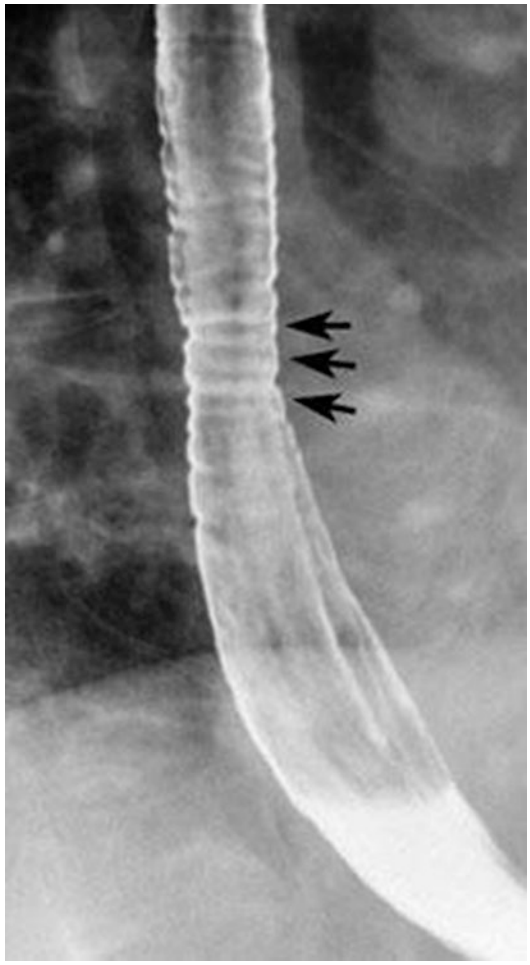

Fig. 14 EoE with a *ringed esophagus*. This patient has a smooth, tapered stricture in the lower third of the thoracic esophagus. Note multiple distinctive ringlike indentations (*arrows*) in the region of the stricture. This finding should be highly suggestive of EoE on barium studies

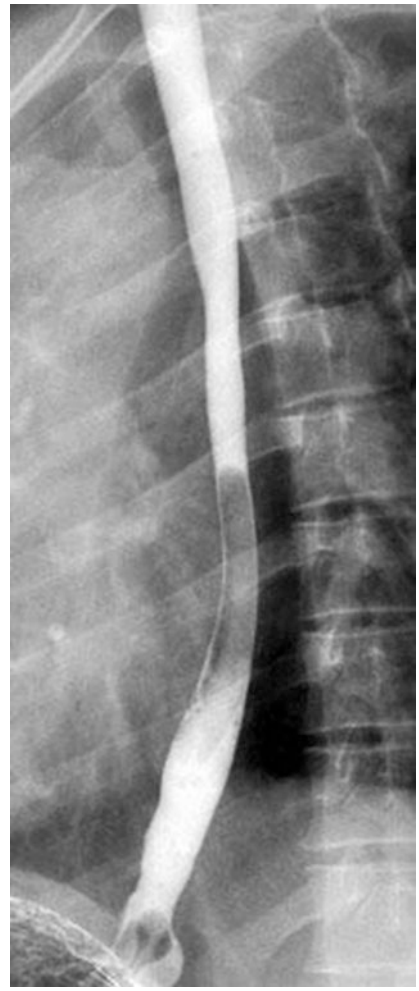

Fig. 15 EoE with a *small-caliber esophagus*. A double-contrast esophagogram shows loss of distensibility of the entire thoracic esophagus. Note how there is diffuse luminal narrowing without a discernible stricture. This finding is characteristic of EoE on barium studies

a *small-caliber esophagus* manifested by smooth, long-segment narrowing of most or all of the thoracic esophagus (that has a mean diameter of less than 20 mm) without a discrete stricture (White et al. 2010, Fig. 15). Lichen planus involving the esophagus is another condition that can be associated with a small-caliber esophagus indistinguishable from that in EoE, but lichen planus typically occurs in older woman with chronic skin rashes rather than young men with an atopic history or asthma, so it usually is possible to differentiate these conditions on the basis of the clinical findings (Rauschecker et al. 2017).

1.5 Radiation Esophagitis

A radiation dose of approximately 4500–6000 rads to the chest can cause severe injury to the esophagus (Goldstein et al. 1975). Acute radiation esophagitis usually occurs 1–3 weeks after the initiation of radiation therapy. This condition may be manifested by ulceration or, even more commonly, by a granular appearance of the mucosa and decreased distensibility due to edema and inflammation of the irradiated segment (Collazzo et al. 1997). Within several months after completion of radiation therapy, a smooth,

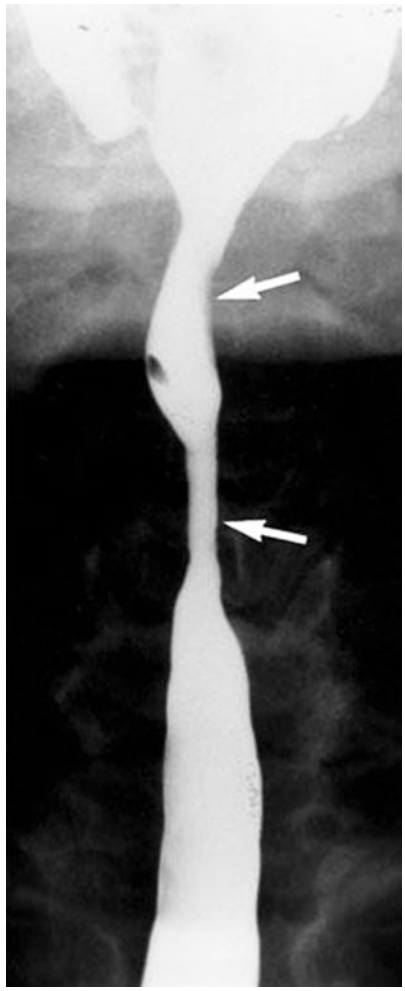

Fig. 16 Radiation stricture. A smooth, tapered stricture (*arrows*) is seen in the cervical and upper thoracic esophagus in this patient who underwent a total laryngectomy and radiation therapy for laryngeal carcinoma

tapered area of concentric narrowing may be seen within the radiation portal due to the development of a radiation stricture (Fig. 16). Fistula formation is another uncommon complication of chronic radiation injury (Carlyle et al. 1976).

1.6 Caustic Esophagitis

Whether accidental or intentional, ingestion of lye or other caustic agents can lead to a severe form of esophagitis with ulceration, scarring, and stricture formation (Dafoe and Ross 1969). If esophagography is attempted after a patient ingests a caustic

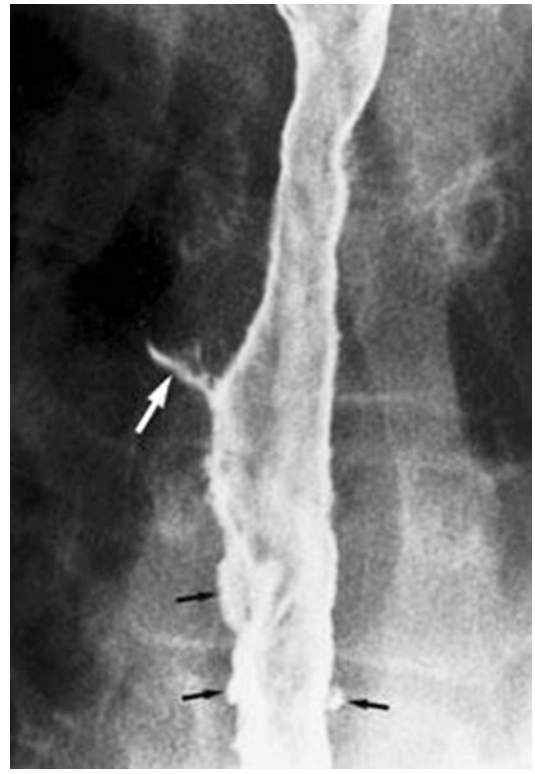

Fig. 17 Acute caustic esophagitis. A study with water-soluble contrast material shows narrowing and ulceration (*black arrows*) of the midesophagus with a small, sealed-off perforation (*white arrow*). This patient had ingested lye

agent, water-soluble contrast media should be used because of the risk of perforation. Such studies may reveal abnormal motility, ulceration, or even esophageal disruption (Fig. 17). If the patient survives, repeat studies may reveal marked stricture formation, typically involving a long segment of the thoracic esophagus. Patients with chronic lye strictures also have an increased risk of developing squamous cell carcinoma of the esophagus, so a new area of mucosal irregularity within a preexisting lye stricture should raise concern about the possibility of a developing carcinoma (Appelqvist and Salmo 1980).

1.7 Other Esophagitis

Alkaline reflux esophagitis is caused by reflux of bile or pancreatic secretions into the esophagus after partial or total gastrectomy (Levine et al. 1991a).

These patients may develop mucosal nodularity, ulceration, or, in severe disease, long, rapidly progressive strictures in the distal esophagus (Levine et al. 1991a). The risk of alkaline reflux esophagitis can be decreased by performing a Roux-en-Y esophagojejunostomy to prevent reflux of bile into the esophagus.

Nasogastric intubation is an unusual cause of esophagitis and stricture formation (Banfield and Hurwitz 1974). Most of these strictures develop after prolonged or repeated intubation, and they may progress rapidly after removal of the tube. It has been postulated that the strictures result from severe reflux esophagitis caused by constant reflux of acid around the tube (Graham et al. 1959). Strictures caused by nasogastric intubation tend to be long-segment strictures in the distal esophagus that progress rapidly on follow-up radiographic examinations.

Other less common causes of esophagitis include acute alcohol-induced esophagitis, Crohn's disease, chronic graft-versus-host disease, Behcet's disease, and, rarely, skin disorders involving the esophagus, such as epidermolysis bullosa dystrophica and benign mucous membrane pemphigoid.

2 Neoplasms

2.1 Benign Tumors

2.1.1 Papilloma

Squamous papillomas are the most common benign mucosal tumors in the esophagus. Histologically, these lesions consist of a central fibrovascular core with multiple digit-like projections covered by hyperplastic squamous epithelium (Miller et al. 1978). Papillomas usually appear on double-contrast esophagography as small, sessile polyps with smooth or slightly lobulated borders. Because papillomas may be difficult to distinguish radiographically from early esophageal cancer and also because of the uncertain risk of malignant degeneration, biopsy or resection of esophageal papillomas is recommended by some investigators (Zeabart et al. 1979). Rarely, patients may have innumerable papillomas in the esophagus, a condition known as esophageal papillomatosis (Sandvik et al. 1996).

2.1.2 Adenoma

Esophageal adenomas are rare benign lesions which are almost always found to arise in metaplastic columnar epithelium associated with Barrett's esophagus (Levine et al. 1984). Because these lesions have the same potential for malignant transformation as colonic adenomas, endoscopic or surgical resection is warranted (Levine et al. 1984). Adenomas typically appear on esophagography as sessile or pedunculated polyps in the distal esophagus near the gastroesophageal junction.

2.1.3 Glycogenic Acanthosis

Glycogenic acanthosis is a benign disorder in which glycogen accumulates in the squamous epithelial cell lining of the esophagus. It is a common degenerative condition, occurring primarily in middle-aged or elderly individuals (Glick et al. 1982). Glycogenic acanthosis is manifested on double-contrast esophagography by multiple small, rounded nodules or plaques in the middle or, less commonly, distal esophagus (Glick et al. 1982). Major considerations in the differential diagnosis for these lesions include reflux and *Candida* esophagitis. However, the nodules in reflux esophagitis are more poorly defined and are usually located in the distal esophagus, whereas the plaques in *Candida* esophagitis tend to have a linear configuration and typically develop in immunocompromised patients with odynophagia. Thus, it usually is possible to differentiate these conditions on the basis of the clinical and radiographic findings.

2.1.4 Leiomyoma

Leiomyomas are the most common benign submucosal tumors in the esophagus (Goldstein et al. 1981). Unlike stromal tumors elsewhere in the gastrointestinal tract, esophageal leiomyomas almost never undergo sarcomatous degeneration, and unlike gastric leiomyomas, they almost never ulcerate (Totten et al. 1953; Glanz and Grunebaum 1977). Patients with esophageal

leiomyomas are usually asymptomatic but occasionally may present with slowly progressive dysphagia (Seremetis et al. 1976).

When esophageal leiomyomas grow into the mediastinum, they can be recognized on chest radiographs by the presence of a mediastinal mass, occasionally containing punctate areas of calcification. Leiomyomas usually appear on barium studies as smooth submucosal lesions (Fig. 18) indistinguishable from other mesenchymal neoplasms such as granular cell tumors, lipomas, hemangiomas, fibromas, and neurofibromas, except that leiomyomas are more likely on empirical grounds. CT may be helpful for differentiating submucosal esophageal masses from extrinsic mediastinal tumors compressing the esophagus.

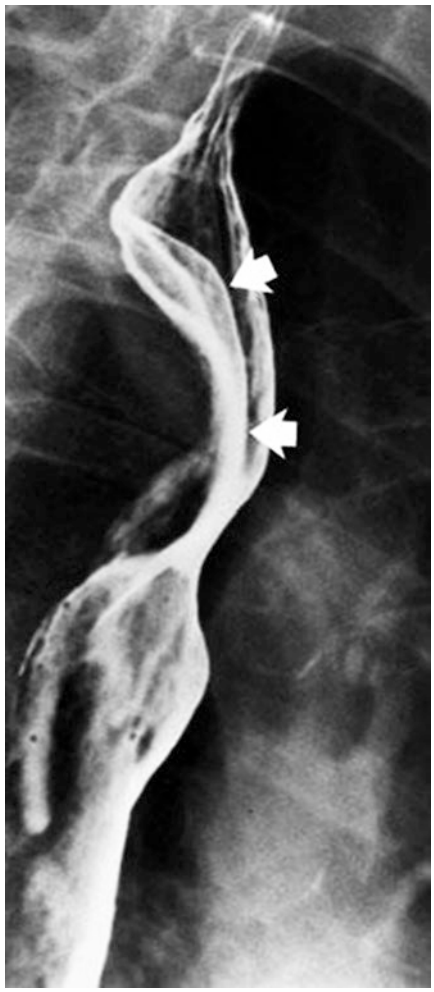

Fig. 18 Leiomyoma. Double-contrast view shows a smooth submucosal mass (*arrows*) in the upper thoracic esophagus

2.1.5 Fibrovascular Polyp

Fibrovascular polyps are rare, benign submucosal tumors arising from the cervical esophagus, usually at the level of the cricopharyngeus (Levine et al. 1996). Histologically, these lesions are composed of fibrous, vascular, and adipose tissue covered by normal squamous epithelium. They gradually elongate into the thoracic esophagus, forming a pedunculated mass. Some fibrovascular polyps can grow to gigantic sizes, causing dysphagia or wheezing secondary to extrinsic compression of the trachea. Fibrovascular polyps usually appear on barium studies as smooth, expansile masses in the upper or midesophagus (Fig. 19), sometimes associated with a discrete pedicle that originates near the cricopharyngeus. When fibrovascular polyps contain a large amount of adipose tissue, they may be recognized by the presence of fat within the lesions on CT or MRI (Whitman and Borkowski 1989).

2.1.6 Granular Cell Tumor

Granular cell tumors arise from Schwann cells of the peripheral nervous system (Gershwind et al. 1978). Approximately 7% of granular cell tumors occur in the gastrointestinal tract, and one-third of these lesions are found in the esophagus (Johnston and Helwig 1981). Granular cell tumors usually appear on esophagography as small, round, or ovoid submucosal masses that often are mistaken for leiomyomas (Rubesin et al. 1985). Most patients with granular cell tumors are asymptomatic, so these lesions usually are detected as incidental findings. However, large granular cell tumors that cause dysphagia may require local excision (Rubesin et al. 1985).

2.1.7 Duplication Cyst

Although duplication cysts are not true neoplasms, they are included in this section as they may present as submucosal masses. Esophageal duplication cysts comprise about 20% of all

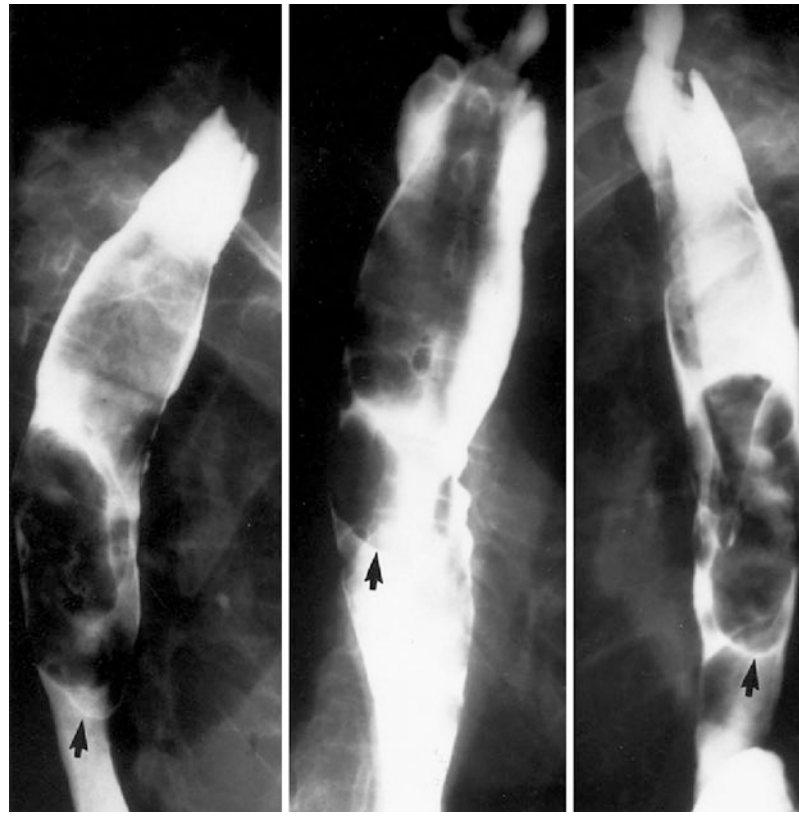

Fig. 19 Giant fibrovascular polyp. A smooth, sausage-shaped mass is seen expanding the lumen of the upper and midesophagus on three separate views (*arrow* denotes distal tip of lesion)

duplication cysts in the gastrointestinal tract (Macpherson 1993). These cysts are developmental anomalies of the primitive foregut, often containing ectopic gastric mucosa. The cysts may or may not communicate with the esophageal lumen and usually are located in the right lower mediastinum. Most adults are asymptomatic but some may have symptoms caused by obstruction, bleeding, or infection of the cyst.

Duplication cysts sometimes can be recognized on chest radiographs by the presence of a mass in the right lower mediastinum. The cysts typically appear on barium studies as smooth submucosal masses in the esophagus. When duplication cysts communicate with the esophageal lumen, they may be recognized as tubular, branching outpouchings that fill with barium (Fig. 20). Duplication cysts usually appear as homogenous low-attenuation structures on CT and as high-signal-intensity structures on T2-weighted MR images (Rafal and Markisz 1991).

2.2 Malignant Tumors

2.2.1 Esophageal Carcinoma

Esophageal carcinoma constitutes about 1% of all cancers in the United States and 7% of all gastrointestinal tumors (Livingston and Skinner 1985). Affected individuals usually develop dysphagia only after the tumor has invaded periesophageal lymphatics or other mediastinal structures. As a result, most patients have advanced lesions at the time of presentation, with overall 5-year survival rates of less than 10%. Occasionally, however, early esophageal cancer (defined as tumor limited to the mucosa or submucosa without lymphatic metastases) may be detected as a result of early onset of symptoms or screening of asymptomatic patients in high-risk groups. Unlike advanced carcinoma, early esophageal cancer is a curable lesion with 5-year survival rates as high as 95% (Levine et al. 1986). Histologically, 50% of esophageal cancers are squamous cell carcinomas and the remaining

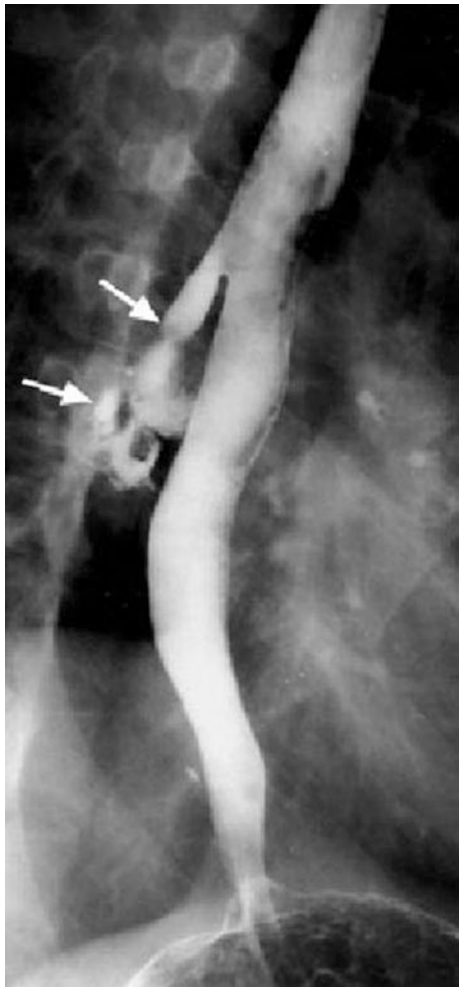

Fig. 20 Communicating duplication cyst. Single-contrast view shows a tubular, branching structure (*arrows*) communicating with the posterior wall of the midesophagus (courtesy of Marie Latour, M.D., Philadelphia, PA)

50% are adenocarcinomas arising in Barrett's esophagus (Pera et al. 1993).

Tobacco and alcohol are the major risk factors for developing squamous carcinoma of the esophagus in the United States. Other conditions known to predispose to the development of esophageal carcinoma include achalasia, lye strictures, head and neck tumors, Plummer–Vinson syndrome, and tylosis (Carter and Brewer 1975; Appelqvist and Salmo 1980; Levine and Halvorsen 2000). Some authorities advocate periodic screening of patients with these conditions to detect developing cancers at the earliest possible stage.

Unlike squamous cell carcinomas, esophageal adenocarcinomas are virtually always found to arise in patients with underlying Barrett's esophagus. The reported prevalence of adenocarcinoma in patients with Barrett's esophagus is about 10% (Levine et al. 1995). Studies using incidence rather than prevalence data indicate that the relative risk of adenocarcinoma developing in patients with Barrett's esophagus is 30–40 times greater than that in the general population (Spechler et al. 1984). These adenocarcinomas evolve through a sequence of progressive epithelial dysplasia in areas of preexisting columnar metaplasia. Many experts therefore advocate periodic endoscopic surveillance of patients with known Barrett's esophagus in order to detect dysplastic or carcinomatous changes at the earliest possible stage.

Double-contrast esophagography has a sensitivity of more than 95% in detecting esophageal cancer, a figure comparable to the reported endoscopic sensitivity of 95–100% when multiple brushings and biopsy specimens are obtained (Levine et al. 1997). Furthermore, endoscopy rarely finds cases of esophageal carcinoma that are missed on double-contrast studies (DiPalma et al. 1984). We therefore believe that double-contrast esophagography is a sensitive technique for detecting esophageal cancer and that endoscopy is not warranted in patients with normal findings on double-contrast studies.

Early esophageal cancers are usually small, protruded lesions less than 3.5 cm in size. These tumors may be manifested on double-contrast studies by plaque-like lesions (often containing a flat central ulcer, Fig. 21), by sessile polyps with a smooth or slightly lobulated contour, or by focal irregularity of the wall. Early adenocarcinomas in Barrett's esophagus may also be manifested by a localized area of wall flattening or irregularity within a preexisting peptic stricture. Superficial spreading carcinoma is another form of early esophageal cancer characterized by a confluent area of nodules or plaques (Levine et al. 1986). Although these lesions may be confused with focal *Candida* esophagitis, the plaques in candidiasis tend to be discrete lesions with normal intervening mucosa, whereas the nodules

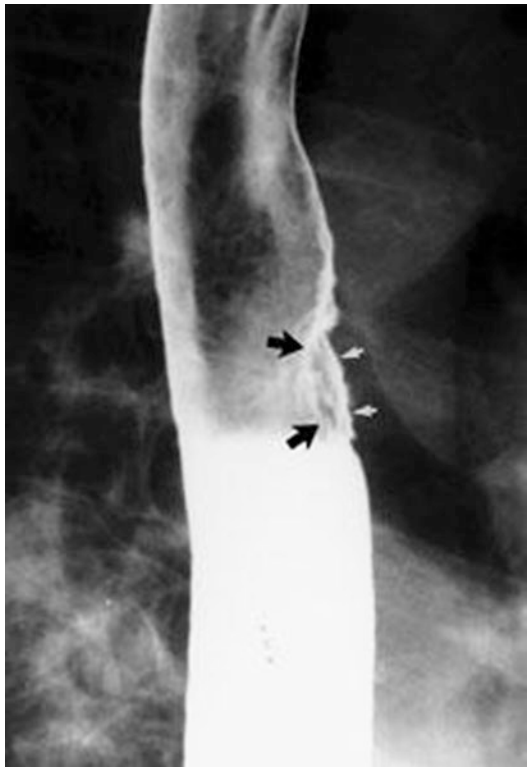

Fig. 21 Early esophageal carcinoma. Double-contrast view shows a plaque-like lesion (*black arrows*) in the mid-esophagus with a flat central ulcer (*white arrows*)

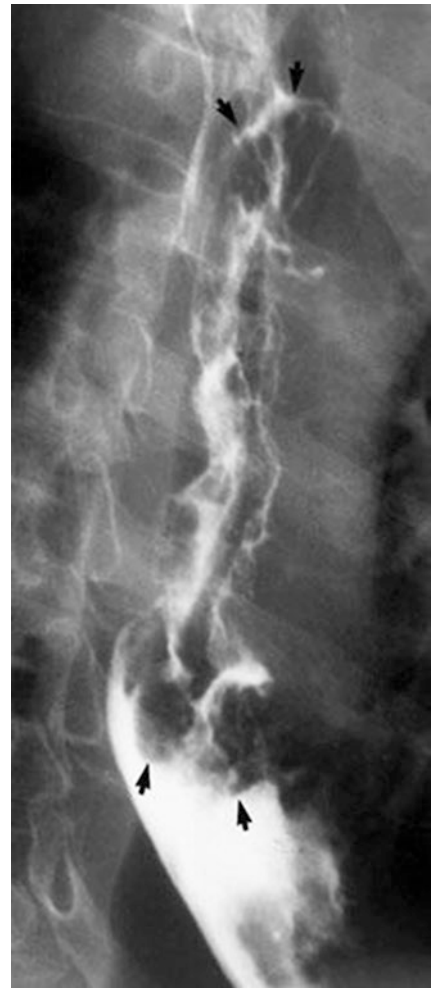

Fig. 22 Advanced infiltrating squamous cell carcinoma. Single-contrast view shows an irregular segment of narrowing in the midesophagus with abrupt, shelf-like proximal and distal borders (*arrows*)

in superficial spreading carcinoma tend to coalesce, producing a continuous area of disease. Although early esophageal cancers are generally thought to be small lesions, some early cancers may be relatively large intraluminal masses more than 3.5 cm in diameter (Levine et al. 1986).

Advanced esophageal carcinomas usually appear on barium studies as infiltrating, polypoid, ulcerative, or varicoid lesions. Infiltrating carcinomas are manifested by irregular luminal narrowing, nodularity, ulceration, and abrupt, often shelf-like borders (Fig. 22). Polypoid carcinomas appear as lobulated intraluminal masses. Primary ulcerative carcinomas are necrotic lesions with a giant, meniscoid ulcer surrounded by a radiolucent rim of tumor (Fig. 23, Gloyna et al. 1977). Finally, varicoid carcinomas are those in which submucosal spread of tumor produces thickened, tortuous longitudinal defects, mimicking the appearance of varices. However, varicoid tumors have a fixed configuration and relatively abrupt borders, whereas varices tend to change in size and shape at fluoroscopy. Also, varices rarely cause dysphagia because they are soft and compressible. Thus, it usually is possible to differentiate varices from varicoid tumors on clinical and radiologic criteria.

Squamous cell carcinomas and adenocarcinomas of the esophagus cannot be reliably differentiated on the basis of the radiographic findings. Nevertheless, squamous cell carcinomas tend to involve the upper or midesophagus, whereas adenocarcinomas are mainly located in the distal

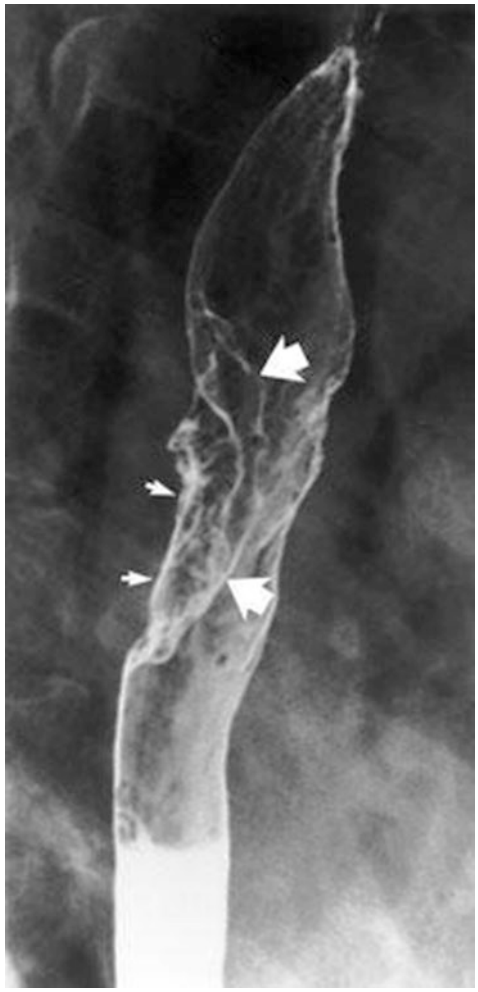

Fig. 23 Primary ulcerative carcinoma. Double-contrast view shows a polypoid lesion (*large arrows*) in the mid-esophagus with a flat area of central ulceration (*small arrows*)

esophagus. Unlike squamous carcinomas, esophageal adenocarcinomas also have a marked tendency to invade the gastric cardia or fundus. In fact, 50% of all cancers involving the gastroesophageal junction are esophageal adenocarcinomas invading the stomach.

Esophageal carcinomas tend to metastasize to other parts of the esophagus via a network of rich submucosal lymphatic channels. These lymphatic metastases may appear as polypoid, plaque-like, or ulcerated lesions that are separated from the primary tumor by normal intervening mucosa (Glick et al. 1986). Tumor may also spread subdiaphragmatically to the gastric fundus via submucosal esophageal lymphatic vessels. These metastases to the stomach may appear as large submucosal masses, often containing central areas of ulceration.

Appropriate treatment strategies for esophageal carcinoma depend on accurate staging of the tumor. Various imaging techniques such as CT, MR, and endoscopic sonography are used for staging esophageal carcinoma (Takashima et al. 1991; Vilgrain et al. 1990). The tumor stage is assessed by evaluating the depth of esophageal wall invasion and the presence or absence of lymphatic or distant metastases.

2.2.2 Other Malignant Tumors

Non-Hodgkin's lymphoma and, rarely, Hodgkin's lymphoma may also involve the esophagus. Esophageal lymphoma may be manifested on barium studies by submucosal masses, polypoid lesions, enlarged folds, or strictures (Carnovale et al. 1977). Spindle-cell carcinoma is another rare tumor characterized by a polypoid intraluminal mass that expands the lumen of the esophagus without causing obstruction (Agha and Keren 1985). Other malignant tumors of the esophagus include leiomyosarcoma, malignant melanoma, and Kaposi's sarcoma.

3 Webs

Webs are thin mucosal folds arising from the anterior wall of the lower hypopharynx or upper cervical esophagus. Cervical esophageal webs have been reported in 3–8% of upper gastrointestinal barium studies (Ekberg and Nylander 1983). Most patients are asymptomatic, but some may present with dysphagia. An association of cervical esophageal webs with iron-deficiency anemia and pharyngeal carcinoma has been reported in northern Europe (also known as the Plummer–Vinson or Paterson–Kelly syndrome), but this association has not been observed in the United States (Ekberg and Nylander 1983).

Webs are characterized by 1–2 mm wide, shelf-like filling defects along the anterior wall of the hypopharynx or cervical esophagus that protrude to

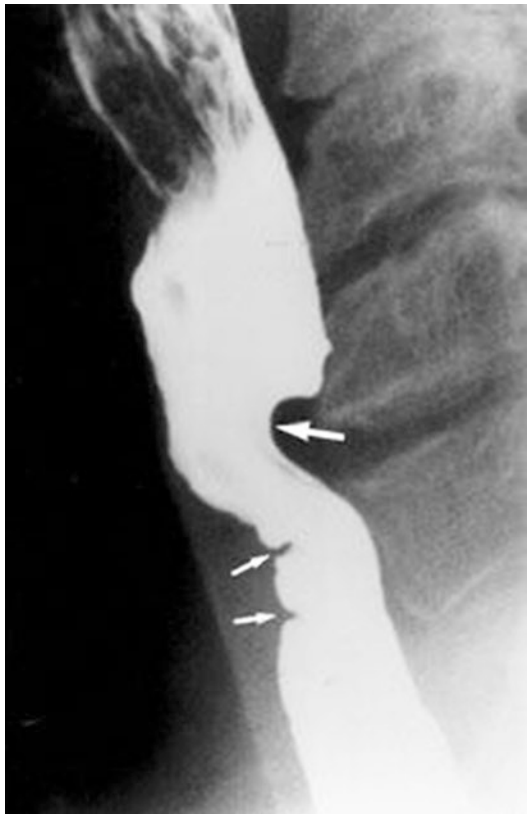

Fig. 24 Cervical esophageal webs. Lateral view of the pharynx and cervical esophagus during swallowing shows two thin, weblike indentations (*small arrows*) on the anterior wall of the cervical esophagus. Also note a rounded indentation posteriorly (*large arrow*) at the pharyngoesophageal junction due to incomplete relaxation of the cricopharyngeus

various depths into the esophageal lumen (Fig. 24). The use of dynamic or rapid sequence imaging and large barium boluses increases the detection rate of webs. In more severe cases, webs may be associated with a jet phenomenon and proximal dilatation of the pharynx (Taylor et al. 1990).

4 Rings

Lower esophageal rings are found in 6–14% of patients who undergo esophagography, but less than 1% of patients with rings are symptomatic (Schatzki and Gary 1956). The term Schatzki ring should be reserved only for those patients with lower esophageal rings who present with dysphagia. These rings almost always occur at the gastroesophageal junction. Histologically, the superior surface of the ring is lined by squamous epithelium and the inferior surface by columnar epithelium. The exact pathogenesis of Schatzki rings is uncertain but some are thought to develop as a result of scarring from reflux esophagitis (Chen et al. 1987).

Lower esophageal rings appear on barium studies as 2–3 mm in height, weblike constrictions at the gastroesophageal junction, almost always above a hiatal hernia (see Fig. 27b). The rings can be missed if the distal esophagus is not adequately distended at fluoroscopy, so it is important to obtain prone views of the esophagus during continuous drinking of a low-density barium suspension. It has been shown that rings with a maximal luminal diameter of more than 20 mm rarely cause dysphagia, whereas rings with a maximal diameter of less than 13 mm almost always cause dysphagia (Schatzki 1963).

5 Diverticula

Esophageal diverticula may be classified as *pulsion* or *traction* diverticula. The more common pulsion diverticula result from esophageal dysmotility with increased intraluminal pressures in the esophagus, whereas traction diverticula are caused by scarring in the soft tissues surrounding the esophagus. Diverticula most commonly occur in the region of the pharyngoesophageal junction (i.e., Zenker's diverticulum), midesophagus, and distal esophagus above the gastroesophageal junction (i.e., epiphrenic diverticulum).

5.1 Pulsion Diverticula

Pulsion diverticula tend to be located in the distal esophagus and are often associated with fluoroscopic or manometric evidence of esophageal dysmotility. These diverticula are usually detected as incidental findings in patients who have no esophageal symptoms. However, a large

epiphrenic diverticulum adjacent to the gastroesophageal junction may fill with debris, causing dysphagia, regurgitation, or aspiration. Pulsion diverticula appear on barium studies as rounded outpouchings from the esophageal lumen that have wide necks. They often do no empty completely when the esophagus collapses and may be associated with other radiologic findings of esophageal motor dysfunction (Levine 2000a, b).

5.2 Traction Diverticula

Traction diverticula occur in the midesophagus and are usually caused by scarring from tuberculosis or histoplasmosis involving subcarinal or perihilar lymph nodes. Traction diverticula are true diverticula containing all layers of the esophageal wall and therefore maintain their elastic recoil. As a result, they tend to empty their contents when the esophagus collapses at fluoroscopy (Levine 2000a, b). Traction diverticula often have a triangular or tented appearance caused by traction on the diverticulum by the fibrotic process in the adjacent mediastinum (Fig. 25). Thus, it often is possible to distinguish traction diverticula from pulsion diverticula on barium studies.

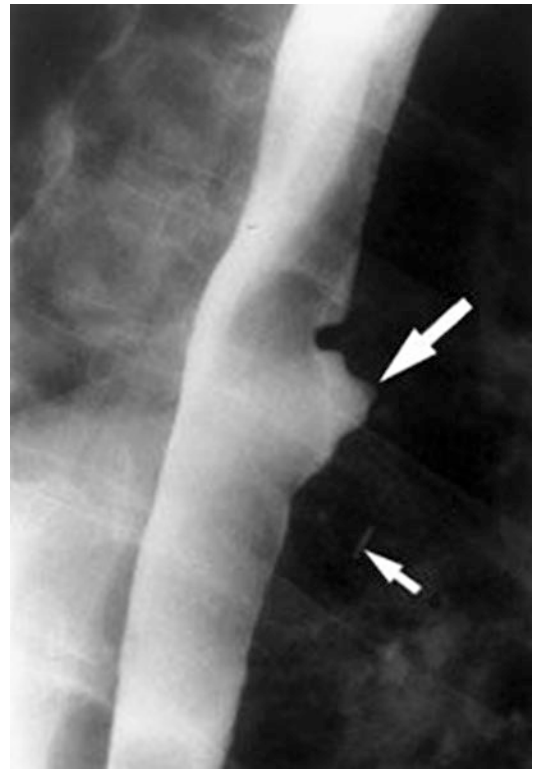

Fig. 25 Traction diverticulum. Single-contrast view shows a triangular outpouching (*upper arrow*) from the midesophagus. Note a surgical clip (*lower arrow*) in the adjacent mediastinum. The diverticulum resulted from postsurgical scarring in this region

6 Varices

Esophageal varices can be classified as *uphill* or *downhill*. Uphill varices are caused by portal hypertension with increased pressure in the portal venous system transmitted upward via dilated esophageal collaterals to the superior vena cava. In contrast, downhill varices are caused by superior vena cava obstruction with downward flow via dilated esophageal collaterals to the portal venous system and inferior vena cava. Uphill varices are much more common than downhill varices.

6.1 Uphill Varices

Uphill esophageal varices develop as a result of portal hypertension or other causes of portal venous obstruction. Varices appear on barium studies as serpiginous or tortuous longitudinal filling defects in the distal half of the thoracic esophagus (Fig. 26). They are best seen on mucosal relief views of the collapsed esophagus using a high-density barium suspension to increase mucosal adherence (Cockerill et al. 1976). Even with proper technique, esophageal varices may be seen as a transient finding due to periodic filling and emptying of the varices with esophageal peristalsis or distention. The differential diagnosis for varices includes submucosally infiltrating esophageal carcinomas (varicoid carcinomas) and esophagitis with thickened folds due to submucosal inflammation and edema.

Esophageal varices are characterized on CT by a thickened, lobulated esophageal wall containing tubular structures that enhance

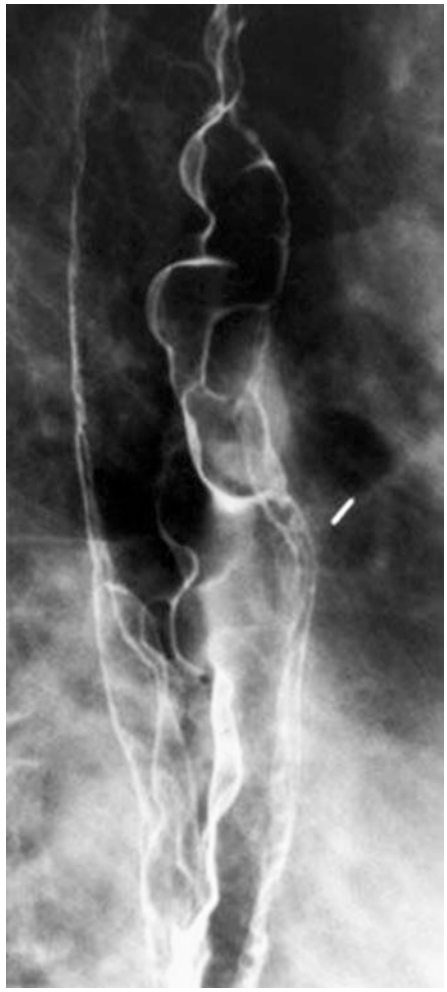

Fig. 26 Esophageal varices. Double-contrast view shows serpiginous longitudinal defects etched in *white* in the lower third of the esophagus due to uphill esophageal varices

markedly after intravenous administration of contrast material. Additional varices may be seen elsewhere in the abdomen at other sites of communication between the portal and systemic venous circulations. Angiography of the celiac or superior mesenteric arteries can be used to confirm the presence of extensive collateral flow and varix formation in and around the distal esophagus.

However, the need for portal venography for presurgical planning of portosystemic shunts has decreased with the widespread use of transjugular intrahepatic portosystemic shunting (TIPS) procedures.

6.2 Downhill Varices

One of the most common causes of downhill varices is bronchogenic carcinoma with mediastinal metastases and superior vena cava obstruction. Additional causes include other primary or metastatic tumors involving the mediastinum, mediastinal irradiation, sclerosing mediastinitis, substernal goiter, and central catheter-related thrombosis of the superior vena cava. Most patients with downhill varices present clinically with superior vena cava syndrome and many have melena and iron-deficiency anemia from variceal bleeding.

Downhill varices typically appear as serpiginous longitudinal filling defects which, unlike uphill esophageal varices, are confined to the upper or midesophagus. Chest radiographs or CT often reveals the underlying cause of superior vena cava obstruction.

7 Foreign Body Impactions

In adults, esophageal foreign body impactions are most commonly caused by inadequately chewed pieces of meat (Nandi and Ong 1978). Most of these foreign bodies pass spontaneously into the stomach, but 10–20% require some form of therapeutic intervention. Although the risk of perforation is less than 1% during the first 24 h, this risk increases substantially after 24 h because of ischemia and pressure necrosis at the site of impaction (Barber et al. 1984). Affected individuals typically present with acute onset of dysphagia, substernal chest pain, and/or a foreign body sensation.

Contrast studies are sometimes performed in patients with suspected food impaction to confirm the presence of obstruction and determine its level and also to rule out esophageal perforation. An impacted food bolus typically appears as a polypoid defect with an irregular meniscus superiorly (Fig. 27a). Because of the degree of obstruction, it may be difficult to assess the underlying esophagus at the time of impaction. It is therefore prudent to perform a follow-up barium study after the impaction has been relieved to determine if this impaction was caused by a

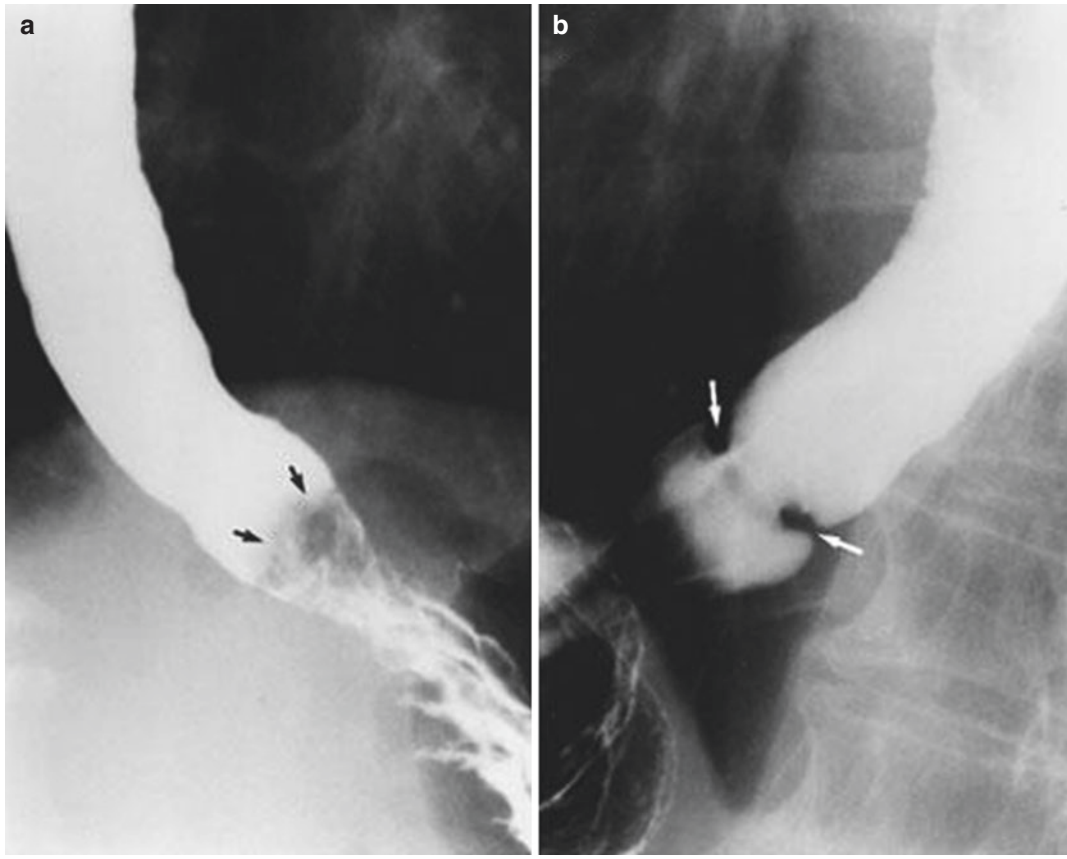

Fig. 27 Food impaction caused by a Schatzki ring. (**a**) Initial view shows a polypoid defect in the distal esophagus with an irregular meniscus superiorly (*arrows*) due to impacted meat in this region, (**b**) after the impaction has been relieved, a repeat view shows an underlying Schatzki ring as the cause of the impaction. Note the smooth, symmetric ringlike constriction (*arrows*) at the gastroesophageal junction above a small hiatal hernia

pathologic area of narrowing. The most common causes are Schatzki rings (Fig. 27b) and peptic strictures. Rarely, food impactions may even result from giant thoracic osteophytes impinging on the esophagus (Underberg-Davis and Levine 1991; Levine 2000a, b).

8 Fistulas

Esophageal airway fistulas usually result from direct invasion of the tracheobronchial tree by advanced esophageal cancer (Fig. 28). Such fistulas have been reported in 5–10% of patients with esophageal cancer, often occurring after treatment with radiation therapy (Fitzgerald et al. 1981; Little et al. 1984). Other causes of esophageal airway fistulas include esophageal instrumentation, trauma, foreign bodies, and surgery (Vasquez et al. 1988). Affected individuals typically present with violent episodes of coughing and choking during deglutition. When an esophageal airway fistula is suspected on clinical grounds, barium should be used instead of hyperosmolar water-soluble contrast agents, which may cause severe pulmonary edema if a fistula is present.

Esophagopleural fistulas may be caused by esophageal carcinoma, radiation therapy, surgery, or instrumentation. Such patients may present with a pleural effusion, pneumothorax, or hydropneumothorax. When an esophagopleural fistula is suspected, the presence and location of the fistula can be confirmed by a study with water-soluble contrast media.

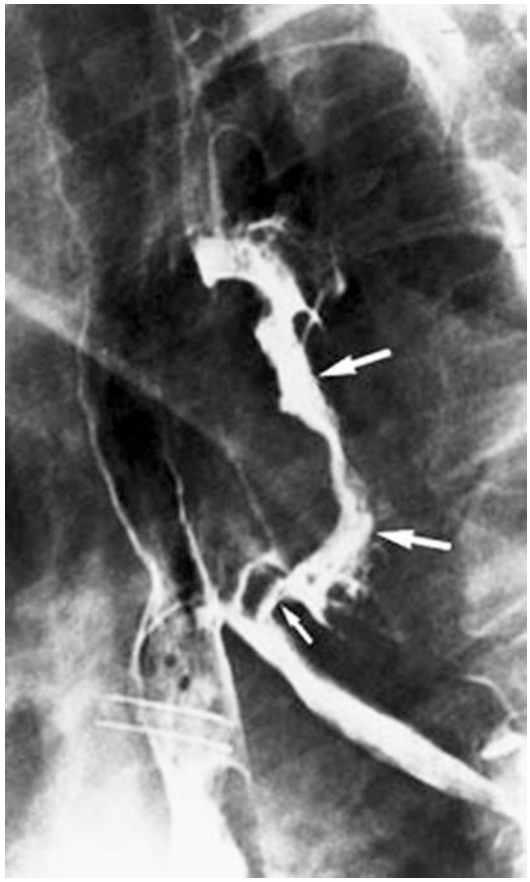

Fig. 28 Advanced esophageal carcinoma with esophagobronchial fistula. An infiltrating carcinoma (*large arrows*) is seen in the midthoracic esophagus with barium entering the airway via an esophagobronchial fistula (*small arrow*)

Aortoesophageal fistulas are extremely rare but are associated with a high mortality rate. Such fistulas may be caused by a ruptured aortic aneurysm, aortic dissection, infected aortic graft, swallowed foreign body, or esophageal cancer (Baron et al. 1981, Hollander and Quick 1991). Patients with aortoesophageal fistulas may present with an initial episode of arterial hematemesis followed by a variable latent period, before experiencing massive hematemesis, exsanguination, and death (Baron et al. 1981). Oral studies with water-soluble contrast agents are unlikely to show the fistula because of high aortic pressures, whereas contrast aortography may fail to show the fistula because of occlusion of the fistulous tract by thrombus (Baron et al. 1981).

9 Perforation

If untreated, perforation of the esophagus is associated with a mortality rate of nearly 100% because of a fulminant mediastinitis that occurs in these patients. Early diagnosis is therefore critical. Endoscopy is the most common cause of esophageal perforation, accounting for more than 75% of cases. Other causes include foreign bodies, food impactions, penetrating and blunt trauma, and spontaneous esophageal perforation due to a sudden, rapid increase in intraluminal esophageal pressure (Boerhaave's syndrome).

Cervical esophageal perforation may be manifested on neck radiographs by subcutaneous emphysema, retropharyngeal air (Fig. 29a), and pneumomediastinum. Lateral images of the neck may also show widening of the prevertebral space or a retropharyngeal abscess containing loculated gas and/or air-fluid levels. In contrast, thoracic esophageal perforation may be associated with pneumomediastinum, mediastinal widening, and a pleural effusion or hydropneumothorax (Parkin 1973; O'Connell 1967). In the proper setting, the presence of mediastinal gas on CT should be highly suggestive of esophageal perforation, whereas other findings such as pleural effusion or mediastinal fluid are less specific (White et al. 1993). CT is less reliable for determining the site of perforation.

Esophagography often is performed on patients with suspected esophageal perforation (Figs. 29b and 30). Although barium is the most sensitive contrast agent for detecting small leaks, it can potentially cause a granulomatous reaction in the mediastinum. In contrast, water-soluble agents do not incite a mediastinal reaction and are readily absorbed from the mediastinum if a leak is present. However, water-soluble contrast agents are less radiopaque than barium and can miss as many as 15–50% of esophageal perforations (Buecker et al. 1997). These agents can also cause severe pulmonary edema if aspirated into the lungs. It is therefore recommended that the examination be repeated with high-density barium to detect subtle leaks if the initial study with water-soluble contrast media shows no evidence of perforation (Swanson et al. 2003).

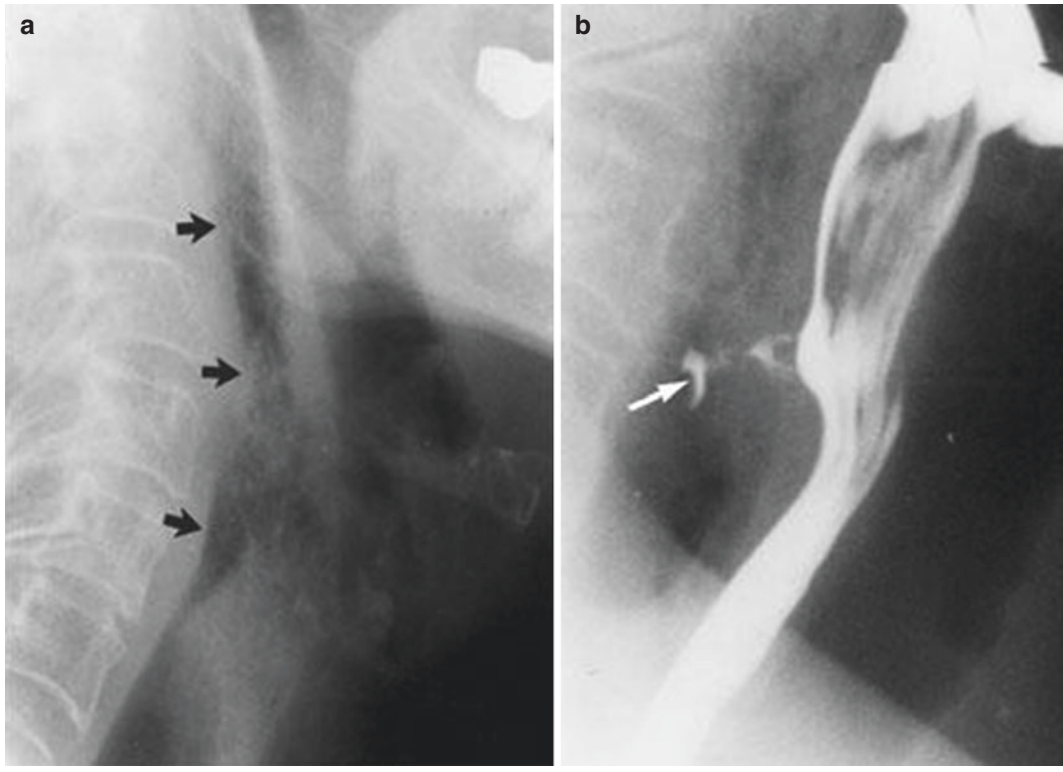

Fig. 29 Perforation of the cervical esophagus. (**a**) Lateral view of the neck shows mottled gas in the retropharyngeal space, (**b**) a subsequent study with water-soluble contrast material shows a small, sealed-off perforation (*arrow*) from the posterior aspect of the pharyngoesophageal junction. This perforation was caused by traumatic endoscopy

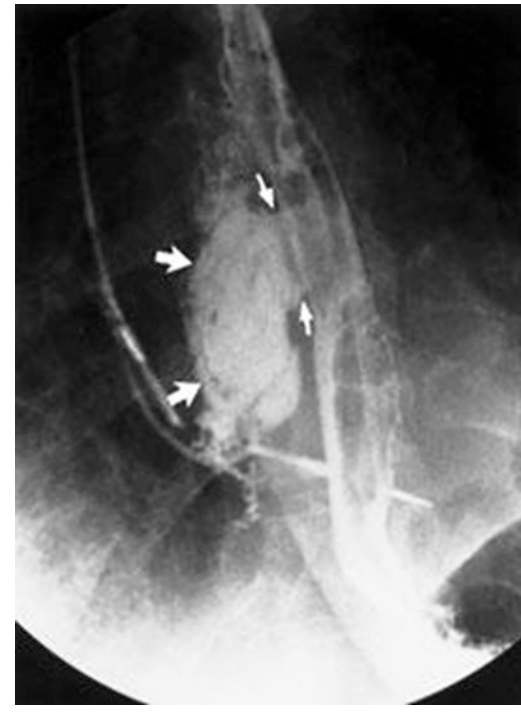

Fig. 30 Perforation of the thoracic esophagus. A study with water-soluble contrast material shows focal extravasation of contrast from the right lateral wall of the lower esophagus (*small arrows*) into a collection (*large arrows*) in the adjacent mediastinum. This perforation occurred as a complication of endoscopic dilatation

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The Pediatric Esophagus

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Contents

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Abstract

A child's feeding and swallowing problems can have anatomic and functional causes that are congenital (due to embryologic malformations), or can be acquired after birth. The anatomy of the upper GI tract is uniquely demonstrable on imaging. The radiologist is a key member of the team that diagnoses and cares for these children.

1 Introduction

Feeding one's child and watching it grow and thrive is one of the chief joys of parenting, so anything that interferes with this is likely to prompt a quick demand for medical attention. Symptoms such as vomiting, choking, irritability, and food refusal are all very distressing to both the parent and the child. However, because the gastrointestinal (GI) tract in a child, particularly a young infant, is relatively short and compact, abnormalities at the level of the pharynx, esophagus, stomach, small bowel, or even colon can result in puzzlingly similar clinical manifestations. Determining a cause for the symptoms often falls to the radiologist, who has the unique opportunity to observe the GI tract in action.

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2 Imaging Methodology and Techniques: Showing Anatomy and Function for Diagnostic Efficacy

The range of procedures available to image the pediatric esophagus is the same as that available for adults, but the choice is influenced by the odds of finding certain types of pathologic abnormalities. Moreover, the application of these procedures differs from that in adults because of the unique challenge of obtaining a diagnostic examination in the pediatric patient.

2.1 Fluoroscopy

Fluoroscopy is the mainstay of esophageal examination, as it displays not only anatomy but, just as importantly, function. The area examined may be confined to the esophagus, but usually the esophagus is seen in the context of the entire upper GI tract, from the mouth to the ligament of Treitz. This examination is usually done with the child supine or in the lateral position on the fluoroscopy table. Swallows in the true lateral position are extremely important to look for contrast in the trachea and deformity or narrowing of the esophagus from the posterior or anterior aspect. True anteroposterior projections look for esophageal displacement or narrowing from the sides. Recording video clips of the fluoroscopy is extremely helpful, as abnormalities may be fleeting.

Volitional swallow and good distension of the esophagus are of paramount importance. These can only be achieved with a comfortable, cooperative patient. Infants and older children are easier to manage, whereas toddlers and young children are more apt to be frightened and less persuadable. The room should be as warm and as light as possible, and the child should be allowed to keep its clothing on; only large metallic fastenings should be removed, and the child should wear a protective gown. A pad or blanket should be put on the fluoroscopy table. The child should be allowed to hold a favorite blanket or stuffed animal. The fluoroscopy image intensifier should be introduced as a big "tent" or "house." The child should be shown how the image intensifier will get very close to it but will not touch it. Colorful stickers on the face of the image intensifier give the child something to look at. A video machine playing a children's movie or cartoon is an excellent distraction.

The choice of contrast medium can improve the chances of getting a good examination. Standard oral barium sulfate preparations have the consistency of milk, and some are sweetened with sorbitol or the like, and a very hungry infant is usually very cooperative and needs no additional persuasion. It is helpful to use the type of nipple that the infant is familiar with, and also to enlarge the end hole slightly. With an older toddler, hiding the contrast medium in a familiar cup with a straw can be successful. Barium can be flavored with different fruit drink powders or with chocolate syrup; give the child what it chooses. Water-soluble iodinated contrast medium has a bitter taste that is more difficult to disguise, and in the concentrations often necessary for it to be seen on fluoroscopy it is not as benign as barium if it is aspirated. In postsurgical examinations when there is risk of perforation of the esophagus, however, its use may be mandated.

There are times when the child refuses to cooperate. It is helpful at this point to "triage" the clinical questions: What is the most important question to be answered? The next most important? You must do this, because structuring the examination to answer one question may take away your chance to answer another. If the examination cannot be rescheduled for another day when the child might be more hungry or better rested, then the contrast medium must be administered manually. Assistance from parents and/or technologists is necessary. Wrapping the child's legs in a sheet can often help persuade it that resistance is futile. A small syringe (5 mL for a toddler, 10 mL for an older child) is used to put aliquots of contrast medium as far back in the child's mouth as possible. At least a small amount is generally swallowed, allowing appreciation of pharyngeal function and esophageal motility. If this fails, then a small feeding tube is passed

through the child's nose and into the distal esophagus. With the child in the lateral position, the radiologist pulls the tube back slowly, hand-injecting at intervals sufficient volume to distend the esophagus, until the entire esophagus is imaged. This gives a poor assessment of esophageal motility, however, and there is danger of aspiration. In addition, a "normal" study performed only with a tube will miss the abnormality associated with swallowing that can be found in up to half the patients referred for examination (Vazquez and Buonomo 1999).

Assessing gastroesophageal reflux (GER) fluoroscopically takes patience. It is best to do this at the end of the examination. The child's stomach should be full and the child should be relaxed and distracted. If the preceding part of the study has been unpleasant, the child might be allowed to feed in its parent's arms until its stomach is full, and then it should be placed again beneath the fluoroscope. Darkening the room and minimizing noise might encourage the child to fall asleep in a supine position. Videos or recorded music provides solace and distraction for the toddler. The fluoroscope should be positioned to show the esophagus, and then one should image for only about 1 s out of every 7–10 s, for a total of 5 min (less than 1 min of fluoroscopy time). Significant reflux, i.e., reaching the clavicles, cervical esophagus, or pharynx, will persist long enough for it to be recorded. Crying reinforces the diaphragmatic hiatus and minimizes reflux, so assessment in an inconsolable child may have to be abandoned.

The modified barium swallow is conducted very differently. Here, the child's usual feeding position is duplicated in a chair or seat, and graded food textures are offered, opacified with contrast medium. A trained feeding therapist should be in attendance and should choose the textures to be tested, and a familiar person should do the feeding. Because of the confines of the imaging chair and the fluoroscopy image intensifier, imaging is usually done from the lateral projection only. The study is recorded on video alone. Because the child is less restrained, the radiologist must work to keep the pharynx centered in the screen.

2.2 Radiation Dose Reduction

Throughout any fluoroscopic examination, the radiologist must be constantly mindful of the accumulating radiation dose. Grids should not be used for children less than adult size. The thyroid has to be part of the field of view, but gonads, pelvic bone marrow, and ocular lenses should be rigorously excluded by coning and shielding. Intermittent review of the recorded video may find that an abnormality has been imaged that escaped direct visualization, and that additional imaging is unnecessary. Pulsed fluoroscopy can dramatically reduce the patient dose with relatively minor image degradation (Hernandez and Goodsitt 1996). Digital fluoroscopy units have the added advantage of "last image hold," whereby the image present on the screen when the examiner stops fluoroscoping remains there and can be captured as a permanent digital image. Since the examiner can react more quickly to seeing a pathological event than the spot image device can record it, there is a better chance that it will be caught. This also avoids the dose from spot exposure technique. The use of magnification causes the fluoroscope to increase output to maintain image brightness and thereby multiplies the dose; it should be used only when absolutely necessary.

2.3 Advanced Imaging Techniques

Nuclear medicine offers a low-dose way to monitor an entire feeding and postprandial period to look for aspiration and reflux. Technetium-99 m is the isotope of choice to label a meal. The limitation is not on imaging time, but rather on patient movement during scanning: misregistration introduces an uninterpretable artifact, so sedation is sometimes necessary (del Rosario and Orenstein 1998).

CT and MRI are sometimes necessary for imaging extraesophageal structures. CT interpretation is made difficult by the lack of mediastinal fat planes and intravenously administered contrast medium is usually necessary. Scanning is quick in the newer, multidetector machines and sedation is rarely, if ever, needed. Care must be

taken to adapt the scan parameters to the weight of the child and to keep the radiation dose as low as possible. MRI excels in imaging the mediastinum and its vascular structures, where cardiac and respiratory gating ensures interpretable images without administration of contrast medium. However, the long imaging time means that sedation is usually indicated.

The application of ultrasound is limited because of the location of the esophagus deep to the air-filled lungs. GER can be imaged from the epigastric region using color-Doppler ultrasonography (Jang et al. 2001). The practicality and efficacy remain to be determined, however.

3 Congenital Esophageal Abnormalities: Their Basis in Embryology

Abnormalities of the pediatric esophagus can be loosely classed as either anatomic or functional, with congenital and acquired lesions in each category. Congenital anatomic abnormalities originate in defective morphogenesis early in embryonic life (Berrocal et al. 1999; Moore 1989). Lateral tracheoesophageal folds form in the embryonic foregut during the fourth week of development. These fuse and allow the esophagus and trachea to lengthen independently. The trachea remains united with the developing pharynx cranial to the folds, through the laryngeal aditus. The esophagus is initially very short, but reaches its final length as the embryo grows. The epithelium of the esophagus proliferates and almost obliterates the lumen; recanalization occurs during the eighth week of development. Defects in the progression of fold fusion, recanalization, or lengthening result in congenital anatomic abnormalities that the radiologist is usually called upon to characterize.

3.1 Esophageal Atresia and Tracheoesophageal Fistula

Incomplete differentiation of the presumptive trachea from the esophagus in the fourth week of embryonic development results in a spectrum of abnormalities that come to clinical attention immediately, when the infant cannot swallow oral secretions and a tube cannot be passed to the stomach. The largest group (82%) (Buonomo et al. 1998) has esophageal atresia (EA) with a distal tracheoesophageal fistula (TEF). This is visible on a plain radiograph, with an air-filled sac projecting in the neck, perhaps with a coiled tube, and air in the stomach and gut. Studies with contrast medium are not necessary and would cause aspiration. If imaging is necessary, air insufflation of the upper sac under fluoroscopy may suffice; otherwise, careful injection of a very small amount of low-osmolarity water-soluble contrast medium may delineate the needed field. The infant's head should be elevated and the contrast medium quickly removed. A few babies in this spectrum (6%) have an isolated TEF (Fig. 1). A few others not considered part of this group have a laryngeal cleft, a high defect at the level of

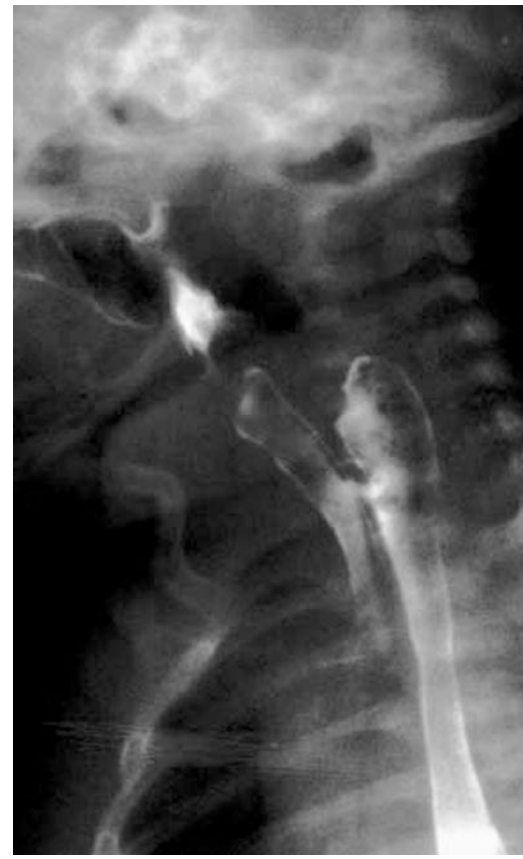

Fig. 1 Newborn male with choking and hypoxemia with feeding. Lateral view from barium swallow delineates TEF, with contrast in the trachea

the aditus that can be confused clinically and fluoroscopically with a TEF.

The surgeon may wish the radiologist to more extensively study a smaller group prior to surgery: the 10% that have atresia without a TEF or with a TEF from the proximal esophageal segment. These babies will have no air distally in the GI tract. The timing of the surgery may depend on the growth of the proximal and distal esophageal segments; the smaller the distance between the ends, as demonstrated by the approximation of radio-opaque catheters under fluoroscopy (Rossi et al. 1998), the more successful the repair. Postoperative follow-up must be alert for early anastomotic leaks, late anastomotic strictures, and recurrent fistulas (Cumming and Williams 1996). Pneumothorax, pneumomediastinum, or pleural effusion might be signs on plain radiographs of developing complications.

All of these infants must be screened for the skeletal, renal, anal, and cardiac anomalies that can coexist with EA–TEF in the VATER or VACTERL associations in about half of the patients (Buonomo et al. 1998). Vertebral and limb abnormalities can be diagnosed by plain radiography, whereas ultrasonography is the most efficient screen for the brain and heart. Anorectal malformations may be apparent clinically. Repair of the TEF may not relieve all respiratory symptoms; tracheomalacia almost always occurs when there is a TEF and the residual tracheal weakness may demand its own surgical intervention.

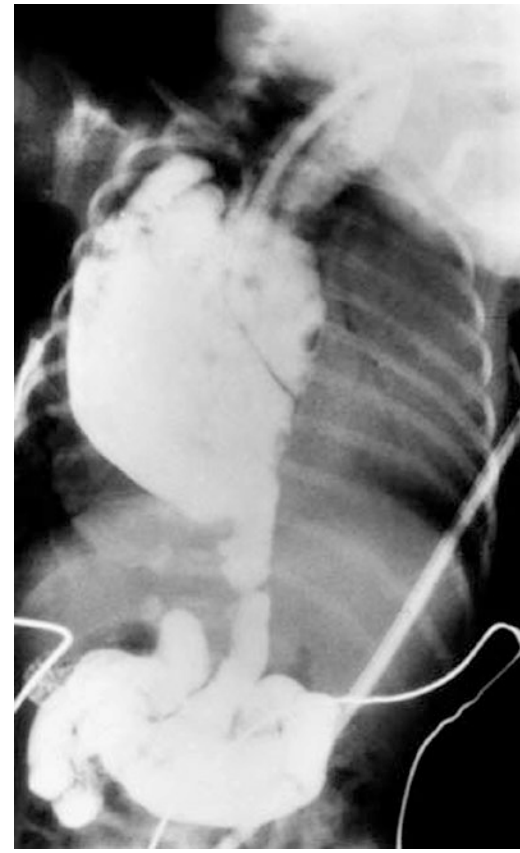

Fig. 2 Newborn female with cystic right chest mass on prenatal ultrasound. Barium fills the intrathoracic stomach and short esophagus

3.2 Other Causes of Esophageal Narrowing

If the esophagus is intact, diagnosis may be delayed until the infant begins to exhibit feeding difficulties: food refusal, slow feeding, and vomiting. Again, the spectrum of possible embryologic errors gives several differential diagnostic possibilities. The esophagus may be very short, due to defective lengthening. Plain radiography and barium upper GI tract study show the stomach in the chest (Fig. 2). Defective luminal recanalization can result in webs (often in the midesophagus, but can occur at any level) or longer segment fibromuscular stenosis, usually in the lower third of the esophagus (del Rosario and Orenstein 1998). Embryonic remnants in the esophageal wall can cause luminal narrowing. These can take the form of respiratory tract traces, such as cartilage, which will stiffen the wall and interfere with peristalsis. This can occur in conjunction with TEF and EA, and may be overlooked owing to the magnitude of these other abnormalities (Dohil and Hassall 1998).

A smoothly curving defect in the barium-filled esophagus indicates an extraluminal mass that may be intrinsic to the esophageal wall or extrinsic to the esophagus. The esophagus is the second most common site for duplication, after the ileum (Berrocal et al. 1999). It can form a cyst lined with secretory mucosa that causes increasing symptoms as it grows. The mucosa can also be gastric in differentiation; its presentation will be due to ulceration. The location is usually in the intrathoracic esophagus. The same type of

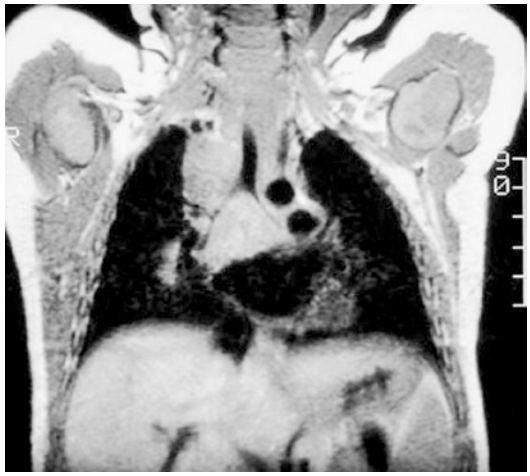

Fig. 3 Six-month-old male, 2 months after a visit from foreign relatives. Coronal MRI shows compression of mediastinal structures by pericarinal and paratracheal adenopathy. The patient was treated for tuberculosis

embryologic error in the respiratory tree forms bronchogenic cysts (Nobuhara et al. 1997). In their usually central location, close to the carina, they can cause respiratory symptoms that may mask feeding problems and delay diagnosis. If complicated by infection, their presence may be detected by a mediastinal air–fluid level on a plain radiograph (Hedlund et al. 1998). Leiomyomas are rare, smooth muscle tumors, and the esophagus is an unusual place for them, but they can occur. In children, they are more likely to be multiple or infiltrative than in adults. Leiomyomatosis is a very rare condition seen in about 5% of patients with Alport syndrome where widespread involvement of the esophagus and, occasionally, the tracheobronchial tree by smooth muscle proliferation leads to debilitating symptoms (Guest et al. 2000). Pericarinal adenopathy of sufficient magnitude in a small infant can compress the esophagus as well (Fig. 3).

Narrowing of the cervical esophagus has a slightly different differential list, influenced by the proximity of the branchial clefts. Cysts can form from second cleft remnants, whereas the third and fourth clefts can fistulize to the piriform sinuses. Cysts of the thyroid, thyroglossal duct, thymic remnants, or larynx can also occur. Duplication is a rare finding in this region (Wootton-Gorges et al. 2002).

Because of the complexity of embryonic morphogenic processes, multiple errors can coexist. It behooves the radiologist to recognize patterns of malformation when they occur, but not to be a slave to them. In so doing, the radiologist might reject the possibility of a certain abnormality because it does not "fit the pattern," and thereby misses a diagnosis. For example, a child with thoracic vertebral anomalies who had other VATER/VACTERL elements excluded as an infant should not be dismissed as having behavioral problems if it presents later with feeding difficulties. Rather, a search for a neuroenteric cyst or a duplication cyst should be considered, both of which can also coexist with spina bifida, hemivertebra, and fusion defects (Berrocal et al. 1999). Finding one abnormality should not stop the search for others. Case reports abound in the literature illustrating odd and unexpected assortments of allied anomalies: EA–TEF with esophageal stenosis (Newman and Bender 1997), TEF with web and duplication (Snyder et al. 1996), and anomalous origin of a bronchus from the esophagus (Lallemand et al. 1996).

3.3 Vascular Anomalies

Vascular rings and slings deserve special mention, as they can be definitively described radiologically and treatment can be planned accordingly. Like other abnormalities that narrow rather than interrupt the esophagus, these may come to clinical attention when the child's diet changes from liquid to solid. The embryonal system of parallel, interconnecting dorsal and ventral arteries normally recedes focally to leave the familiar left aortic arch and its branches. Variation in the pattern of recession can leave the fetus with arteries that cross and impinge on mediastinal structures (Strife et al. 1998). Two entities that form anatomically complete rings that encircle the trachea and esophagus and are fairly common are the double-aortic arch (Fig. 4) and the right arch with aberrant left subclavian artery and intact ductus or ligamentum (Fig. 5). These patients will present with respiratory and feeding

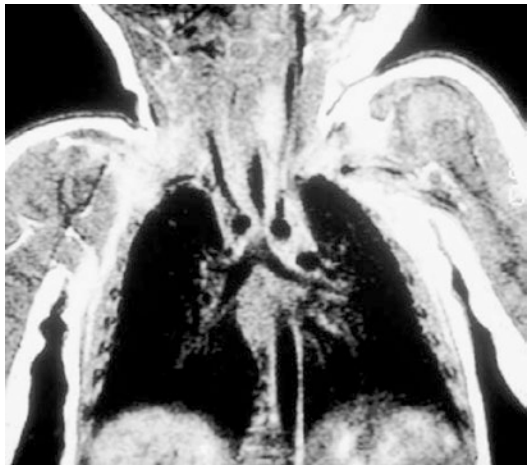

Fig. 4 Five-month-old male with feeding difficulty, stridor, and distorted esophagus on barium swallow. Coronal MRI shows the trachea compressed between the double-aortic arches

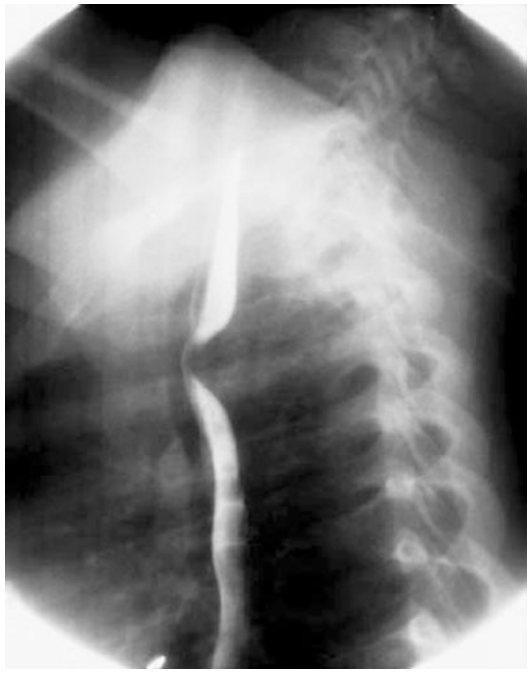

Fig. 5 Two-month-old female with wheezing and regurgitation, and right aortic arch on chest X-ray. Lateral view of barium swallow shows prominent posterior defect. MRI (not shown) confirmed vascular ring with right arch, aberrant left subclavian artery, and intact ligamentum

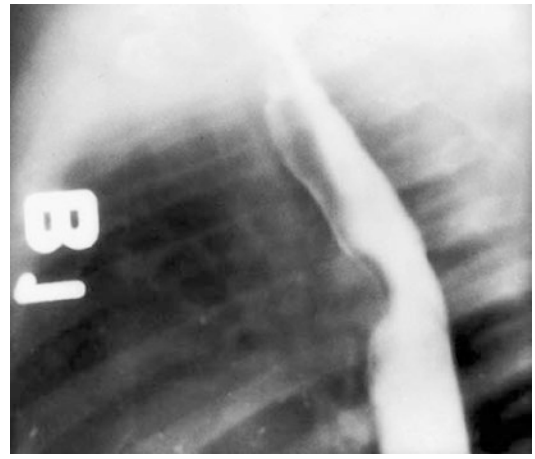

Fig. 6 One-month-old male with wheezing. Chest radiograph (not shown) was remarkable for asymmetric hyperinflation on the right. Lateral view of barium swallow shows anterior defect in the contrast column, compatible with pulmonary sling. Confirmed by MRI (not shown)

difficulties, although when the former is thought to cause the latter diagnosis can be delayed. Surgical treatment is usually mandated. Patients with an arch with contralateral subclavian aberrancy, such as the very common left arch with aberrant right subclavian artery, will not have respiratory symptoms if the ligamentum is broken or elongated. Although a posterior defect may be seen in the barium-filled esophagus from the aberrant vessel, surgery is not usually necessary unless the symptoms interfere with growth. Likewise, a pulmonary sling, where the left pulmonary artery passes between the trachea and esophagus on its way to the left side from its anomalous origin on the right, may distort the esophagus without compression (Fig. 6); its compressive effect on the tracheobronchial tree, however, may be profound and this can secondarily interfere with feeding (Siripornpitak et al. 1997). Where a vascular anomaly is suspected, either primarily or uncovered on a barium esophagram, MRI can definitively delineate it and show its effect on mediastinal structures; angiography is contraindicated. A contrast-enhanced CT scan with 3D reconstruction can show the abnormality very well, but the radiation dose can be quite high. However, CT scanning has become so fast that sedation is almost never necessary. Thus, the radiation dose may be acceptable when the sedation needed for MRI poses a greater risk, as in a child with a narrowed airway.

4 Congenital Functional Abnormalities: The Interplay of Anatomy and Maturation

4.1 Dysphagia

Swallowing demands a certain level of central nervous system maturation and function. Musculoskeletal structures in the face and neck must act in flawless concert to safely deliver ingested food past the larynx and into the esophagus. Similar functions are brought into play to protect the airway during reflux or vomiting. Swallows can be observed in the 12-week fetus, and passage of amniotic fluid through the GI tract is essential for its growth and development. However, the oral phase of swallow requires skills that come with later fetal maturity (Derkay and Schechter 1998). The suckle behavior of premature infants is characterized by short bursts of quick jaw movements and tongue compressions. This persists in the mature infant as nonnutritive sucking, an important behavioral adjunct to successful feeding. However, premature infants cannot reliably mount the negative intraoral pressure required for extraction of fluid from the nipple and formation of a swallow bolus. Thus, an esophagram of such an infant may show fluid loss from the mouth, uncontrolled entry of fluid to the pharynx, nasopharyngeal reflux, penetration of fluid to the larynx and trachea, lack of cough response, and poor coordination of breathing and swallowing. All of these are causes for great concern when they occur in the term or near-term infant, but may prompt only watchful waiting and cautious reevaluation at a later time in a baby who could have a postconception age of 25–32 weeks at the time of the first examination. However, in both groups the finding of contrast in the trachea should be scrutinized carefully to exclude the possibility of a TEF or laryngeal cleft. Using a small, thin-walled nipple and observing swallows at the start of the examination before the patient tires help the premature infant show its best abilities.

Infants and children with central nervous system dysfunction secondary to primary brain dysplasia (due to prenatal infection or vascular events, or to chromosomal abnormality; Eicher et al. 2000) and perinatal hypoxemia or hemorrhage form a large and growing population of patients with impaired swallowing. Loss of swallow skills from head trauma, malignancy, or degenerative disorders adds these patients to this group as well. Occasionally, progressive dysphagia is the presenting symptom that leads to diagnosis (Elta et al. 1996), or it may be only one of many problems. Advances in salvage and supportive care have made the basic ability to be fed the remaining determinant of survival in this population. It is the job of the radiologist, often in tandem with a feeding therapist, to determine a patient's level of function, whether there are any anatomic impediments to safe feeding, and what food textures can be fed (Gisel et al. 1998). The esophagram is often used to elucidate the basic anatomic framework and exclude obstruction, followed by a modified barium swallow concentrating on the swallow mechanism (Mercado-Deane et al. 2001).

4.2 Gastroesophageal Reflux

GER is near-universal in infants, decreasing in frequency with growth and maturation. It still occurs in normal children as well. It becomes pathologic when associated with pain, respiratory symptoms, or dysphagia. Transient lower esophageal sphincter (LES) relaxation has been implicated in allowing reflux episodes to occur, but many factors contribute to the transition of reflux from a benign to a malignant classification (del Rosario and Orenstein 1998). One such factor is decreased esophageal clearance, from supine positioning, dysmotility, or infrequent swallowing. The presence of a nasogastric feeding tube can also impede acid clearance, although the number of reflux episodes is unchanged; a large tube can convert a nonrefluxer to a refluxer, however (Noviski et al. 1999). Straining, a favorite maneuver to provoke reflux in adults during a fluoroscopic examination, does not do the same in children, unless it happens to coincide with a transient LES relaxation (Kawahara et al. 2001). High gastric volume (due to large feeds or

delayed gastric emptying) and increased osmolality in gastric contents are associated with more and longer periods of lowered LES pressure (Salvia et al. 2001). Hiatus hernia promotes reflux because of the loss of diaphragmatic hiatal support for the LES.

The most important morbidity associated with GER is aspiration. The effects of gastric acid on the tracheobronchial tree visible on a plain radiograph may be subtle hyperinflation due to vagal-mediated bronchospasm or flagrant peribronchial inflammation, atelectasis, or pneumonia. In the child who is usually in a supine position, the upper lobes, particularly on the right, may be more involved; a child who is more erect will deposit the aspirate into the lower lobes. Even aspiration of saliva, if it occurs chronically, is far from benign. Distinguishing between salivary and gastric aspiration can be important for therapy, and in cases where GER studies fail to show expected reflux a nuclear medicine salivagram can be useful (Cook et al. 1997).

4.3 Achalasia

Successful passage of a food bolus through the esophagus depends on sequential relaxation and closing of the upper and lower sphincters that divide the esophagus from the pharynx above and the stomach below. Achalasia of the LES is unusual in children, constituting only about 5% of the total number of cases (Buonomo et al. 1998). In older children (mean age of onset being about 9 years) the radiologic appearance is like that in adults, with a distended, static esophagus terminating in a "beak" at the LES. In younger patients, the distension is less evident. The classic therapy is surgical myotomy; in recent years hydrostatic balloon dilatation has become popular (Upadhyaya et al. 2002). However, in all patients there is an underlying dysmotility that affects the entire esophagus, such that relief of the LES obstruction does not restore normal esophageal function. Follow-up with barium and radionuclide swallows in a series of patients showed persistent esophageal dilatation and contrast medium retention despite an open cardia (Chawda et al. 1998). Chawda et al. also indicated that radionuclide studies could substitute for barium swallows for functional follow-up, at a lower radiation dose.

Cricopharyngeal achalasia is still rarer, with scattered cases reported (de Caluwe et al. 1999). The characteristic cricopharyngeal bar (a posterior indentation in the barium column during swallow) can be seen intermittently in normal patients, but true achalasia of the upper esophageal sphincter (UES) results in obstruction to passage of the bolus, with discoordinate swallowing, cough, nasopharyngeal reflux, and aspiration. Arnold–Chiari malformation can be a cause, and should be excluded (del Rosario and Orenstein 1998). The same treatments used for LES achalasia can apply here, but in some cases conservative treatment with gavage feeding showed a slow return to normal UES function.

Special mention should be made of children with Down syndrome. They are disproportionately represented among patients with congenital GI tract abnormalities, including esophageal webs, EA–TEF, duodenal atresia, and Hirschsprung's disease. They also have a high rate of esophageal dysmotility and LES achalasia, up to 30% in one study (Zárate et al. 2001).

5 Acquired Anatomic Abnormalities: Idiopathic and Iatrogenic

5.1 Foreign-Body Ingestion

The most frequent acquired abnormality among children is the ingested foreign body. The bounty of case reports in the literature attests to the child's endless ingenuity in this regard. Coins are the most frequently swallowed object (Harned et al. 1997); the local demographics will determine if the second most frequent items are fish bones or other metal objects such as batteries and keys (Cheng and Tam 1999; Loh et al. 2000). Diagnosis is straightforward in the case of a radio-opaque item: a lateral radiograph of the lower face and neck and an anteroposterior radiograph of the chest and abdomen to cover

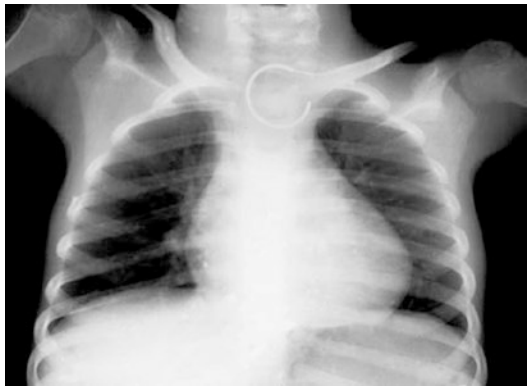

Fig. 7 Sixteen-month-old female with 2-week history of food refusal. AP scout radiograph for modified barium swallow. Hoop earring is seen impacted at the thoracic inlet. Patient transferred to the endoscopy service

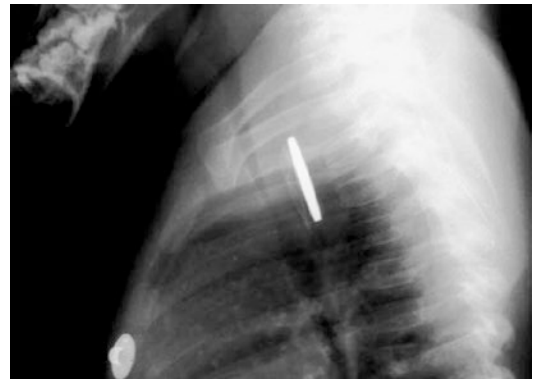

Fig. 8 Eleven-month-old female with drooling, wheezing, irritability, and food refusal. Lateral chest radiograph. Coin in the esophagus is seen on edge. Just anterior to it is the faint outline of a piece of broken plastic. The trachea is narrowed, indicating mediastinitis. This patient is not a candidate for extraction by Foley catheter because of the multiplicity, sharp edges, and complications

the entire GI tract from the nose to the anus will locate it. The lateral examination is recommended because of the young child's ability to habituate to foreign bodies in the pharynx and nasopharynx, which could be missed on chest X-ray (Fig. 7). Diagnosis of a bone ingestion is more difficult, but one study confirmed the appearance on plain radiography in 26% of cases (Cheng and Tam 1999). If the foreign body passes the UES, it will tend to impact at points where the esophageal lumen narrows: the thoracic inlet, carina, and LES. There is no consensus in the literature about predicting passage on the basis of the size and location at diagnosis, but there is unanimity in the assertion that all esophageal foreign bodies should be removed within 24 h. The risk of inflammation and perforation is high and containment is poor, as the esophagus has no serosa.

The retrieval method for the foreign body depends on the institution, the kind of object, and how long it has been impacted. Coins are most frequently removed under fluoroscopy using a Foley catheter (Harned et al. 1997). Sharp, small, or multiple objects should be removed endoscopically or surgically, as should coins where the radiographic appearance suggests tracheal compression or edema, or possible perforation (pneumomediastinum, pleural effusion) (Kaye and Towbin 1996). Button batteries, such as for cameras and hearing aids, should be removed immediately as they cause chemical damage to the mucosa on contact and are a prominent cause of perforation (Samad et al. 1999).

The consequences of delayed removal are grave. High impactions at the UES can present as wheezing, cough, and vocal cord paralysis (Virgilis et al. 2001). Sharp objects such as fish bones can lacerate the mucosa, leaving hematomas (a minor complication in this series), or perforate (7% of patients), causing mediastinitis, a retropharyngeal abscess, and an aortoesophageal fistula (Loh et al. 2000). Pieces of plastic often have sharp edges and can erode and perforate (Fig. 8). The level of perforation does not necessarily determine the nature of the complication, as the mediastinitis that inevitably follows can transmit infection to distant sites, such as an intervertebral disk (Fonga-Djimi et al. 1996). Because it is smooth, a coin in the esophagus can be initially asymptomatic. However with time, it too can erode and cause infection or perforation; one case report detailed a brain abscess that followed delayed extraction (Louie et al. 2000).

5.2 Iatrogenic Foreign Bodies

Nasogastric intubation is one of the most frequent hospital interventions, although inadvertent

perforations rarely occur. The neonate is most frequently affected, probably because of the small diameter of the tract relative to the size of the tube, and the fact that the tube must pass through an even narrower lumen at the UES. If the UES is closed because of spasm, the tube can perforate the pharynx. Films at that point might be reminiscent of EA, with the tube curling in the neck. Air in the mediastinum, expanded retropharyngeal soft tissues, and pleural effusion will help alert the radiologist to the correct diagnosis. Cautious administration of water-soluble contrast medium may show a pseudodiverticulum or a free perforation (Sarin et al. 2000).

Thoracostomy tubes are placed to drain air or fluid from the pleural space. There is a tendency for the operator to place the tube as far medially as possible to ensure that it does not become dislodged. However, should the tube rest against mediastinal structures such as the esophagus, pressure necrosis can result (Cairns et al. 1999). When a percutaneous gastrostomy tube is changed, the internal rubber bumper is often left in the stomach to pass in the stool. Occasionally, this can cause gastric outlet obstruction. In one case, the remnant migrated into the distal esophagus and impacted, where, despite it being soft and malleable, it ulcerated the mucosa and caused scarring (Nowicki et al. 1996).

5.3 Mucosal Destruction

Widespread trauma to the esophageal mucosa can result in perforation acutely, or eventually lead to scarring and narrowing. The cause can be chemical burns, infection, or inflammation. Corrosive ingestions do the most damage when the agent is an alkali, such as drain cleaner. Burns are found most usually in the mouth, with fewer patients exhibiting pharyngeal involvement and still fewer with esophageal burns. In one series, 29% of patients had complications, and about half of these required esophageal replacement (de Jong et al. 2001). Contrast esophagram evaluation is generally delayed until after the initial inflammation subsides; if it is done earlier, it tends to underestimate the extent of damage. It is most valuable in assessing esophageal function in cases of moderate burns and gauging the extent of strictures and the results of dilatation. Immunosuppressed patients with oral candidiasis can develop candidal esophagitis. Graft-versus-host disease, a feature of the same population, can behave similarly. Where the mucosa is too friable for endoscopy, contrast medium swallow can help assess the extent of ulceration, response to therapy, and occurrence of strictures. In advanced, invasive candidiasis cases, perforation can occur, necessitating esophageal replacement (Gaissert et al. 1999). Stevens–Johnson syndrome, or toxic epidermal necrolysis, is characterized by skin and mucosal lesions, precipitated by certain drugs or infectious agents. Oral lesions are frequent (60–80% of patients), and their severity can mask esophageal involvement. Strictures are not common sequelae, however (Lamireau et al. 2001).

Reflux esophagitis has several recognized complications. Barrett esophagus, where a specialized epithelium known to be preneoplastic is found in an esophageal segment of variable length, is found particularly in patients predisposed to severe GER: those with severe neurologic impairment who are mainly recumbent, those with chronic lung disease such as cystic fibrosis who cough and have pulmonary toilet in the head-down position, and those with primary esophageal dysmotility or hiatus hernia (Hassall 1997). Mucosal irregularity, ulceration, and narrowing can be seen in studies using contrast medium. Schatzki rings, less familiar in children than in adults, are found in a similar group of patients (Buckley et al. 1998). Esophagitis can have a predictable outcome (multiple mucosal rings), but an unusual cause: eosinophilia with food allergy, not reflux (Siafakas et al. 2000).

5.4 Miscellaneous Causes of Esophageal Dysfunction

Esophageal perforation due to blunt chest trauma is a familiar scenario for an adult in a motor vehicle accident, but is very rare in a child. Diagnosis

can be delayed unless there is a high index of suspicion (Sartorelli et al. 1999). Iatrogenic perforation during stricture dilatation is more common, 21% in one series where balloon dilatation was used (Kang et al. 1998). Anastomotic (after EA repair) and peptic strictures reacted the same way to dilatation. Another series documented fewer than that 1% perforations with bougie and olive dilators (Panieri et al. 1996). Contrast medium swallows in these series showed abnormalities ranging from mucosal disruption to frank perforation or fistula.

Nissen fundoplication is the surgical procedure of choice to control GER. It has its own complications, however, which can adversely affect the patient's ability to eat (Trinh and Benson 1997). Tightening the gastroesophageal junction is a delicate balance: tight enough to prevent reflux but loose enough to permit bolus passage. Patients who have had an EA–TEF repaired already suffer from dysmotility of the esophagus below the anastomosis. This promotes reflux and is usually the reason for the Nissen fundoplication. However, the ability to propel the bolus may then be completely compromised. Fundoplications can completely break down, but more often a large paraesophageal hernia forms that extends into the chest through the loosened hiatus. This can compress the distal esophagus still further and impede bolus passage. Many Nissen fundoplication patients are fed not by mouth but by gastrostomy tube and it is tempting, when asked to look for recurrent reflux to explain the patient's vomiting, to only inject the tube. However, giving just a few milliliters of barium by mouth can find the possible distal esophageal obstruction and show the distended esophagus filled with secretions that the patient regurgitates.

Two final acquired complications can narrow the esophagus. In one, an arterial switch procedure puts the aorta into a position to compress the esophagus (McElhinney et al. 1998). The other represents the end stage of any of a number of diseases that cause portal hypertension (Buonomo et al. 1998). Extrahepatic portal obstruction is much more common in children. Varices form around the distal esophagus, causing vermiform defects in the margins of the contrast medium column.

6 Acquired Functional Abnormalities: The Diagnosis of Exclusion

Difficult feeding or food refusal suspected to be psychogenic in origin is a frequent reason for ordering a modified barium swallow prior to instituting behavioral therapy. There are some historical cues that can support this request: early history of prematurity or surgical procedures that interfered with the evolution of feeding skills, or bizarre dietary choices that have no logic. However, all of this chapter has attempted to show that there can be a compelling anatomic or functional abnormality to explain the symptoms, and that it is the radiologist's job to find it. History clues, such as suddenness of onset, wheezing, coughing, irritability, and taking liquids but refusing solids, all point toward a physical cause. A formal upper GI tract examination should precede any modified swallow. It is a small, "low-tech" effort that can reap impressive results. Once the radiologist is satisfied that the child is normal anatomically and functionally, a psychogenic diagnosis might be entertained.

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High-Resolution Manometry of the Pharynx and Esophagus

Nathalie Rommel

Contents

Abstract

This chapter describes the use of high-resolution manometry (HRM) for the assessment of pharyngeal, upper esophageal sphincter, and esophageal function during deglutition. Based on color plot technology, pressure patterns in both the pharynx and the esophagus are described in health and swallow pathology. The analysis of these patterns is determined by specific metrics that describe the deglutitive motor function that can be driving bolus flow as seen on videofluoroscopy or detected by impedance. Esophageal motor function is worldwide classified using the Chicago classification. Although currently such a classification is not available yet for the pharynx and UES dysfunction, recently much progress has been made in deriving clinically relevant pharyngeal HRM metrics. HRM can, combined with videofluoroscopic or impedance assessment, identify the motor patterns driving the pathogenesis of different dysphagic phenotypes.

1 Introduction

High-resolution manometry (HRM) refers to the technology that allows computerized recording of intraluminal pressure data in space and time. This diagnostic assessment uses advanced digital data acquisition methods to display numerous

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pressure signals as pressure topography so that the distance along the pharynx or esophagus, amplitude of the contraction, and time are presented in one color plot. In contrast to conventional manometry using a small number of recording sites, HRM records intraluminal pressures at a large number of closely spaced intervals along the entire pharynx, upper esophageal sphincter (UES), and/or esophagus. Through the use of color patterns of pressure signatures, called Clouse plots, the HRM technique has become more user friendly and is subsequently increasingly used to investigate the muscular function of the upper gastrointestinal tract (Clouse et al. 2000).

Esophageal HRM aims to differentiate normal from abnormal esophageal motor function, to identify the etiology of esophageal dysphagia and to guide management of esophageal motility disorders. HRM in the pharyngoesophageal segment (PE segment) during swallowing aims to distinguish normal from abnormal deglutition, to identify the etiology of dysphagia, and to guide therapeutic decisions in order to reduce the impact of a swallowing disorder.

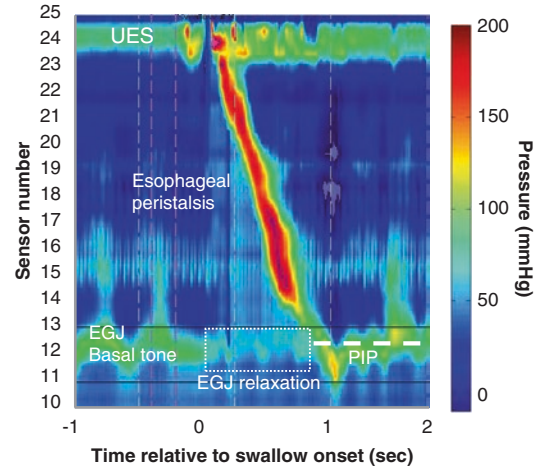

Fig. 1 Anatomical and physiological orientation on an esophageal high-resolution manometry (HRM) plot of a liquid swallow in a healthy volunteer. During deglutition, three manometric regions can be identified: the upper esophageal sphincter (UES), the esophageal body with its peristaltic wave, and the esophagogastric junction (EGJ). The EGJ includes both the lower esophageal sphincter and the diaphragmatic crura, manometrically identified as the pressure inversion point (PIP)

2 HRM to Identify Anatomy

2.1 Esophageal Body

A typical esophageal Clouse plot shows two pressure bands at either end created by the basal tone in the upper esophageal sphincter and the lower esophageal sphincter (Clouse and Staiano 1991). During swallowing, a consecutive series of contracting segments represent the esophageal peristalsis, moving from UES towards LES. The most proximal 1/3 consists of striated, skeletal musculature whereas the most distal 2/3 of the esophageal body consists of smooth muscle fibers. In between the striated and smooth muscle segments of the esophagus, a transition zone (TZ) has been identified, in which contractile strength is known to be reduced.

The distance between the UES and LES basal pressure zones corresponds with the length of the esophagus (Fig. 1).

Furthermore, the diaphragmatic crural contractions can be identified by localizing the pressure inversion point (PIP) which is the point where intrathoracic (inspiratory) and intra-abdominal (expiratory) pressures are opposed in relation to respiration. The PIP needs to be located within the LES high-pressure zone, indicating that the diaphragmatic crura and the intrinsic LES are in line (Fig. 1). This location of diaphragm is necessary for the diagnosis of a hiatal hernia, in which case the LES and crura are not aligned.

2.2 Pharyngeal and UES Anatomy

Pharyngeal anatomy consists of superior, middle, and inferior pharyngeal constrictors and can only be localized during deglutition. During swallowing, three manometric regions can be identified along the PE segment: the soft palate (velopharynx), the tongue base (oropharynx/hypopharynx), and the UES (Fig. 2). The UES anatomy is composed of the cricopharyngeus muscle (CP),

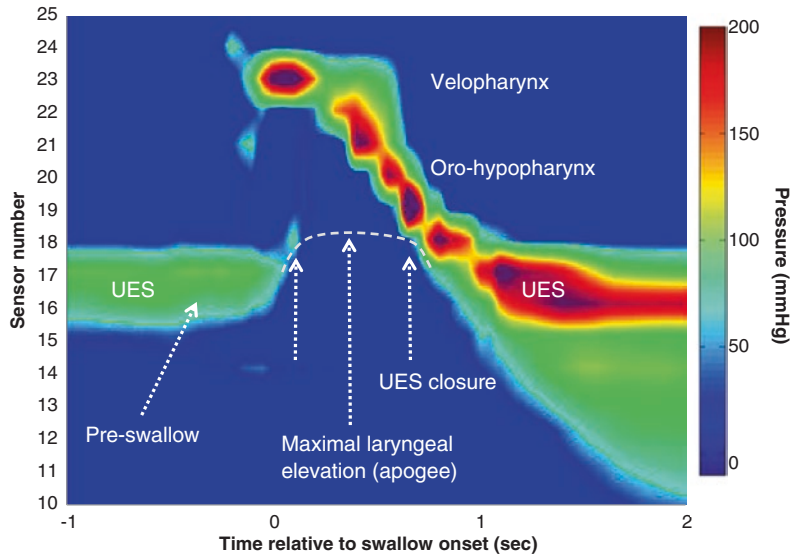

Fig. 2 This figure shows the anatomical and physiological orientation on a pharyngeal high-resolution manometry (HRM) color plot of a liquid swallow in a healthy subject. During swallowing the velopharyngeal and hypopharyngeal region can be identified as well as the upper esophageal sphincter high-pressure zone. The color plot shows the different manometrically detectable element of the pharyngeal swallow: velopharyngeal closure, onset of UES relaxation, orad movement of the UES during laryngeal elevation, UES apogee (UES position during maximal laryngeal elevation) with UES relaxation, initiation of the pharyngeal stripping wave, and UES basal tone pre- and post-swallow

the inferior pharyngeal constrictor, and the most proximal striated segment of the esophagus and can be localized manometrically both in rest and during deglutition. In rest, a tonic UES resting pressure can be recorded and analyzed. During deglutition, the UES opening mechanism is dependent on neural relaxation of the tonically contracted cricopharyngeus muscle, on traction forces by the suprahyoid muscles, on intrabolus pressure generated by the lingual and pharyngeal propulsion of the bolus, and finally on the distensibility of UES musculature (Kahrilas et al. 1988; Cook et al. 1989a, b).

3 HRM to Identify Physiology

3.1 Pharyngeal and UES Physiology

The pharyngeal phase of swallowing consists of a complex series of timed actions at the level of the pharynx. Using a HRM color plot, laryngeal elevation can be identified by the orad movement or proximal excursion of the UES. Secondly, the pharyngeal stripping wave can be identified as a peristaltic sequence of pressure increase over time along the entire pharynx. Thirdly, the UES relaxation is seen by a pressure drop over time at the level of the high-pressure zone of the UES and finally the reconstitution of the UES resting pressure initiating proximal esophageal contraction can be identified by an increased pressure in the UES and the proximal, striated part of the esophagus (Fig. 2).

3.2 Esophageal Physiology

Esophageal motor function and motility disorders are worldwide evaluated using the Chicago Classification (CC), a classification scheme that through consensus has been designed by an international working group, to characterize and evaluate esophageal and EGJ function during deglutition (Kahrilas et al. 2015). Extensive lit-

erature is available using the CC and in the most recent version V3.0 is currently considered the golden standard for evaluation of esophageal motor disorders (Kahrilas et al. 2015).

The esophageal phase of swallowing is initiated at the start of the pharyngeal swallow with instant UES relaxation and LES relaxation occurring as the peristaltic wave moves distally through the esophageal body, indicated by a change in color. Confirmed by the Chicago Classification (Kahrilas et al. 2015), two smooth muscle contraction segments can be recognized within the peristaltic wave, whereby the contraction vigor, contraction pattern, and intrabolus pattern of during peristalsis have to be evaluated. The assessment of contractile vigor is based on the distal contractile integral (DCI), a metric that corresponds to the volume of the contraction and is calculated by multiplying the length times, duration times, and mean pressure (above 20 mmHg) of the contraction between the transition zone and the EGJ (Kahrilas et al. 2015).

Further, three contraction patterns are distinguished: premature contractions, fragmented contractions, and intact or normal contraction. Premature contractions are present when the time latency, called distal latency (DL), between UES relaxation and the point where peristalsis slows down (contraction deceleration point, CDP) is less than 4.5 s. Fragmented contraction pattern is present when the esophageal peristalsis (above 20 mmHg) is interrupted over more than 5 cm, but the remaining peristalsis has a normal DCI (over 450 mmHg s cm) (Kahrilas et al. 2015).

The intrabolus pressure is characterized by a simultaneous and rapid increase of intraesophageal pressure (above 30 mmHg) and is a marker to resistance of bolus flow. It can be (1) panesophageal if it extends from the EGJ to the UES, (2) compartmentalized if it extends from the contractile front to a sphincter, or (3) called EGJ pressurization if it occurs within the EGJ in case of a hiatal hernia (Kahrilas et al. 2015).

The relative localization of the two components of the EGJ, the lower esophageal sphincter (LES) and the crural diaphragm (CD), defines the EGJ morphology. The EGJ resting pressure is evaluated during a period without swallowing and is assessed for each individual swallow using an integrated relaxation pressure (IRP). The IRP refers to the median EGJ pressure measured for the 4 s of maximal relaxation (continuous or non-continuous) in the 10 s after UES relaxation (Kahrilas et al. 2015). When subsequently the esophageal peristaltic wave has been completed, EGJ basal tone reconstitutes. LOS basal tone is a parameter that is not included in the CC as the scheme focuses on deglutitive esophageal metrics.

4 HRM to Assess the Pharyngeal Phase of Swallowing

Normal PE function during deglutition results in effective bolus transport from the oropharyngeal cavity to the esophagus and depends upon adequate lingual propulsion, pharyngeal contraction, and UES relaxation. To quantify these swallow-related events, a number of manometric parameters have been proposed in the past, mainly within low-resolution manometric setup. Over the last 10 years, an increasing number of HRM studies have been published on parameters for the evaluation of PE function. Many of these studies do however have limited datasets of normal values and also there exists a large variety among the manometric systems and catheters used. Some of the limitations encountered by low-resolution pharyngeal manometry are overcome by the development of HRM. The currently available high-resolution solid-state catheters incorporate up to 36 pressure sensors. These multiple closely spaced sensors (mostly 1 cm apart) ensure at least one sensor recording pressure in the UES during the axial movement of the UES high-pressure zone during the swallow. A pressure topography real-time display during acquisition is also helpful in optimal positioning of the catheter.

4.1 Pharyngeal Function

The most reported and clinically used parameter to assess the strength of the pharyngeal contraction

is the peak pharyngeal amplitude (mmHg) (Fig. 2). Peak pharyngeal pressure is the average of the peak amplitudes recorded along the pharyngeal peristaltic wave, which moves from the proximal to the distal pharynx and consists of a consecutive contraction until the hypopharyngeal pressure wave progresses into the UES. Peak pharyngeal contraction is known to be influenced by age (Shaw et al. 1995; van Herwaarden et al. 2003), bolus variables (volume and consistency), and subject position (Castell and Castell 1993; Castell et al. 1990; Olsson et al. 1994). Mean peak pressure of a normal swallow as measured by solid-state HRM data is on average 140 mmHg and ranges from 107 to 194 mmHg (Omari et al. 2011).

Recently, HRM parameters such as pharyngeal contractile integral (Nativ-Zeltzer et al. 2016), pharyngeal contraction time, pressure rise rate of pharyngeal contraction, velocity, and pressure gradient have been suggested as objective measures for the evaluation of deglutition (McCulloch et al. 2010; Hoffman et al. 2010; Mielens et al. 2011). These parameters are novel and algorithm derived but their clinical relevance is still under further exploration.

4.2 Upper Esophageal Sphincter Compliance

To assess UES compliance, both UES relaxation and opening need to be evaluated. UES opening and UES relaxation are closely interlinked but differ: UES opening is an active event rather than the simple consequence of UES relaxation (Jacob et al. 1989) with the diameter of the opening varying according to bolus volume (Cook et al. 1989a, b) and consistency (Dantas et al. 1990a, b). Manometry as a stand-alone technique allows measurement of UES relaxation, not UES opening in terms of the diameter. *It is important to realize that UES opening cannot be measured using HRM.*

The effectiveness of the UES relaxation is measured both through its extent and by its duration. The extent of the *UES relaxation* is typically measured by UES nadir pressure which is the minimum pressure during relaxation (McCulloch et al. 2010; Kwiatek et al. 2009). The UES nadir pressure is an easy-to-determine point on a manometric line plot. During complete UES relaxation, UES nadir pressure decreases to atmospheric pressure and can be a negative pressure (McCulloch et al. 2010).

To calculate UES relaxation duration, several methods have been suggested which are either a calculation through advanced algorithms (UES relaxation interval) (Ghosh et al. 2006b) or "manual" calculation of the time between onset and offset of the UES pressure drop. The challenge with the latter method is the fact that the onset and offset of UES relaxation are difficult to determine consistently. Some authors used the time between maximal UES pressure before and after UES relaxation (Hoffman et al. 2012; McCulloch et al. 2010) and others use the time duration at 10% of the resting pressure baseline (Meyer et al. 2012). The most recently proposed metric is the UES integrated relaxation pressure (IRP) measuring the median of the lowest pressures recorded during deglutition during 0.25 s (Nativ-Zeltzer et al. 2016).

In general, there is still a lack of standardization in the calculation of PE manometric parameters as well as a large variation in the normal values across ages.

4.3 Pharyngeal Response to UES Function

In cases where UES dysfunction is apparent, the pharyngeal pressure pattern in response to impaired bolus flow across the sphincter may be altered. Pharyngeal *intrabolus pressure* (IBP) which is a manometric marker for the resistance to bolus flow at the level of the UES increases in case of UES obstruction (Fig. 3). IBP is a manometric parameter reflecting the pressure in the bolus, and therefore needs to be measured during bolus flow. To determine IBP accurately using manometry, simultaneous videofluoroscopy or impedance measurement is required to confirm actual bolus presence during the swallow. To date, there exists no consensus on the calculation

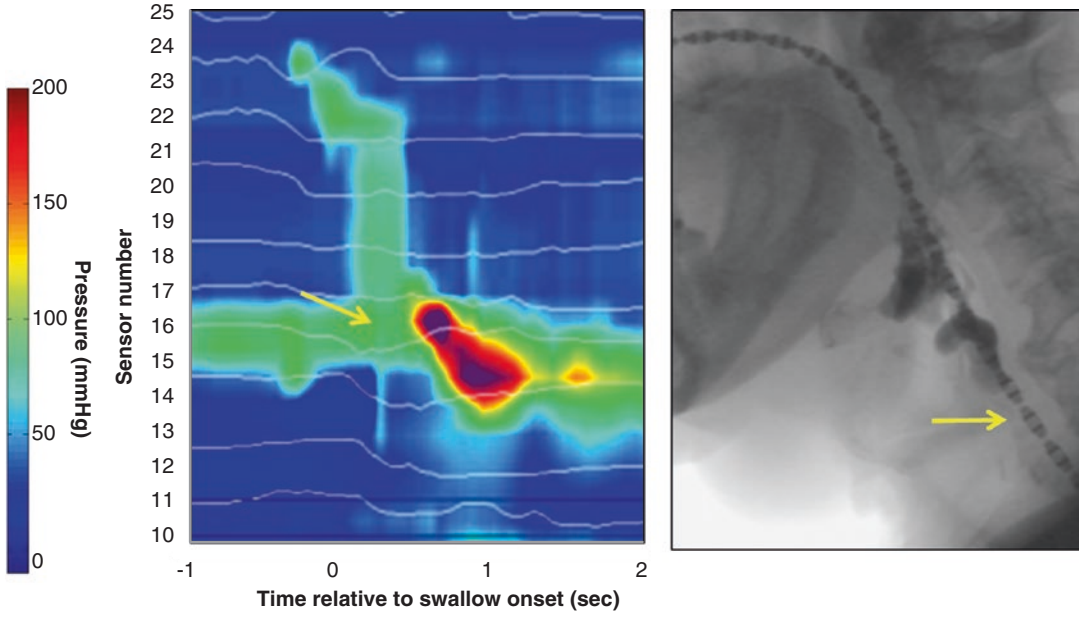

Fig. 3 HRM plot with simultaneous lateral videofluoroscopic view of an incomplete UES relaxation in a 73-year-old male with Parkinson's disease with dysphagia for solids. Increased intrabolus pressure as the result of resistance to bolus flow across the non-relaxing UES

of IBP. IBP can be measured using the median IBP, the integral (area under the pressure curve before onset of pharyngeal stripping wave) (Dejaeger et al. 1994), and the deglutitive sphincter resistance (DSR) described as the median IBP during relaxation interval (Ghosh et al. 2006a), or as an intrabolus pressure gradient (IBPG) (Williams et al. 2001; Pal et al. 2003). The location and magnitude of IBPG reflect the existence and location of abnormal constriction, and IBP and IBPG structure reflect decompensation of the pharyngeal swallow (Williams et al. 2001; Pal et al. 2003).

5 Dysphagia Characterized Using HRM

5.1 Pharyngeal and UES Dysphagia

Swallowing disorders such as cricopharyngeal bar, UES achalasia, UES opening dysfunction, and Zenker's diverticulum are typically characterized by a videofluoroscopic swallow study. Only a few of these abnormalities have been characterized manometrically. The following section describes the most frequent dysphagia pathologies seen in a tertiary clinical setting, illustrated by HRM color plots.

5.1.1 Pharyngeal Peristalsis

Mean peak amplitude of the pharyngeal contraction allows differentiation of pharyngeal paralysis, hypocontractility, hypercontractility, and focal failure in the pharyngeal peristaltic wave. Pharyngeal contraction is considered *hypocontractile* (Fig. 4) if its peak amplitude is less than 100 mmHg (Massey 2013; Omari et al. 2011). In case no pharyngeal pressures can be generated, *pharyngeal paralysis* would be indicated (Fig. 5). On the other hand, when the pharyngeal contraction is over 200 mmHg it may be considered *hypercontractile* (Massey 2013; Omari et al. 2011) (Fig. 6). High pharyngeal pressures may be compensatory in response to increased resistance to bolus flow across the UES.

Focal failure of pharyngeal contraction wave may be related to muscle dysfunction of

the posterior pharyngeal wall or may reflect an anatomical abnormality such as a cervical osteophyte. The position of the osteophyte is indicated by a sharp increased pressure due to contact of the osteophyte with the pressure sensors. While 1–2 cm proximal to this location, no pressure is recorded because the presence of the osteophyte prevents occlusion of the lumen on the catheter.

5.1.2 Cricopharyngeal (UES) Dysfunction

Absent UES Relaxation (Often Referred to as Cricopharyngeal (CP) Achalasia)

Cricopharyngeal achalasia has been associated with numerous conditions (myotonic dystrophy, MS, ALS, cortical and lateral medullary stroke, etc.) and its pathogenesis remains largely

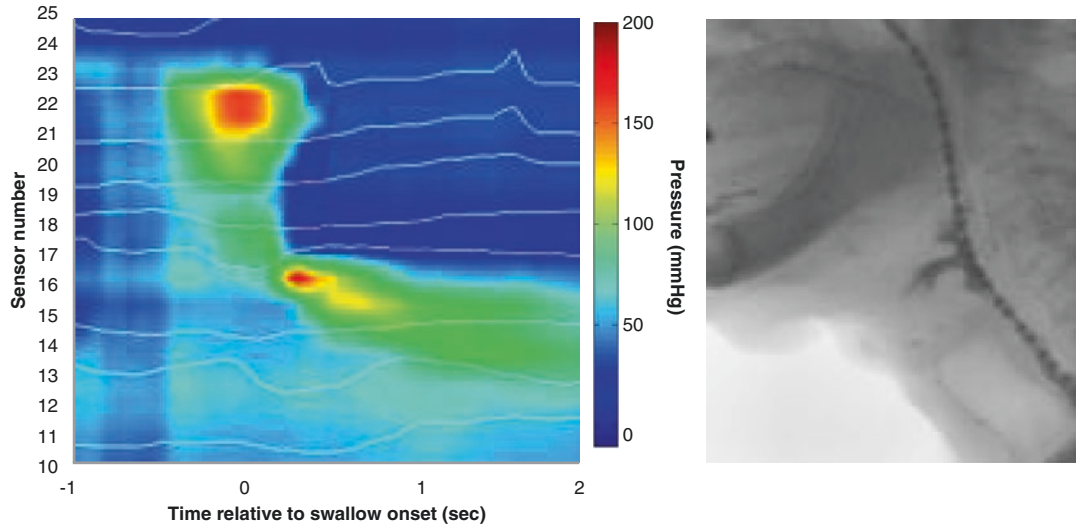

Fig. 4 HRM plot with simultaneous lateral videofluoroscopic view illustrating a hypocontractile pharynx in 61-year-old female patient presenting with dysphagia on liquids

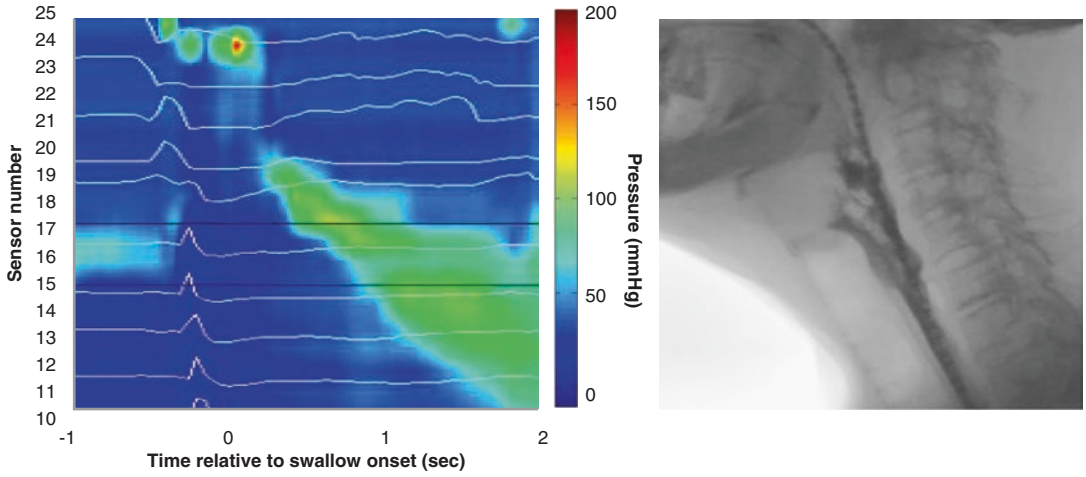

Fig. 5 HRM plot with simultaneous lateral videofluoroscopic view showing a liquid swallow of a 56-year-old patient referred to assess aspiration risk. The swallow is characterized by pharyngeal paresis (absent pharyngeal peristalsis) and complete UES relaxation

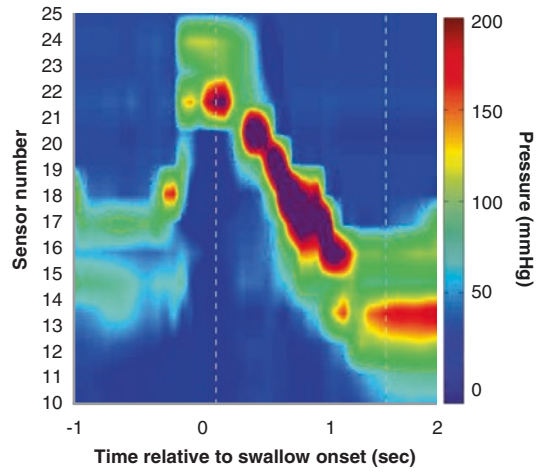

Fig. 6 HRM plot illustrating a hypercontractile pharynx and short UES relaxation in a 53-year-old male presenting with dysphagia on solids

unknown. Clinically, the patient may present with specific symptoms of dysphagia such as nasal regurgitation on both liquids and solids, difficult coping with saliva, choking on liquids and solids, coughing, pharyngeal food impaction, dehydration, and malnourishment. CP achalasia is defined as a condition in which the CP muscle or the motor neurons supplying it exhibit patterns of inhibitory activity that are incomplete, short, or incoordinated (Dudnick et al. 1992). Crucial in the diagnosis of UES dysfunction is the fact the UES fails to relax during deglutition (Fig. 3). It is well described that absent UES relaxation clearly differs from failure of the UES to open, which can be solely related to poor pharyngeal contractility. Nevertheless, the diagnosis of inadequate UES relaxation or UES achalasia is often based on the radiological swallow study alone. Therefore, supplementation with HRM will allow the needed differentiation between pharyngeal and UES dysfunction in the pathogenesis of inadequate UES opening documented on videofluoroscopy. Therefore, the diagnosis of UES achalasia should be made based on videofluoroscopy combined with manometric assessment.

Incomplete Cricopharyngeal Relaxation

Successful deglutitive UES opening depends upon complete and timed UES relaxation. The most recent HRM parameter used to distinguish between normal abnormal function and the UES relaxation is the IRP 0.25 (Nativ-Zeltzer et al. 2016). In cases of inadequate UES opening, bolus residue may pool in the sinus pyriformis before the swallow has been initiated and may lead to aspiration before and during the swallow.

Cricopharyngeal Bar

A cricopharyngeal bar is defined as a posterior indentation of the esophageal lumen between cervical vertebrae 3 and 6 causing a reduction in the upper sphincter diameter during deglutition. A cricopharyngeal bar is a radiological finding seen on a lateral radiograph (Leonard et al. 2004) and is thought to be caused by reduced compliance by CP fibrosis (Dantas et al. 1990a, b). In most patients, the cricopharyngeal bar does not cause symptoms unless the CP bar is prominent enough to narrow the UES diameter. The decrease in transverse and sagittal UES diameter may in turn result in resistance to bolus flow across the PE segment (Dantas et al. 1990a, b; Leonard et al. 2004). In the case of symptoms related to cricopharyngeal bar with resistance to bolus flow, manometry shows an increased pharyngeal intrabolus pressure (Pal et al. 2003) despite complete UES relaxation (Fig. 7).

Posterior Pharyngeal (Zenker's) Diverticulum

A Zenker's diverticulum is an abnormal anatomical structure in the pharynx, herniating posteriorly just proximal to the cricopharyngeal muscle (Zenker and Von Ziemssen 1878). The pouch situated between the inferior pharyngeal constrictor and the cricopharyngeus muscle consists

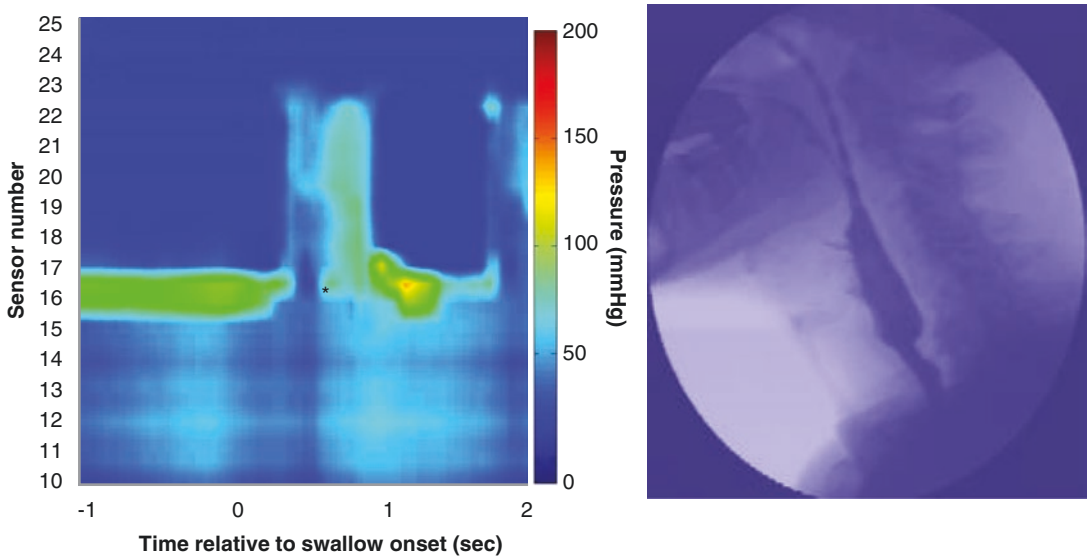

Fig. 7 HRM plot with simultaneous lateral videofluoroscopic view of a cricopharyngeal bar during a liquid swallow. Cricopharyngeal bar as well as pharyngeal weakness and increased intrabolus pressure as a marker of resistance to bolus flow. On the HRM plot a distinct pressure segment (*) can be identified. This increased pressure corresponds with the posterior indentation seen on the lateral radiological image

of mucosa and submucosa, surrounded by fibrous tissue (Zenker and Von Ziemssen 1878). When this posterior pharyngeal herniation increases in size, it tends to be left sided in the majority of the cases (Cook 2013). A Zenker's diverticulum is thought to be secondary to a poorly compliant but normally relaxing UES unable to fully distend during UES opening (Cook 2013). This restricted opening of the cricopharyngeus may be the result of muscle fiber degeneration and fibroadipose tissue replacement. Patients may complain of nonspecific dysphagia symptoms such as halitosis and commonly present with aspiration, weight loss, recurrent respiratory infections, and regurgitation of undigested food (Jamieson et al. 1988). To detect a Zenker's diverticulum or other small pharyngeal diverticula, a radiological swallow study is the preferred diagnostic test. Most importantly, it allows evaluation of the functional impact of the diverticulum during deglutition and thus the presence of bolus residue, regurgitation, and timing and extent of aspiration. In case of a Zenker's, intraluminal manometry shows typically increased pharyngeal intrabolus pressure at the time of bolus flow across the UES (McConnel et al. 1994), normal UES resting pressure, complete UES relaxation, and an adequate coordination between pharyngeal contraction and UES relaxation (Cook et al. 1992) (Fig. 8).

5.2 Esophageal Motor Disorders

The Chicago Classification V3.0 (Kahrilas et al. 2015) distinguishes four categories of esophageal motility disorders: disorders with EGJ dysfunction, major disorders of peristalsis, minor disorders of peristalsis, and normal motility. Table 1 describes the hierarchical analysis of EPT studies according to the Chicago Classification. The first step in the CC is to evaluate the EGJ deglutitive relaxation as defined by the upper limit of normal (ULN) of the IRP. In case of IRP abnormality, the CC identifies patients meeting the criteria for achalasia (elevated IRP and absent peristalsis), which is then subdivided into achalasia subtypes (types I, II, and III) (Fig. 9). Subsequently, patients with elevated IRP but preserved peristalsis are classified as esophagogastric outflow obstruction (EGJOO) patients (Fig. 10). Both

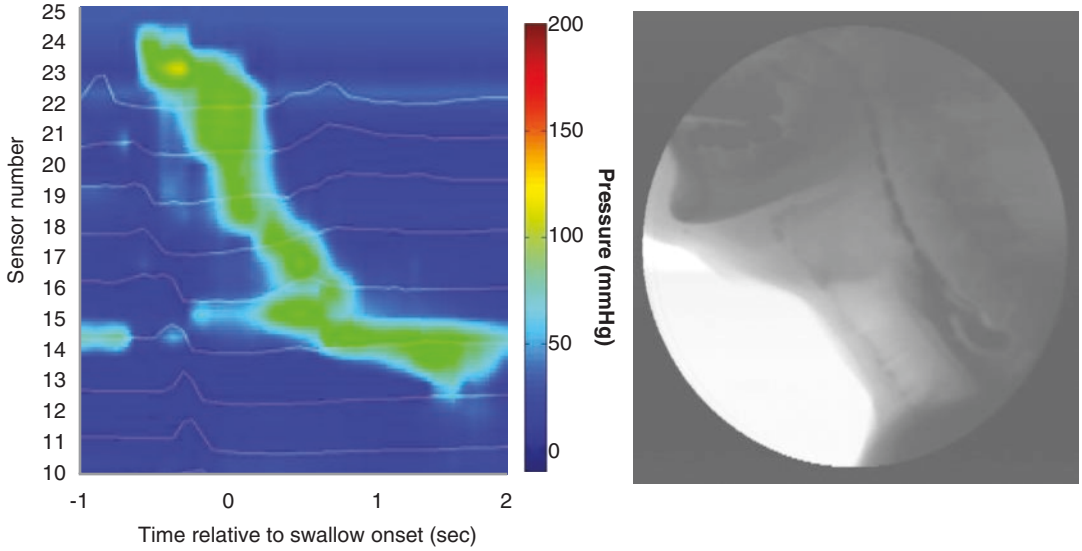

Fig. 8 HRM plot as well as lateral radiological image of a liquid swallow in a 43-year-old male patient with Zenker's diverticulum (posterior pharyngeal diverticulum). A HRM marker of Zenker's diverticulum is a broader high-pressure zone proximal to the UES after the swallow. This pressure increases with increasing consistency and increased volume trapped in the pouch

Table 1 This table describes the hierarchical analysis of esophageal high-resolution manometry studies according to the Chicago Classification for esophageal motility disorders (Kahrilas et al. 2015)

EGJ disorders	**IRP ≥ normal** 100% failed peristalsis or spasm	→	**Achalasia** **Type I:** no contractility **Type II:** ≥20% pan-esophageal pressurization **Type III:** ≥20% spasm (DL <4.5 s)
	IRP ≥ normal Not type I–III achalasia	→	**EGJ outflow obstruction** Incompletely expressed achalasia Mechanical obstruction
Major disorders of peristalsis	IRP normal **Short DL or high DCI or 100% failed peristalsis**	→	**Distal esophageal spasm (DES)** ≥20% premature (DL < 4.5) **Jackhammer esophagus** ≥20% DCI >8000 mmHg cm s **Absent contractility** No scorable contraction (DCI <100 mmHg cm s), consider achalasia
Minor disorders of peristalsis	IRP normal **≥50% ineffective swallows**	→	**Ineffective motility (IEM)** ≥50% ineffective swallows (DCI <450 mmHg cm s) **Fragmented peristalsis** ≥50% fragmented swallows (breaks >5 cm) and not ineffective (DCI >450 mmHg cm s)
Normal	IRP normal **>50% effective swallows**	→	**Normal esophageal motility**

Starting with the evaluation of the EGJ deglutitive relaxation and followed by analysis of the pressure patterns in the esophageal body, the CC identifies four large categories of motility disorders

groups of patients are referred to as patients with a disorder of EGJ outflow obstruction, the first group of motility disorders within CC V3.0.

The second group of patients are patients with major disorders of peristalsis. Their IRP is within normal limits but the peristaltic motor patterns are either absent, hypercontractile, or premature. These abnormal motor patterns have not been observed in normal subjects and correspond, respectively, with the diagnosis of esophageal aperistalsis (Fig. 11), a jackhammer esophagus (Fig. 12), and distal esophageal spasms.

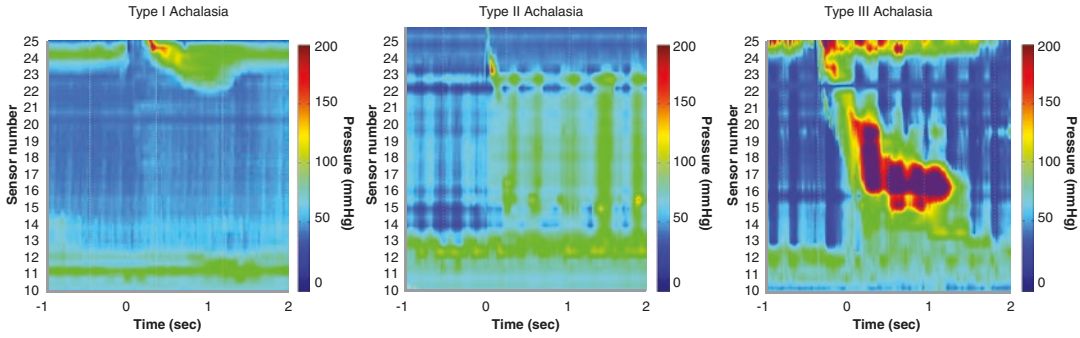

Fig. 9 HRM plot of the three subtypes of esophageal achalasia. No distal pressurization is observed in type I, pan-esophageal pressurization is seen in type II, and premature contractions and hypercontractile patterns are observed in type III

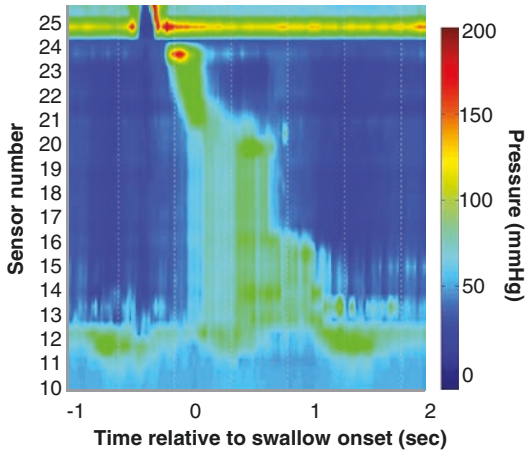

Fig. 10 Example of a manometric trace of esophageal outflow obstruction (EGJOO) according to the Chicago Classification (V3.0)

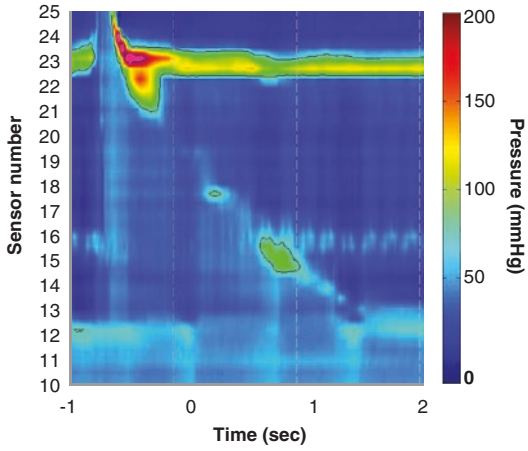

Fig. 11 HRM plot illustrating absent peristalsis during deglutition of a liquid swallow

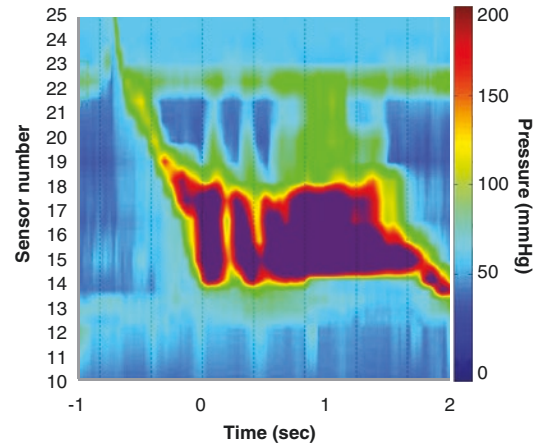

Fig. 12 HRM plot showing a hypercontractile esophageal motor pattern, called a jackhammer esophagus according to the Chicago Classification. This motor pattern is a major motor disorder, not seen in asymptomatic subjects

Minor disorders of peristalsis are the third category of esophageal motor patterns described within the CC. These are patients with a normal IRP, but with impaired esophageal clearance secondary to ineffective esophageal motility or fragmented peristalsis in more than half of the assessed swallows. Ineffective esophageal motility (IEM) means that at least half of the swallows present with a DCI less than 450 mmHg s cm (Fig. 13). Fragmented peristalsis refers to motor patterning with at least half of the swallows showing a segmental break of at least 5 cm but with a preserved DCI (over 450 mmHg s cm). A segmental break is a gap in the 20 mmHg isocon-

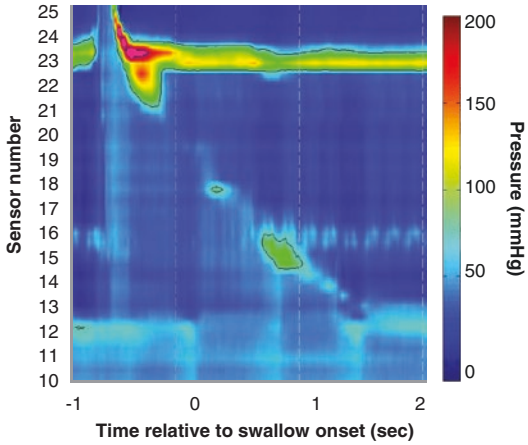

Fig. 13 HRM plot illustration ineffective esophageal motility (IEM), which has been classified as a minor motor esophageal abnormality, also seen in asymptomatic subjects

tour of the peristaltic contraction between the UES and EGJ measures in the axial length.

Finally, the fourth and normal category describes the patients with a relaxing EGJ and functional esophageal contractility.

5.3 Clinical Implementation

There are multiple reasons for why HRM as a technique to assess the pharynx and UES function has not been fully used to the potential it holds, compared to the revolutionary progress made using HRM to understand motility patterns of the esophagus. Not only is one diagnosing a totally different structure with specific challenges such as complex anatomy and geometry, axial mobility, and asymmetry of the structures as well as rapid sequence of events, but also the differences in catheter dimensions and recording sites bring a considerable variation in the normal values for different parameters. Although performing a pharyngeal manometry has improved markedly using HRM (Rommel and Hamdy 2016), the equipment cost for solid-state manometry remains high. The further differentiation of UES patterns will be crucial as there is so far only sparse evidence that there is influence on management or that the HRM parameters assessed are adequate predictors of therapy outcome or disease progress.

Conclusion

HRM has improved the use of manometry in performing pharyngeal and esophageal function studies. The HRM technology has allowed a revolutionary progress in the clinical implementation of manometry to classify esophageal motor disorders, specifically by using the Chicago Classification. The use of HRM in the pharynx and UES during deglutition still has a longer way to go. At this stage, it allows evaluation of motor function through pattern recognition; however as a stand-alone technique its limitations become quickly obvious as patterns poorly relate to aspiration risk (Omari et al. 2011). The most complete understanding of bolus transport as the result of contraction patterns in the pharynx and UES requires simultaneous videomanometry or manometry-impedance recordings during swallowing. HRM is indispensable in understanding PE physiology, but has been impeded by conceptual and technical issues. Future research should focus on consistent definitions and calculations of the objective HRM parameters preferably performed in large normal healthy populations to start with.

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Impedance Planimetry

Johannes Lenglinger

Contents

Abstract

Impedance planimetry is an imaging technique that provides in vivo esophageal distensibility data in real time. A catheter equipped with a cylindrical bag is gradually distended with a conductive solution. Impedance and intrabag pressure readings are used to calculate the distensibility index as ratio of the cross-sectional area at the narrowest spot to intrabag pressure. In healthy volunteers esophagogastric junction distensibility, obtained at 40 mL bag filling volume, shows a wide variation of 2.7–7.1 mm^2/mmHg. In achalasia patients distensibility is significantly lower (≤1.6 mm^2/mmHg) and normalizes after successful treatment. Post-interventional distensibility index values in the range of 4.5–8.5 mm^2/mmHg predict good outcome. Impedance planimetry imaging has recently been integrated into a dilatation catheter for treatment of achalasia and a feasibility study reported technical success in all therapeutic interventions using this device. In patients affected by eosinophilic esophagitis distensibility of the esophagogastric junction is lower than in healthy controls and in the tubular esophagus a distension plateau is reached at a narrower luminal diameter, reflecting the remodeling of the esophageal wall in this disease. In patients with small hiatal hernias impedance planimetry is able to display the lower esophageal sphincter and the crural diaphragm as spatially separated regions of reduced distensibility. Each

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component is more distensible than the single esophagogastric junction in subjects without hiatal hernia. Conflicting data exist regarding esophagogastric junction distensibility in patients with gastroesophageal reflux disease. Two studies found higher and one reported lower values compared to asymptomatic controls. Intra- and postoperative impedance planimetry studies showed that laparoscopic antireflux surgery results in a significant reduction of esophagogastric junction distensibility, being significantly more pronounced after a Nissen than a Toupet fundoplication. Impedance planimetry is the only diagnostic tool available in clinical routine to examine mechanical wall properties in vivo. It complements other diagnostic procedures like endoscopy, videofluoroscopy, and high-resolution (impedance) manometry in the assessment of esophageal function in various disease states and has become a valuable tool for monitoring and tailoring therapeutic interventions.

Abbreviations

CSA	Cross-sectional area
DI	Distensibility index,
EGJ	Esophagogastric junction
EoE	Eosinophilic esophagitis,
FLIP	Functional lumen imaging probe
LES	Lower esophageal sphincter
POEM	Peroral endoscopic myotomy

1 Introduction

The esophagus is a muscular tube of 20–25 cm length that transports ingesta from the pharynx into the stomach. Sphincters at the proximal and distal end of the organ contribute to the regulation of in- and outflow. The high-pressure zone at the esophagogastric junction (EGJ) is crucial for the protection against reflux of gastric contents into the esophagus. Esophageal transport function and gastroesophageal reflux activity are determined by organ geometry, muscular tone at the sphincter regions, wall compliance, and esophageal body peristalsis. Esophageal motility is mainly assessed by manometry that measures radial squeeze pressures in the esophageal body and the sphincter regions. But even high-resolution manometry, the current state-of-the-art method for studying esophageal motor function, shows poor correlation with symptoms and radiological transit studies. This is because measurements of muscular tone and phasic contractions are unable to display regional narrowing or increased wall stiffness. Impedance planimetry is an imaging technique that has been developed to characterize biomechanical properties of the esophageal wall. It combines estimations of esophageal lumen cross-sectional areas (CSA) with pressure readings and thus provides an assessment of distensibility. The application of this imaging modality in the diagnostic workup of esophageal disorders is the subject of this chapter.

2 Technical Principles of Impedance Planimetry

Impedance planimetry is an examination technique that uses measurements of AC voltage to estimate cross-sectional areas of a liquid conductor contained in a cylindrical bag. An array of ring electrodes mounted on the catheter segment inside a cylindrical bag mounted near the tip of the catheter delineates the measurement area. The outermost electrodes are connected to a low-voltage AC current source. The bag is nearly infinitely compliant up to a stated diameter. Via infusion ports near the ends the bag is gradually filled with a saline solution. Voltage measurements are made between pairs of electrodes. Since electrical current, conductivity of the fluid, and distance between the electrodes are constants, impedance (the resistance to AC current flow) is proportional to the CSA of the conductor, i.e., the liquid column. Impedance measurements are converted to diameter estimations and a dynamic image of the bag geometry is created and displayed on a screen in real time at 10 Hz. Simultaneously, a solid-state pressure transducer monitors intrabag pressure. The distensibility

index (DI), defined as the ratio of the smallest CSA in the region of interest to intrabag pressure, is the most commonly used parameter to characterize distensibility (Kwiatek et al. 2010). Currently, an impedance planimetry device is commercially available as EndoFLIP® device (Endolumenal Functional Lumen Imaging Probe, Crospon Ltd., Galway, Ireland). This consists of central unit with a touchscreen display and a motor syringe which is connected to a disposable catheter. Several bag sizes are available that comprise up to 16 impedance tracings over a measurement area of 4–16 cm length with diameters of 20–25 mm (Fig. 1).

Main applications of impedance planimetry are the assessment of esophagogastric junction and esophageal body distensibility as these regions are easily accessible by catheter and have a narrow lumen. First, an automated sequence to purge air from the catheter is performed during a test distension in a calibration tube. Thereafter the catheter is inserted into the esophagus transnasally or transorally and advanced until the center of the measurement bag is centered at the region of interest. By convention, distensibility at rest is assessed with filling volumes of 10–60 mL in 10 mL increments, depending on bag size and measurement area.

3 Impedance Planimetry of the Esophagus in Healthy Volunteers

3.1 Esophagogastric Junction

In healthy subjects the high-pressure zone at the EGJ is to the most part located at the level and below the diaphragmatic hiatus. Resting pressure is highest at the hiatus. Conversely, with the FLIP catheter straddling the EGJ, the measurement bag assumes an hourglass shape with volumetric distension and the hiatus is the least distensible area. CSA and intrabag pressure increase with filling volume with a tendency towards a higher DI at higher volumes. Median values of the smallest

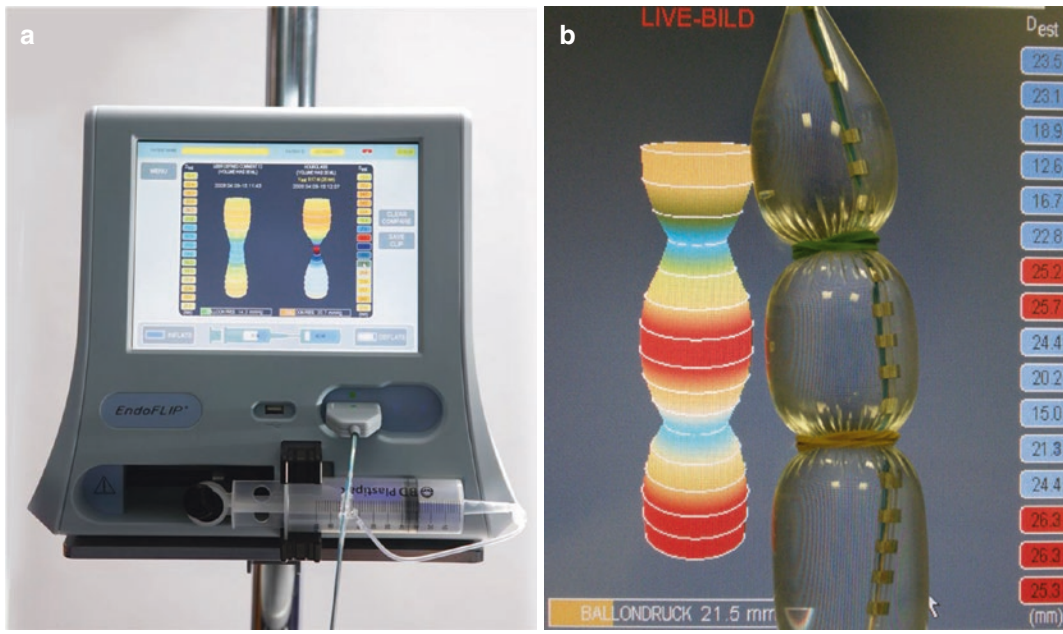

Fig. 1 (**a**) EndoFLIP® control and display unit operated via touchscreen. A disposable catheter is connected to a single-use syringe containing a saline solution of known electrical conductivity. The syringe is clamped to the central unit and motor controlled. (**b**) The EndoFLIP® catheter with the measurement bag filled and narrowed by two rubber bands, held in front of the corresponding image on the screen

CSA were 38, 94, and 264 mm^2 at distension volumes of 20, 30, and 40 mL, respectively (Kwiatek et al. 2010). Several studies have reported EGJ distensibility data of healthy controls at 40 mL distension volume (Fukazawa et al. 2014; Lin et al. 2013; Rieder et al. 2013). Median DI values of 2.7–7.1 mm^2/mmHg and a lower limit of normal of 2.4 mm^2/mmHg were described (Fig. 2).

3.2 Tubular Esophagus

FLIP measurements in the esophageal body are challenging to perform and to interpret. The tubular geometry of the organ is reflected by a cylindrical configuration of the measurement bag, hampering the exact anatomic localization of the measurement area. Therefore, a catheter with a measurement length of 16 cm has been developed, allowing control of bag localization by placing the distal part across the EGJ. With more proximal bag placement distension-induced repetitive antegrade contractions frequently interfere with distensibility measurements. Filter settings during acquisition or post-processing of data can be applied to compensate for the effects of distension-related contractions. The preferred metric for assessment of esophageal body distensibility is the distensibility plateau, i.e., the point of narrowest diameter (or CSA) along the esophagus that resists further distension with increasing intrabag pressure. This parameter is acquired by plotting the narrowest CSA across the esophageal body as a function of pressure.

In a landmark paper using an 8 cm bag a distension plateau of approximately 400 mm^2

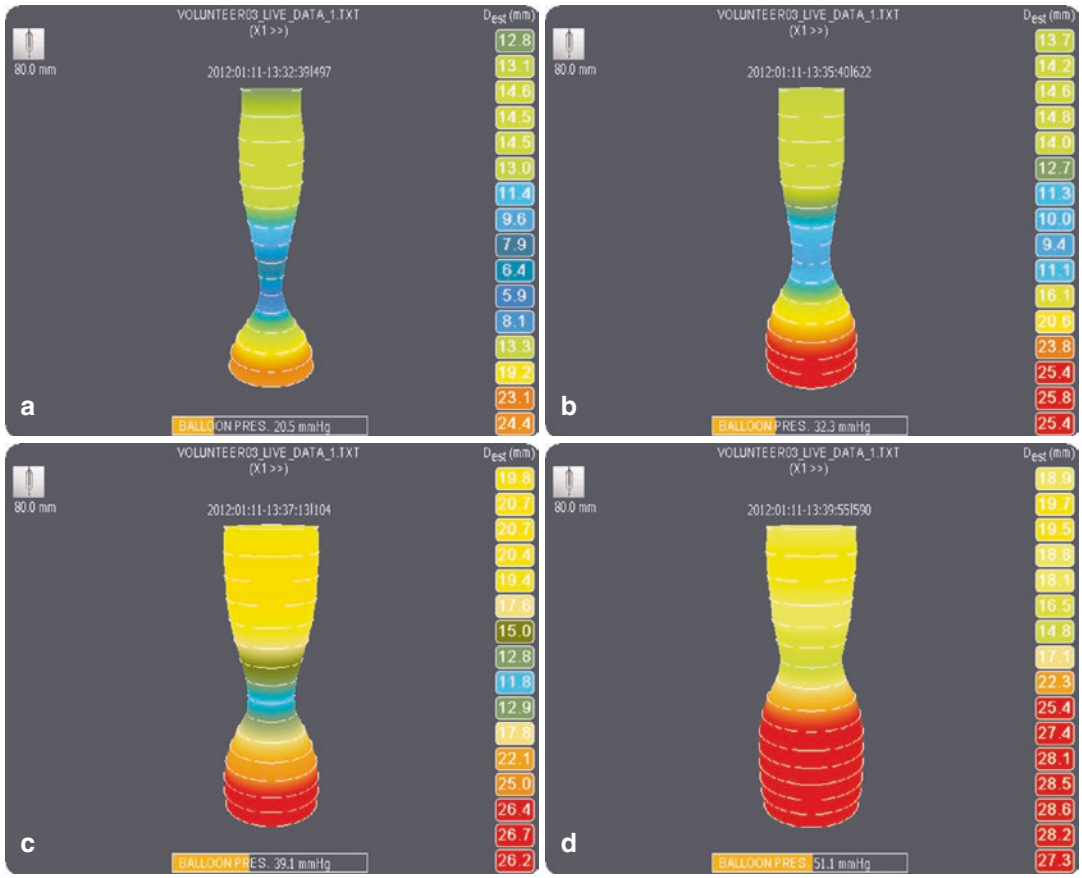

Fig. 2 Distensibility of the esophagogastric junction in a healthy volunteer at volumes of 20 (**a**), 30 (**b**), 40 (**c**), and 50 mL (**d**). Diameter values calculated from the 16 impedance tracings are listed in the column at the right side. Intrabag pressure is displayed below the image

(corresponding to a diameter of 22.6 mm) was reported for most healthy subjects (Kwiatek et al. 2011). A more recent study compared several filter methods and incorporated a temporospatial color-plot display of distensibility similar to high-resolution manometry. Identifying the widest diameter at the narrowest region turned out to be the most accurate method to eliminate effects of spontaneous or distension-induced contractions. In nine healthy subjects a distension plateau of 21.0 (20.3–21.6) mm was reported (Carlson et al. 2016).

3.3 Pharyngoesophageal Sphincter

Normative data of impedance planimetry measurements at the pharyngoesophageal sphincter are confined to a single study (Regan et al. 2013). To ascertain that the airway is not compressed maximal filling volume of the measurement bag was limited to 20 mL. At rest the pharyngoesophageal sphincter was not distended beyond the minimum diameter of 4.8 mm that the EndoFLIP® system can measure. During deglutition a maximal diameter of 9.2 mm for dry swallows and 7.7 mm for 5 mL water swallows at a bag volume of 20 mL was recorded in healthy volunteers. It was also demonstrated that maneuvers like head turn and supraglottic swallow yield higher opening diameters. However, the reported opening diameters of the pharyngoesophageal junction during swallowing are surprisingly low with respect to bolus size at meals. Higher filling volumes were not investigated because of concerns that airway patency might be compromised and because of poor tolerability of the EndoFLIP® bag at this location.

4 Impedance Planimetry for Diagnosis and Management of Dysphagia

In clinical practice a distinction between esophageal versus oropharyngeal dysphagia is commonly made by symptom profile. Oropharyngeal dysphagia mainly involves difficulties in oral bolus control, compromised airway protection, and an impairment to initiate a swallow. In contrast, esophageal dysphagia is characterized by the sensation of failed or incomplete bolus transport after unimpaired deglutition, possibly associated with retrosternal pressure or regurgitation of non-acidified food remnants and mucus. More severely, a bolus may be impacted in the esophagus and require acute endoscopic intervention. Impedance planimetry may provide clinically useful information in various disease states associated with dysphagia, not obtainable by radiology, endoscopy, or manometry. The application of this imaging technique has mainly been studied in achalasia and eosinophilic esophagitis, whereas few data exist concerning EGJ distensibility in gastroesophageal reflux disease or conditions with oropharyngeal dysphagia. FLIP measurements have also been performed to monitor therapeutic interventions at the EGJ and recently dilatation catheters incorporating impedance planimetry imaging have become available.

4.1 Oropharyngeal Dysphagia

A single study validated the EndoFLIP system as a tool for quantitating pharyngoesophageal distensibility in survivors of head and neck cancer, treated by chemoradiotherapy with or without laryngectomy. In 22 of 34 patients a stricture was confirmed. During distension up to 60 mmHg, the mean EndoFLIP-derived narrowest CSA in patients with strictures, in patients without strictures, and in controls were 58, 195, and 227 mm^2, respectively. A cutoff of 114 mm^2 for the CSA at the pharyngoesophageal junction had a perfect diagnostic accuracy in detecting strictures at this level (Wu et al. 2017).

4.2 Achalasia

An impairment of swallow-induced relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophageal body are diagnostic for achalasia. Treatment is directed at reduction of esophageal outflow resistance. Distensibility

measurements at the EGJ should therefore be valuable to characterize the disease state and the response to treatment. Several FLIP studies using a 40 mL distension volume have demonstrated a lower DI at the EGJ in achalasia patients compared to healthy controls. DI was typically ≤1.6 mm^2/mmHg in untreated achalasia (Pandolfino et al. 2013, Rieder et al. 2013, Teitelbaum et al. 2013, Verlaan et al. 2013) and ranged from 2.7 to 7.1 mm^2/mmHg in healthy controls (Fukazawa et al. 2014; Lin et al. 2013; Rieder et al. 2013). Treatment by dilatation or cardiomyotomy aims to reduce outflow obstruction at the level of the LES. The success of treatment, measured by esophageal emptying in a timed barium esophagram and the Eckardt dysphagia score, was significantly correlated with an increase in esophagogastric junction distensibility, but not measurements of LES pressure (Rohof et al. 2012). A DI below 2.8 mm^2/mmHg after pneumatic dilatation or Heller myotomy was significantly correlated with a poor symptomatic outcome (Pandolfino et al. 2013). FLIP may therefore be better suited to characterize EGJ function because luminal opening is a more important determinant of bolus flow than sphincter relaxation. Consequently, intraoperative FLIP measurements were performed intraoperatively. Intra-abdominal pressure induced by pneumoperitoneum during laparoscopic surgery had an impact on the distensibility of the esophagogastric junction, while the effects of general anesthesia and muscle relaxation were reported to be minimal (Nathanson et al. 2012). Intraoperative FLIP measurements at the EGJ during laparoscopic Heller myotomy and peroral endoscopic myotomy (POEM) showed a greater increase in DI by POEM than laparoscopic surgery. A DI between 4.5 and 8.5 mm^2/mmHg after resolution of pneumoperitoneum was found to predict good symptomatic outcome. Eighty eight percent of patients within this DI range had an Eckardt score ≤1 and a GERDQ score ≤7, compared to 47% with a DI above or below (Teitelbaum et al. 2015). Thus, intraoperative impedance planimetry seems to be a useful calibration tool for operations to treat achalasia.

Impedance planimetry imaging has also been incorporated into dilatation catheters. A 30 mm dilatation balloon has been used in a feasibility study to treat newly diagnosed achalasia. Technical success was achieved in all of the ten patients. Median EGJ distensibility significantly increased from 1.1 (IQR 0.6–1.3) before dilatation to 7.0 (IQR 5.5–17.8) afterwards (Kappelle et al. 2015). When the partially distended balloon straddles the EGJ a typical hourglass image is displayed. Therefore, dilatation can be performed without fluoroscopic control. Through-the-balloon endoscopic visualization of the mucosa may be helpful to monitor mucosal integrity during treatment. Postinterventional distensibility measurements in the same session may be performed and allow tailoring of therapy to the intended treatment effect (Fig. 3).

4.3 Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Diagnosis is made by a combination of clinical and histopathologic features. Symptoms in adult patients are mainly dysphagia, food impaction, and chest pain. Multiple biopsies from the proximal and distal esophagus should be evaluated and a minimum number of 15 eosinophil granulocytes per high-power field in at least one biopsy sample is a diagnostic criterion. Distribution of lesions may be patchy and eosinophil microabscesses are often seen. EoE is associated with esophageal remodeling, endoscopically characterized by fixed or transient rings, longitudinal furrows, diffuse esophageal narrowing, and whitish exudates. Histologic remission and symptom control can be achieved by PPI or topical corticosteroid therapy. A six-food elimination diet may be required in some cases. Additionally, balloon dilatation of esophageal strictures may be necessary to relieve dysphagia (Liacouras et al. 2011). Compared to fluoroscopy endoscopy has been shown to be significantly less accurate in detecting esophageal narrowing. Even at a cutoff value of ≤15 mm esophageal lumen diameter, endoscopy had a

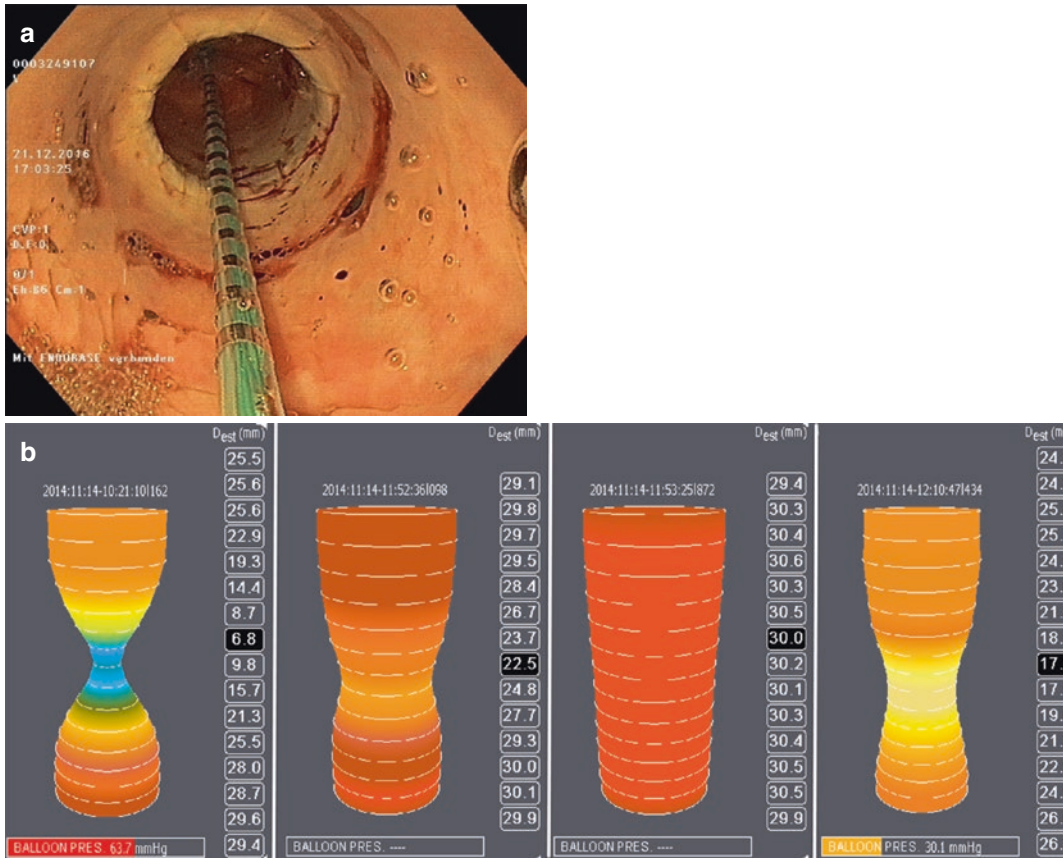

Fig. 3 (**a**) Therapeutic dilatation using a balloon with integrated planimetry imaging (EsoFLIP®) at 22 mm diameter. There is good endoscopic sight through the liquid-filled balloon. Due to the pressure applied by the balloon the mucosa appears pale at the narrowest area and short mucosal tears are visible. The impedance electrodes along the catheter are visualized well. (**b**) Impedance planimetry before, during (at 22 and 30 mm diameter), and post-dilatation. DI at 50 mL bag filling volume increased from 0.57 mm²/mmHg before to 7.81 mm²/mmHg after the intervention

sensitivity of only 25.0% (95% CI 5.5–57.2%) for narrowed esophagus (Gentile et al. 2014). In an initial impedance planimetry study of patients with EoE a lower compliance of the esophagogastric junction and the distal esophageal body compared to healthy controls has been reported (Kwiatek et al. 2011). When using requirement for dilatation therapy and food impaction as endpoints esophageal body distensibility was the only independent predictor. A distensibility plateau of CSA <225 mm² (diameter <17 mm), but not intraepithelial eosinophil count or type of treatment, predicted future food impaction (Nicodème et al. 2013). A highly significant correlation of esophageal body distensibility with a recently validated endoscopic grading system of esophageal rings (EREF score) was also found in a study of 72 patients with EoE. It also confirmed the lack of association between eosinophil count and distensibility (Chen et al. 2016). Taken together, impedance planimetry of the esophageal body appears to be an accurate diagnostic tool to assess esophageal remodeling in EoE. This is of high clinical relevance, since it has been reported that dysphagia resolved in 90% of patients after balloon dilatation, independent of mucosal inflammation (Schoepfer et al. 2010). As noted above, distension-induced contractions are a limiting factor in obtaining distension plateau measurements by the EndoFLIP® system.

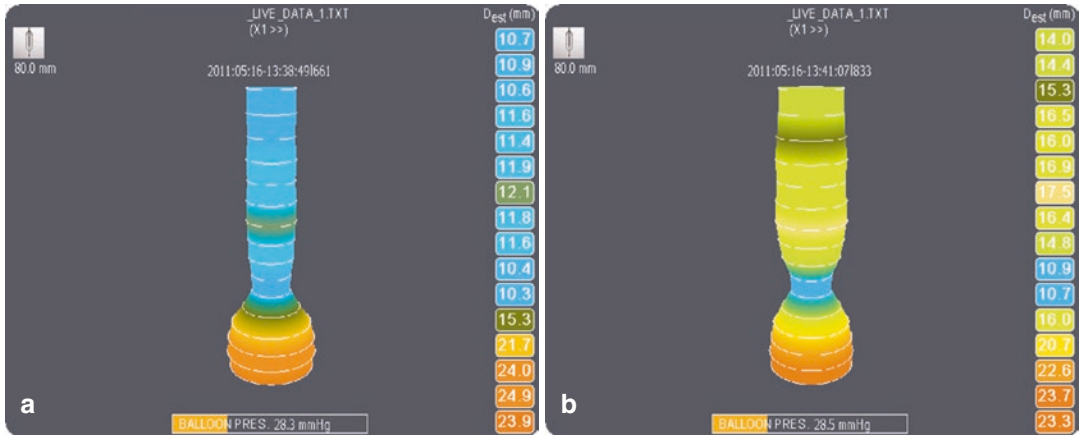

Fig. 4 Distensibility of the esophagogastric junction in a patient with eosinophilic esophagitis. There is only a minimal increase of the smallest cross-sectional area with higher filling volumes. Intrabag pressure rises disproportionally, resulting in a low distensibility at volumes of 40 and 50 mL, indicating that the distension plateau is reached

Mathematical analysis tools that compensate for the effect of contractility are not generally available yet (Fig. 4).

5 Impedance Planimetry in Patients with Gastroesophageal Reflux Disease or Hiatus Hernia

The diaphragmatic crura and the intrinsic LES form an antireflux barrier at the EGJ. Transient lower esophageal relaxations are the main mechanism for reflux episodes. These vagally mediated drops of pressure at the esophagogastric junction mainly occur in the postprandial period and are induced by distension of the gastric fundus (Schoeman et al. 1995). If EGJ anatomy is disrupted and a hiatal hernia is present, a significant proportion of reflux episodes may occur by other mechanisms like straining, deep inspiration, or swallow-induced sphincter relaxation (van Herwaarden et al. 2000). In an impedance planimetry study of healthy controls versus subjects with symptomatic gastroesophageal reflux disease the hiatal diameter increased with increasing distention volume in both groups. Distension pressure was consistently lower in the group of reflux patients than in control subjects at 20, 30, and 40 mL bag volumes. At any given intrabag pressure, the opening of the esophagogastric junction was wider in reflux patients (Kwiatek et al. 2010). It can be deducted from these findings that higher compliance of the EGJ in reflux patients may contribute to gastroesophageal reflux activity. Surprisingly, in a study of 22 healthy volunteers and 18 patients with symptomatic gastroesophageal reflux disease, distensibility at the EGJ was higher in controls than patients and no significant difference in CSA between subjects with abnormal vs. normal esophageal acid exposure was found. An inverse correlation between distensibility and body mass index (BMI) was documented with patients being significantly more overweight than controls. Additionally, esophagitis was endoscopically detected in more than a third of control subjects (7 Los Angeles grade A, 1 grade B). Furthermore, only low distension volumes (20 and 30 mL) were applied in this study (Tucker et al. 2013). In normal anatomy the esophagogastric junction is situated intra-abdominally. Pressure topography displays a single high-pressure zone at the EGJ with contributions from the LES and the diaphragmatic crura. An axial hiatal hernia is present when a part of the stomach is displaced into the thorax through the diaphragmatic hiatus. Two lumenal narrowings can be seen endoscopically

and manometry exhibits two zones of elevated resting pressure, the proximal one representing the LES and the distal one the diaphragmatic hiatus. By convention an axial distance of at least 2 cm between EGJ or LES and diaphragmatic hiatus is required to diagnose a hiatal hernia. In a study of 30 patients with Barrett's esophagus and 14 healthy control subjects impedance planimetry had a 100% sensitivity and a 77.8% specificity to detect an endoscopically diagnosed hiatal hernia by displaying two regions of lower distensibility along the 8 cm measurement segment. This two-component profile was also present in four subjects without endoscopic evidence of a hiatal hernia. The LES component in the hiatal hernia patients was significantly more distensible than the common EGJ in subjects without hernia (DI 6.6 vs. 3.9 mm^2/mmHg, $p < 0.001$, at 50 mL distension volume). The diaphragmatic component was significantly more distensible than the LES component (DI 17.9 vs. 6.6 mm^2/mmHg, $p < 0.001$, at 50 mL bag filling volume) in patients with hiatal hernia (Lottrup et al. 2016) (Fig. 5).

Antireflux surgery aims to restore a functional antireflux barrier at the EGJ in patients with gastroesophageal reflux disease but is frequently complicated by postoperative dysphagia. Bougies have been used with inconsistent success to calibrate hiatal closure and the fundic wrap. The application of impedance planimetry during these procedures may be a promising approach. With this technique surgery can be tailored so that the

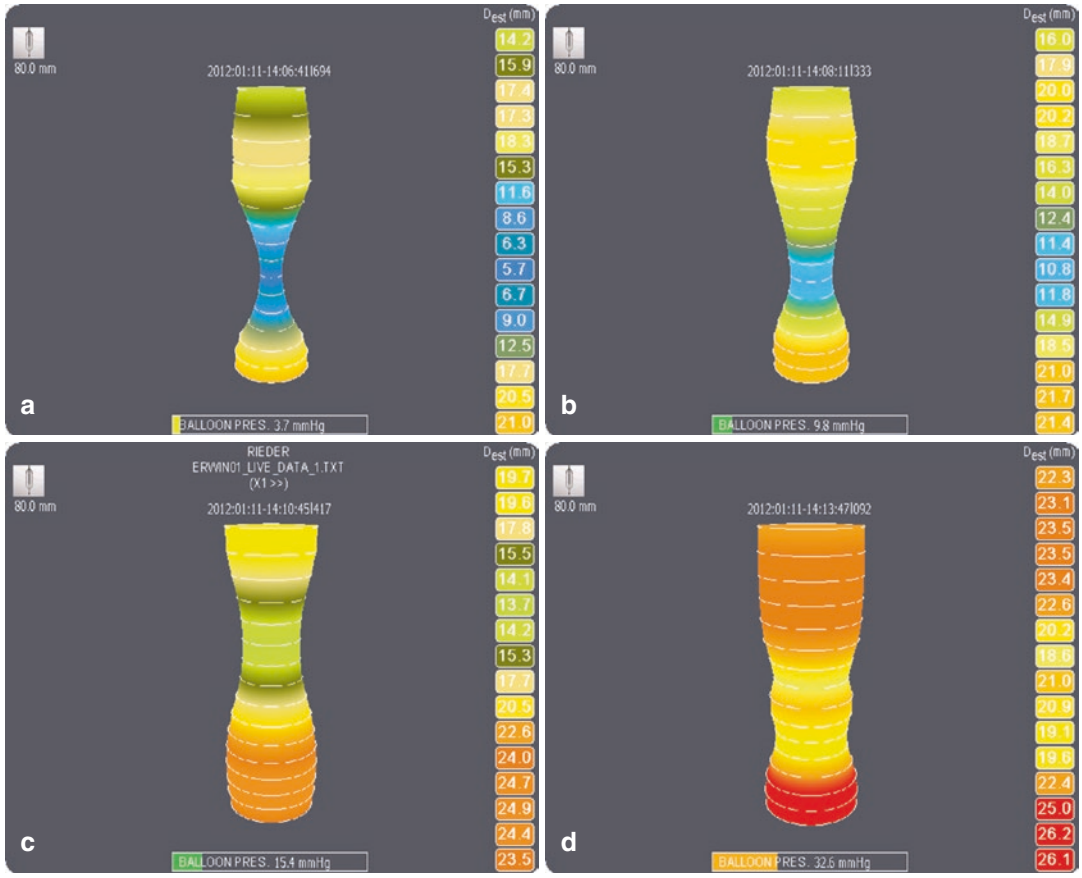

Fig. 5 (**a–d**) Distensibility of the esophagogastric junction in a patient with gastroesophageal reflux disease. The smallest cross-sectional area increases with bag volume. At 50 mL filling volume, the bag almost acquires a cylindrical shape with two slightly narrower regions, indicating a small sliding hiatal hernia. Intrabag pressure increases by a small extent only

desired endolumenal diameter is maintained at a low distension pressure. The concept of using the FLIP catheter as a "smart bougie" during antireflux surgery has been reported previously (Perretta et al. 2011). In a feasibility study in 17 patients undergoing laparoscopic Nissen fundoplication intraoperative distensibility tests with distension volumes of 30 and 40 mL were performed at various stages of the surgical procedure. The induction of pneumoperitoneum, hiatal repair, fundoplication, and resolution of pneumoperitoneum significantly changed EGJ distensibility at 30 mL, whereas only initiating pneumoperitoneum and hiatal closure significantly reduced distensibility with 40 mL distension volume. Hiatal closure had the greatest impact at both distension volumes. Initial and final DI at 30 and 40 mL were 4.23 vs. 0.97 mm^2/mmHg and 3.75 vs. 1.36 mm^2/mmHg, respectively. In two cases a DI <0.7 before extubation was noted. The first patient developed severe dysphagia and required reoperation. The second patient was converted to a partial fundoplication resulting in a higher DI (Ilczyszyn and Botha 2014). In a study designed to compare the effects of Nissen and Toupet fundoplication on EGJ distensibility a similar FLIP protocol was used, but omitted measurements after hiatal repair. Patients with recurrent reflux after fundoplication were included and exhibited similar EGJ distensibility before reoperation compared to reflux patients without previous antireflux surgery (DI 3.2 vs. 3.5 mm^2/mmHg and 3.7 vs. 4.0 mm^2/mmHg at 30 and 40 mL distension volume, respectively). Nissen fundoplication resulted in a significantly greater reduction in distensibility than the Toupet partial wrap (1.4 vs. 1.9 mm^2/mmHg and 2.0 vs. 2.4 mm^2/mmHg at 30 and 40 mL distension volume, respectively) (DeHaan et al. 2016). Studies linking intra- or postoperative FLIP measurements to symptomatic outcome or defining optimal postsurgical distensibility are not available yet.

6 Summary

Impedance planimetry is an imaging technique that provides real-time information about biomechanical properties of the esophageal wall. Small sets of normative data have been published about distensibility measurements of the esophagogastric junction, the esophageal body, and the pharyngoesophageal junction. If symptoms of possible esophageal origin develop in a patient, organ morphology and the state of the mucosal lining are of principal interest. Videofluoroscopy and endoscopy cover these aspects to a huge extent. If mucosal integrity is preserved and tumors or structural lesions are excluded functional disorders have to be considered. Manometry and intralumenal impedance monitoring are sophisticated tools to assess muscular function and bolus clearance. Impedance planimetry is the only diagnostic tool available for clinical routine to examine esophageal wall compliance in vivo and complements endoscopy, videofluoroscopy, and high-resolution (impedance) manometry. At present investigation of esophageal dysphagia is the main application of impedance planimetry. In patients with achalasia or EoE distensibility of the esophagogastric junction is reduced compared to healthy controls. FLIP measurements of the tubular esophagus have a high sensitivity to detect diffuse narrowing or localized strictures in EoE. For this purpose, the concept of a distensibility plateau has been developed. This is defined as the cutoff diameter or CSA that does not further increase with additional bag filling volume, but only leads to a higher intrabag pressure. The same considerations may be applied to other instances of reduced localized opening width like peptic stenosis or Schatzki rings. Special filter settings may be necessary in data analysis to compensate for distension-induced contractions. A newly developed spatiotemporal display of distensibility data similar to high-resolution manometry has improved the assessment of contractile activity and its impact on distensibility. In patients with gastroesophageal reflux disease or hiatal hernia an increased esophagogastric-junction distensibility compared to healthy controls has been described, but another study found EGJ distensibility to be lower in reflux patients compared to healthy controls. Impedance planimetry has been successfully used to monitor and to tailor therapeutic procedures to treat achalasia including laparoscopic cardiomyotomy,

POEM, and pneumatic dilatation. An ideal range of post-procedural EGJ distensibility has been reported. Intraoperative impedance planimetry measurements allow modifying the therapeutic intervention until the desired effect is achieved. Dilatation catheters with impedance planimetry imaging are now available to perform hydraulic dilatations of the EGJ in achalasia patients without fluoroscopic control. A recent expert review from the Clinical Practice Updates Committee of the AGA Institute reviewed potential indications for FLIP measurements in achalasia, EoE, and gastroesophageal reflux disease and formulated five best practice advices. These stated that clinicians should not make a diagnosis or treatment decision based on FLIP assessment alone (1). FLIP assessment was described as a complementary tool to assess EGJ opening dynamics and stiffness of the esophageal wall (2). Distinct protocols and analysis paradigms based on the disease state of interest should be followed utilizing FLIP (3). Clinicians should not use FLIP in routine diagnostic assessments of gastroesophageal reflux disease (4). FLIP should not be used to diagnose EoE but it may have a role in severity assessment and therapeutic monitoring (5) (Hirano et al. 2017).

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Esophagus: Radiologic Evaluation of Esophageal Function

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1 Introduction

Radiologic assessment of the esophagus is an essential part of the diagnosticlutition disorders. The radiologic examination comprises two parts: single- and double contrast examinations to assess the morphology of the esophagus and the esophago-gastric junction, which may reveal signs of esophagitis, tumor, strictures, or rings. Radiologic evaluation of the

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esophagus would be incomplete without assessing esophageal function. Attempts to diagnose esophageal motor dysfunction, such as achalasia, were undertaken in the early days of single-contrast barium radiology (Hurst et al. 1930). The development of cinefluoroscopy and videofluoroscopy has significantly improved the ability to study the motor function of the pharynx and esophagus in detail. The pharyngeal and esophageal transport of liquid and solid boluses can be studied in real time and in slow motion. Although slow motion analysis is more crucial for the assessment of pharyngeal function, video recording of esophageal bolus transport is also essential for a thorough analysis of the esophagus. Subtle abnormalities of motor function may go undetected during real-time observation of swallowing.

2 Normal Function of the Esophagus and the Lower Esophageal Sphincter

The esophagus is a tubular muscular structure, measuring approximately 23 cm in length (Li et al. 1994), which comprises outer longitudinal and inner circular muscle fibers. The proximal part of the esophagus consists of striated muscle fibers, whereas the distal part is composed of smooth muscle. The level of the transition zone between striated and smooth muscle is highly variable, with only the proximal 4 cm of the esophagus always composed of striated muscle. This dual structure of the esophageal musculature comprising striated muscle and smooth muscle fibers is significant in diseases that selectively affect either striated or smooth muscle. At the distal end of the esophagus, the tubular esophagus widens to the vestibular esophagus.

The lower esophageal sphincter between the vestibular esophagus and the stomach measures 3–5 cm in length. The lower esophageal sphincter corresponds to the high-pressure zone at the esophago-gastric junction seen on esophageal manometry (Cohen 1979).

2.1 Primary and Secondary Peristalsis

Swallowing of a bolus triggers a primary peristaltic contraction wave in 95–96% of patients (Richter et al. 1987), which propagates with a velocity of 2–3.5 cm/s. Manometric studies have revealed that the lower esophageal sphincter has a resting pressure. Upon swallowing, the sphincter relaxes some seconds after triggering of swallowing. Radiologically, the lower esophageal sphincter is pushed open by the bolus arriving at the gastroesophageal junction. Immediately after bolus passage, the sphincter re-contracts. The amplitude and propagation velocity of primary peristalsis is modulated by bolus consistency, volume, and temperature (Dooley et al. 1988). If there is residual bolus in the esophagus or if there is a gastroesophageal reflux, a secondary peristaltic contraction wave can be triggered by the volume remaining in the esophagus to clear the esophagus. Both primary and secondary esophageal contractions are peristaltic and considered normal.

2.2 Non-propulsive Contractions

Non-propulsive (formerly called “tertiary”) contractions may also be seen in the esophagus during videofluoroscopy or manometry. They result in segmental muscular contractions, which are not propagated to the distal esophagus. They may occur simultaneously at multiple sites, and they may be repetitive. In young adults, these non-propulsive contractions are rarely seen upon swallowing (Richter et al. 1987). The prevalence and severity of non-propulsive contractions increases with age (Grishaw et al. 1996). Most often, they are signs of abnormal esophageal function.

2.3 Radiologic Evaluation of Esophageal Motor Function

Radiologic evaluation of esophageal function always includes assessment of the esophageal body as well as the pharyngo-esophageal and lower esophageal sphincters. In contrast to the assessment of pharyngeal function, esophageal peristalsis can be assessed in real-time. However, videotaping of a study is helpful to allow repeated analysis of bolus transport that would demonstrate subtle abnormalities. Esophageal function should be assessed in all patients who suffer from dysphagia or globus sensation when referred for a videofluoroscopic study. One must be careful in patients with clinically suspected aspiration. The study should always be initiated with an examination of pharyngeal function. If there is only laryngeal penetration or minimal aspiration of the contrast material, the examiner can proceed to assess esophageal function. In general, the IV administration glucagon or hyoscine butylbromide (Buscopan®) should be avoided. Glucagon and hyoscine butylbromide can alter the esophageal bolus transit and produce relaxation of the gastroesophageal sphincter, resulting in spontaneous gastroesophageal reflux (Anvari et al. 1989). For esophageal motor function studies, low density barium (app. 100% g/v) should be used. Barium at this consistency flows easily and is radio-opaque enough to provide good contrast in the esophagus. Since it is known that bolus viscosity alters peristalsis, thick high-density barium or barium paste should not be used. In case of aspiration, a limited study of esophageal function with iodinated, nonionic contrast material may be considered.

For assessment of esophageal peristalsis, the observation of "single swallows" is essential. Repetitive swallowing inhibits the propagation of esophageal peristalsis (Meyer et al. 1981), a phenomenon which is referred to as "deglutitive inhibition." If the patient swallows repeatedly within 5–10 s, every new peristaltic contraction generated by swallowing will inhibit the preceding peristaltic contraction. Radiologically, this may be misinterpreted as impaired peristalsis or non-propulsive contractions. After the end of a series of repeated swallows, a large contraction wave will "clear" the esophagus. Therefore, the size of the bolus administered is critical for assessment of esophageal peristalsis: we routinely use a bolus size of 10 ml of barium to ensure that the patient swallows only once. In contrast, rapid repetitive swallows maximally distend the esophagus for morphologic evaluation (e.g., the search for Schatzki rings).

Esophageal peristalsis is assessed in the upright and in the prone oblique position. Usually, swallows in the prone oblique position provide more information, because gravity does not support bolus transit. The peristaltic contraction wave occludes the esophageal lumen, giving the bolus tail typically an inverted "V"-shape (Fig. 1). It propels the complete bolus through the esophagus into the stomach. The proximal escape of a small amount of barium is not considered abnormal (Schima et al. 1992). The mean esophageal transit time of fluids is approximately 8 s in the age group 20–59 years, with 10% of swallows taking longer than 10 s (Miles et al. 2016). Swallows in the upright position are sometimes of value, because they may reveal subtle motor abnormalities not seen in the prone oblique position (Sears et al. 1989). In the upright position, bolus transit through the esophagus is normally rapid. The persistence of an air-fluid level ("support level") is indicative of the presence of a disordered motor function or a stenosis (Schober et al. 1993).

The use of up to 10 swallows per patient during videofluoroscopy has been shown to be more sensitive for the detection of subtle motor abnormalities (Hewson et al. 1990). However, in clinical practice, the number of swallows observed must be limited because of radiation exposure, practicability, and patient comfort. Therefore, our routine examination protocol includes the observation of one bolus in the upright position and three boluses in the prone oblique position. The diagnostic value of videofluoroscopic studies can be increased by using solid barium-soaked marshmallows or globules, tablets, or rice (Aksglaede et al. 1992; Schwickert et al. 1993; Ott et al. 1991; Hannig et al. 1990).

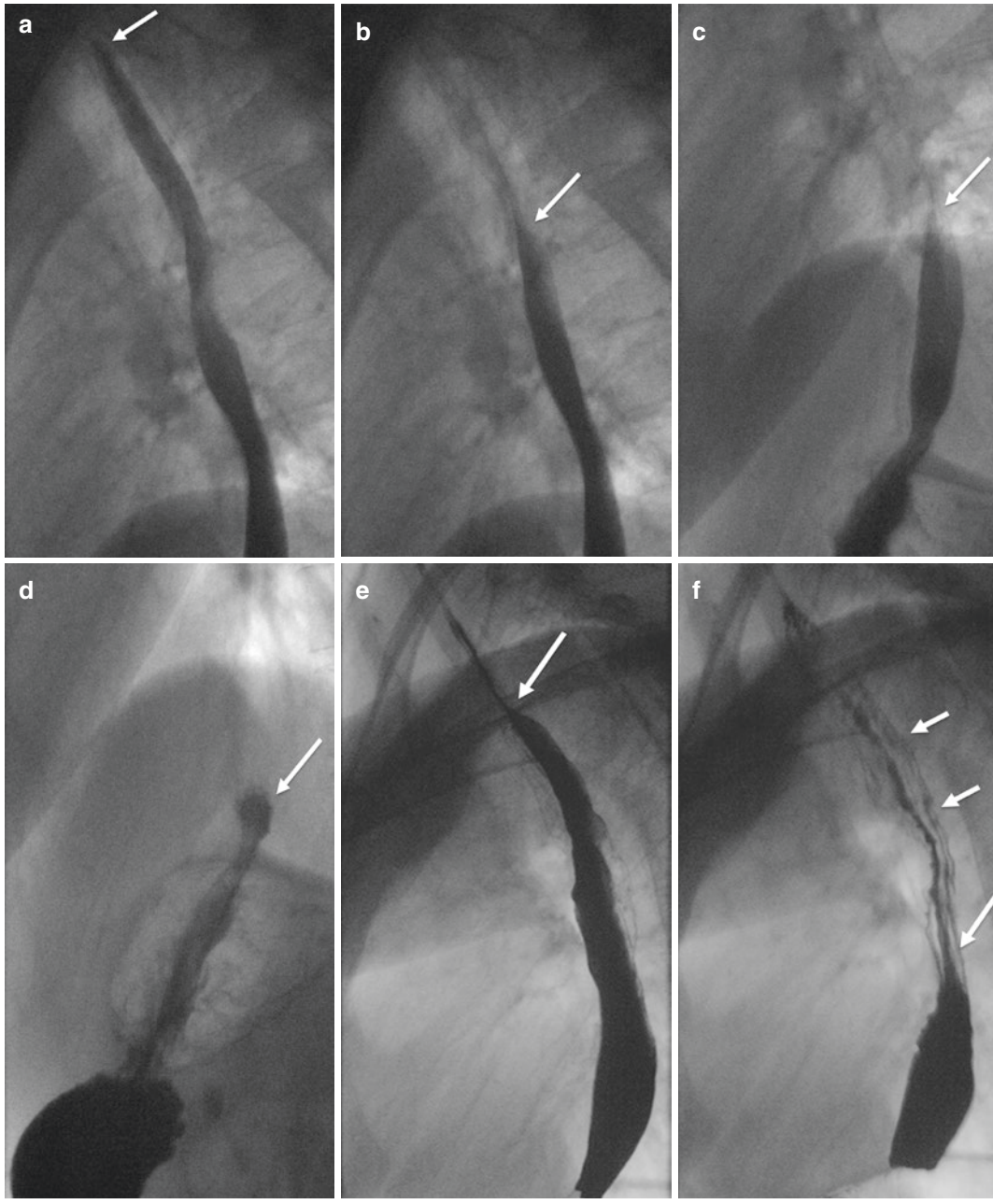


Fig. 1 Videofluoroscopic assessment of peristalsis. (**a–d**) Normal esophageal motility. Patient is placed in the prone oblique position. There is a peristaltic contraction wave, which occludes the esophageal lumen, resulting in the typical inverted "V" shape (*arrows*) of the bolus tail. In Figure (**a**) to (**d**), distal propagation of the bolus is shown. (**e–g**) Failed peristalsis (manometrically confirmed). (**e**) There is a peristaltic wave (*arrow*). (**f**) Upon distal propagation (*arrow*), incomplete contraction of the proximal esophagus is observed (*small arrows*). (**g**) Failure of peristalsis results in proximal escape of the contrast media column (*arrow*)

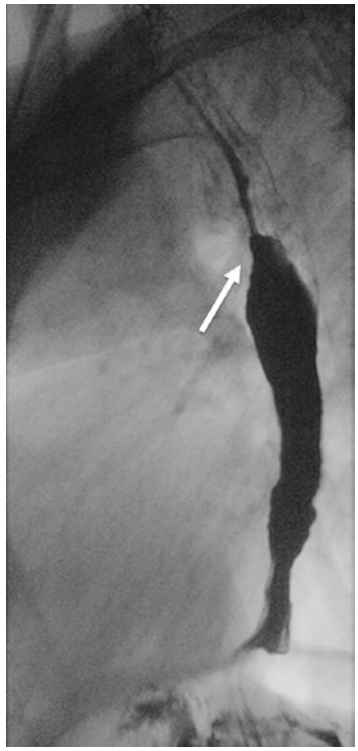


Fig. 1 (continued)

3 Examination Technique (Schima et al. 1995)

1. Upright position, LPO (left posterior oblique): The patients takes a bolus of low-density barium and is asked to swallow only once. The LPO position is preferred to avoid superposition of the esophagus by the spine and to provide better visualization of the gastroesophageal segment.
2. After tilting of the table, the patient is turned to a prone oblique position. The patient takes a bolus with a straw. Up to three swallows in single swallow technique are recorded. Imaging is centered on the tail of the bolus to look for proximal escape and stasis of the contrast material (Fig. 1).
3. Assessment of the gastroesophageal reflux: Reflux may or may not occur spontaneously during the examination. There are also provocative tests to elicit gastroesophageal reflux, including placing the patient in the Trendelenburg position, the water-siphon test, the Valsalva maneuver, and turning of the patient (Stewart 1981). We use only the latter two tests, which are more physiological than the former two. If reflux is noted during the examination, spot-film or video recording should be used to document it. With the invention of PACS systems an attractive alternative to storage of examination data on videotapes has emerged. "Videoflurososcopic" examinations can now be stored directly in a PACS system, which allows easy retrieval of prior examinations for comparison.
4. Solid bolus in the upright position: if the patient suffers from dysphagia for solids and the examination with liquid barium does not reveal the cause, a solid bolus (barium-soaked cookies, marsh mallows, tablets, etc.) may be used. Transit of solid food may be slow in some individuals. There is no standardized reference value for evaluation of solid food transit (Pouderoux et al. 1999). The best indicator for the presence of a significant stenosis (i.e., a Schatzki ring or a malignant stricture) or a motor abnormality is the induction of the typical symptoms of "food sticking in the throat" by a retained solid bolus.
5. Double-contrast and mucosal relief films of the esophagus and the lower esophageal sphincter (see Chapter on Esophageal Morphology).

4 Esophageal Motility Disorders

Esophageal motility disorders are classified according to the Chicago Classification, which is based on esophageal manometry findings. In its recent update (v3.0), motility disorders are defined as either major or minor (Kahrilas et al. Neurogastroenterol Motil 2015; Roman et al. Gastroenterol Clin North Am 2014). Major disorders are achalasia and esophago-gastric junction outflow obstruction, diffuse esophageal spasm (DES), hypercontractile esophagus (or "jackhammer esophagus"), and absent peristalsis. Minor disorders include weak peristalsis, frequently failed peristalsis, rapid contractions, and hypertensive peristalsis (Fig. 1). Secondary motility disorders

Table 1 Classification of esophageal motility disorders

Primary Motility Disorders
Achalasia
Diffuse esophageal spasm
Jackhammer esophagus
Aperistalsis
Minor motility disorders
Secondary Motility Disorders
Connective Tissue Diseases:
Progressive systemic sclerosis
Dermatomyositis
Polymyositis
Mixed connective tissue disease
Lupus erythematosus
Sjögren's syndrome
Endocrine disease:
Diabetes mellitus
Myxoedema
Hyperthyroidism
Metabolic disorders:
Alcohol-induced
Amyloidosis
Infectious disorders:
Chagas disease
Candida
Herpes
Chemical:
Gastroesophageal reflux
Caustic agents
Muscular disorders:
Myasthenia gravis
Muscle dystrophy
Neurologic diseases:
Parkinson's disease
Guillain–Barré syndrome
Poliomyelitis
Amyotrophic lateral sclerosis
Multiple sclerosis
Immunologic
Chronic graft-versus-host disease
Eosinophilic esophagitis
Iatrogenic
Medication (anticholinergic agents, benzodiazepines, barbiturates, etc.)
Radiation
Post-vagotomy

include a long list of motor abnormalities seen in conjunction with other diseases (Table 1). As mentioned, classification of motor disorders is based on manometric findings. So radiologic assessment of esophageal motor function can only indicate peristaltic or lower esophageal sphincter abnormalities, which have then been subjected to manometry for further categorization. Diagnosis of a secondary motor abnormality requires, in addition, the diagnosis of an extra-esophageal disorder known to affect the esophagus. Esophageal motility disorders present with the nonspecific symptom of dysphagia or chest pain. Although the clinical presentation may be the same in patients with different motor abnormalities, it is important to characterize the abnormality precisely. The optimal therapy is based on the specific knowledge of a manometric abnormality and may differ considerably between different groups. However, esophageal manometry is not widely available and in most cases not the first diagnostic test in patients with dysphagia. In these patients, either endoscopy or barium radiography is recommended in many institutions and countries (Frühwald et al. 2006; The Royal College of Radiologists 2007). Radiographic assessment, in particular videofluoroscopic recording, has been shown to be very useful in detecting and reliably characterizing esophageal motor abnormalities (Ott et al. 1987, 1990; Schima et al. 1992). Since association of oropharyngeal and esophageal functional disorders is not an uncommon finding, and symptoms of dysphagia caused by distal esophageal lesions are commonly referred to the neck, assessment of both phases of swallowing is necessary to adequately investigate patients with dysphagia (Gullung et al. 2012).

5 Primary Motor Disorders

5.1 Achalasia

Achalasia is the most widely known esophageal motor disorder, with an incidence of 1 in 100,000 individuals annually and a prevalence of 10/100,000 (Vaezi et al. 2013). It is characterized by aperistalsis

in the esophageal body and incomplete relaxation of the lower esophageal sphincter upon swallowing (Stacher et al. 1994; Richter 2001; Kahrilas et al. 2015). The etiology is not exactly known, but histopathologic lesions have been found in the dorsal motor nuclei of the brain stem, the vagal branches, and the myenteric plexus of the esophagus. The primary region of damage is the esophageal myenteric plexus (Auerbach's plexus), including patchy inflammatory response, loss of ganglionic cells and some myenteric neurofibrosis (Richter 2010). Diagnosis of achalasia should be suspected when patients present with a long history of slowly progressive dysphagia for solids and liquids. Regurgitation of saliva and food immediately after swallowing (in contrast to gastroesophageal reflux) is common. Achalasia may also present with (noncardiac) chest pain. Some patients complain of heartburn, despite the fact that incomplete opening of the lower esophageal sphincter is one of the key features of achalasia (Spechler et al. 1995). Esophageal manometry is the gold standard for the diagnosis of achalasia, which now defines three different subtypes (I–III) based on the presence or absence of panesophageal pressurization of premature contractions during manometry. Radiologically, the main feature is incomplete opening of the lower esophageal sphincter, which is the equivalent of incomplete manometric relaxation of the sphincter upon swallowing. In the esophageal body, aperistalsis is seen.

Videofluoroscopy is the best initial diagnostic test (Richter 2010). Radiologically, there is a typical appearance of esophageal dilatation with beak-like narrowing of the lower esophageal sphincter (Meshkinpour et al. 1992; Francis and Katzka 2010; Vaezi et al. 2013). Early in the disease, the esophagus has a normal diameter (Figs. 2 and 3). With progression of the disease, the esophagus becomes dilated and retains food and saliva (Fig. 4). In advanced cases, esophageal dilatation may be severe (so-called "sigmoid esophagus") (Fig. 5) (Schima et al. 1993). Barium radiography has a low sensitivity in detecting achalasia, as alterations in esophageal morphology are present in advanced cases only. The radiologic staging system for achalasia according to Brombart is based on the grade of esophageal dilatation

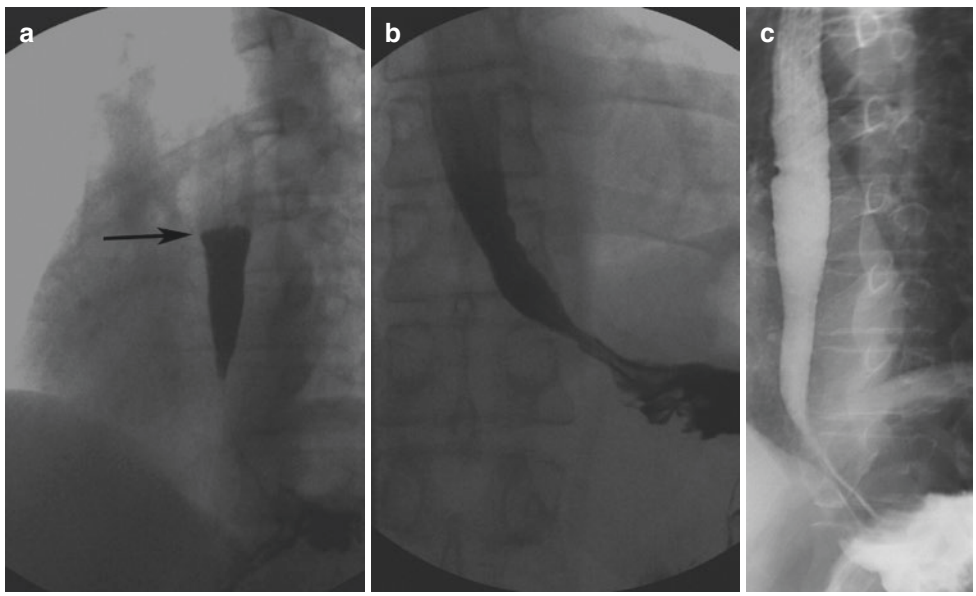


Fig. 2 (**a**, **b**) Achalasia—early stage. (**a**) Videofluoroscopy in the upright position reveals a support level of contrast material indicative of delayed transit (*arrow*). The esophagus is not dilated. (**b**) In supine position, narrowing of the gastroesophageal junction is evident. (**c**) Radiography confirms narrowing of the GE junction. Subsequently manometry was performed, which revealed achalasia type 1

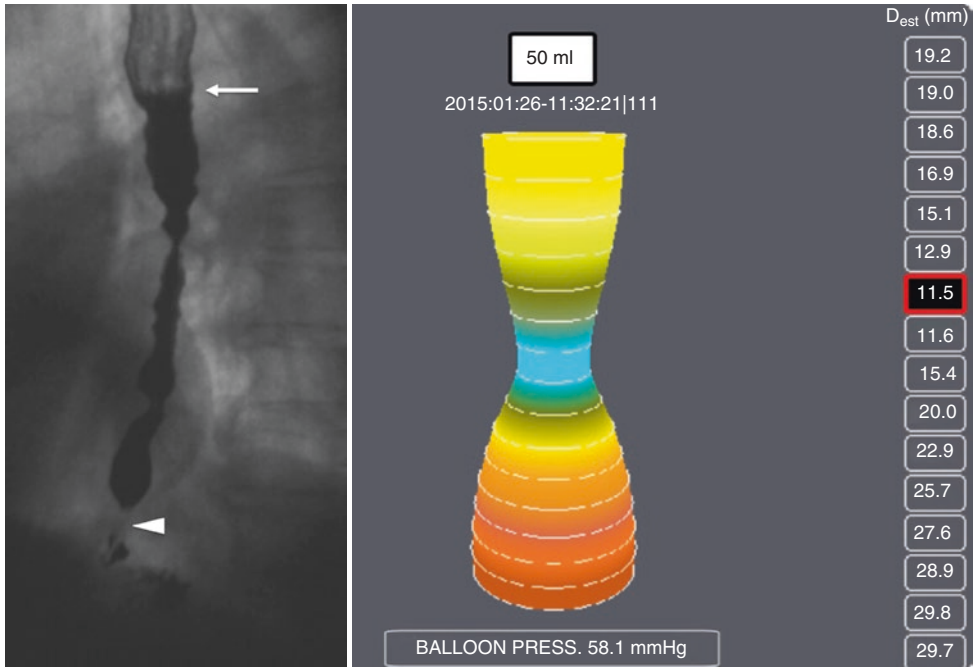


Fig. 3 Achalasia Type II according to the Chicago Classification. (**a**) Videofluoroscopy reveals incomplete lower esophageal sphincter opening (*arrowhead*), failure of regular peristalsis, and uncoordinated non-propulsive contractions with a support level (*arrow*) due to stasis of barium in the esophagus. HR-Manometry (not shown) confirms impaired EGJ relaxation combined with panesophageal pressurization in >20% of swallows and lack of normal peristalsis. (**b**) Impedance planimetry shows reduced distensibility at the esophagogastric junction at a bag volume of 50 ml with an EndoFLIP lumen of 11.5 mm

(<4 cm, 4–6 cm, >6 cm diameter) (Brombart 1980), which explains the low sensitivity of single-contrast upper gastrointestinal studies.

Multi-phasic radiographic evaluations including fluoroscopic assessment of esophageal motility show a support level of contrast material due to slowed esophageal transit. This sign hints at the presence of either a motor abnormality or a distal stenosis (Figs. 2 and 3). The sensitivity of radiologic studies (either barium radiography or videofluoroscopy) for the detection of achalasia has been reported to be 58–95% (Howard et al. 1992; Ott et al. 1987; Schima et al. 1992; Schima et al. 1998). With videofluoroscopy, diagnosis is based not only on morphologic alterations of the esophagus but also on assessment of functional abnormalities. Videofluoroscopy may reveal incomplete lower esophageal sphincter opening with delayed transit into the stomach. The feature of a transient support level of barium in the upright position reported sensitivities can be explained by variations in examination technique and patient populations. As described, the diagnosis is much more difficult to make in patients with early stages of the disease when esophageal dilatation is not yet present. Moreover, there is substantial overlap in radiographic features between different subtypes of achalasia (Goldenberg et al. 1991). Results of radiological studies correlate well with the post-therapeutic outcome in patients with achalasia with even better predictive values than esophageal manometry (Rohof et al. 2013).

In patients with diagnosis of esophageal outflow obstruction by manometry, common causes are anatomic abnormalities such as strictures or hiatal hernias (DeLay et al. 2016). In these cases, a detailed radiological investigation can contribute to the differentiation to functional causes.

Several studies have reported a relation between achalasia and esophageal carcinoma. Patients with long-standing achalasia are at increased risk of carcinoma, primarily resulting from nitrosamine production by bacterial overgrowth due to stasis and subsequent inflammation

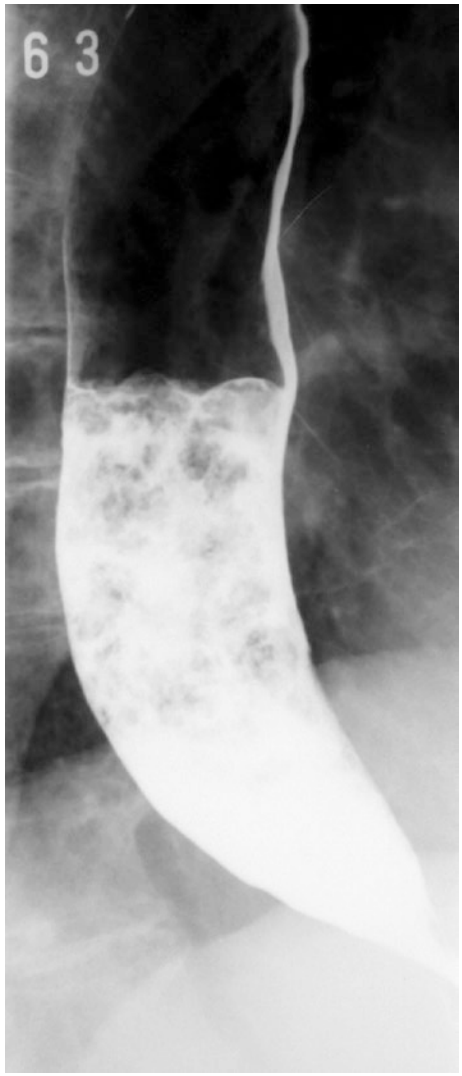


Fig. 4 Advanced achalasia. Barium radiography reveals moderate esophageal dilatation with retention of barium and secretions. There is the typical beak-like narrowing of the lower esophageal sphincter

and dysplasia (O'Neill et al. 2013). The exact cause is unknown, but chronic stasis of food and saliva has been suggested. The reported incidences range from 1.7% to 20% (Meijssen et al. 1992). In a large prospective trial, the risk of developing cancer in patients with achalasia was found to be increased 33-fold, for a total of 3.4 cancers/1000 patients per year. Due to the small absolute risk of developing cancer in patients with achalasia, recent guidelines do not recommend surveillance endoscopy (Evans et al. 2012).

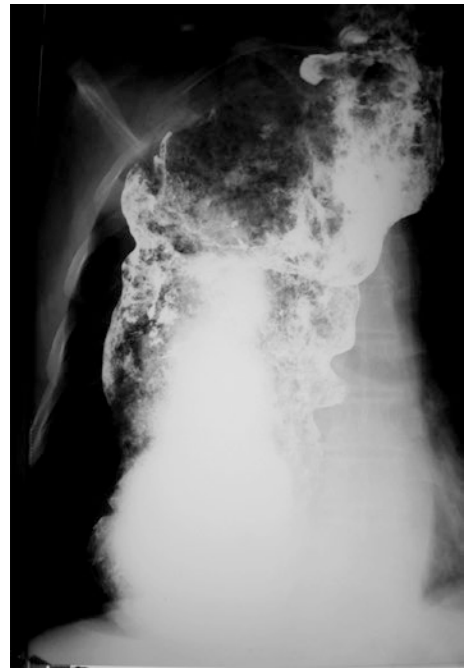


Fig. 5 Long-standing achalasia. In this patient with a 36-year history of untreated achalasia, there is massive dilatation of the esophagus, which nearly fills the right hemithorax (Schima et al: Syncope after eating. New Engl J Med 1993; 328: 1572. © 1993 Massachusetts Medical Society. All rights reserved)

5.2 Pseudoachalasia (Malignancy-Induced Achalasia)

Malignancies involving the gastroesophageal junction can result in a clinical syndrome, pseudoachalasia, that actually is not a primary motility disorder, but mimics idiopathic achalasia. Pseudoachalasia is most often caused by adenocarcinoma of the fundus invading the distal esophagus. Other causes are squamous carcinoma of the distal esophagus with predominantly submucosal spread (Park et al. 2010) and hematogenous metastatic disease of the gastroesophageal junction (Dodds et al. 1986; Parkman and Cohen 1993; Kahrilas et al. 1987; Paulsen et al. 2010). Conventional esophageal manometry may not differentiate between idiopathic achalasia and pseudoachalasia. However, the correct diagnosis can be determined in most cases by observing clinical history and radiologic features. The mean duration of dysphagia is much shorter in patients with malignant pseudoachalasia than in idiopathic

achalasia (1.9 months vs. 4.5 years) (Woodfield et al. 2000), and there is pronounced weight loss over time in malignancy-induced achalasia (Reynolds and Parkman 1989; Tremble 1959). Radiologically, the narrowed segment is longer in pseudoachalasia (4.4 cm vs. 1.9 cm) and reveals nodularity and abrupt proximal borders rather than a beak-like narrowing (Fig. 6) (Woodfield et al. 2000). The muscle-relaxing effect of amyl nitrite inhalation can be used to help make the correct diagnosis during barium radiography. After administration, there is relaxation of the lower esophageal sphincter with a subsequent opening of 2 mm or more in sphincter diameter (Dodds et al. 1986). In pseudoachalasia with tumor infiltration, the sphincter is unaffected by amyl nitrite. Computed tomography is also helpful in differentiating the two syndromes. Circumferential thickening of the lower esophageal sphincter of less than 10 mm is indicative of idiopathic achalasia, whereas pseudoachalasia patients have CT findings of marked or asymmetric wall thickening or a mass (Carter et al. 1997). When pseudoachalasia is suspected on the basis of clinical history and radiologic features, negative findings at endoscopy or biopsy should be viewed with caution (Tremble 1959). Repeated biopsies, endoscopic ultrasound, or even surgical exploration may finally lead to the diagnosis of malignancy-induced pseudoachalasia.

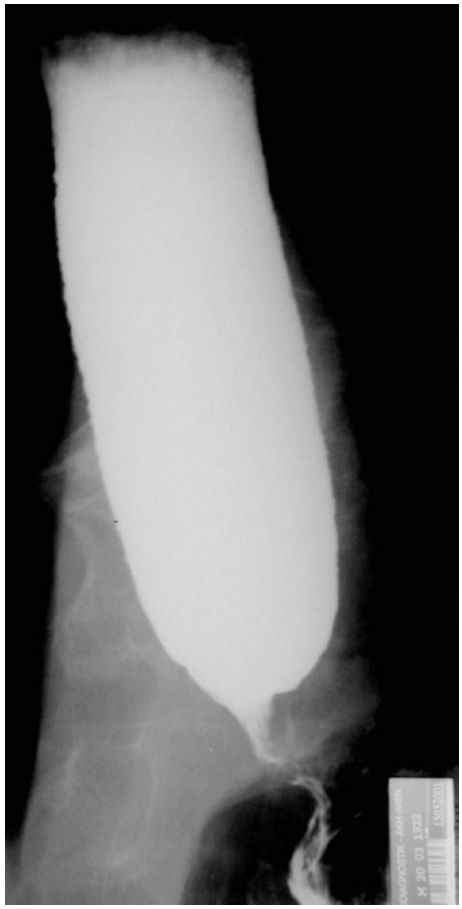


Fig. 6 Pseudoachalasia due to adenocarcinoma of the cardia. Barium radiography reveals moderate esophageal dilatation similar to that seen in achalasia. However, narrowing of the gastroesophageal junction does not appear beak-like. It is more irregular

5.3 Diffuse Esophageal Spasm

The incidence of diffuse esophageal spasm is lower than that of achalasia. Diffuse esophageal spasm is characterized by substernal chest pain, dysphagia, and the manometric evidence of premature contractions on >20% of swallows with intermittent peristaltic contractions (Richter and Castell 1984; Konturek and Lembo 2008; Kahrilas et al. 2015). A recent study showed that heartburn can be found in up to 73% of patients with DES (Martinez et al. 2015).

The classic radiologic features of diffuse spasm are the presence of severe non-propulsive contractions causing esophageal curling or a "corkscrew" or "rosary bead" appearance (Chen et al. 1989; Roman and Kharilas 2012; Fonseca et al. 2017) (Fig. 7). In two large studies by Ott et al., the correct diagnosis of diffuse spasm was made radiologically in 55–71% of patients (Ott et al. 1987; Ott et al. 1990). Incomplete or absent peristalsis and non-propulsive contractions are present in 71–76% of patients (Chen et al. 1989). However, radiologic findings are often nonspecific and do not allow making the diagnosis of diffuse esophageal spasm. Therefore, patients with otherwise unexplained chest pain and radiologic evidence of a nonspecific esophageal contraction abnormality should be referred for manometry. At CT imaging, DES may present as

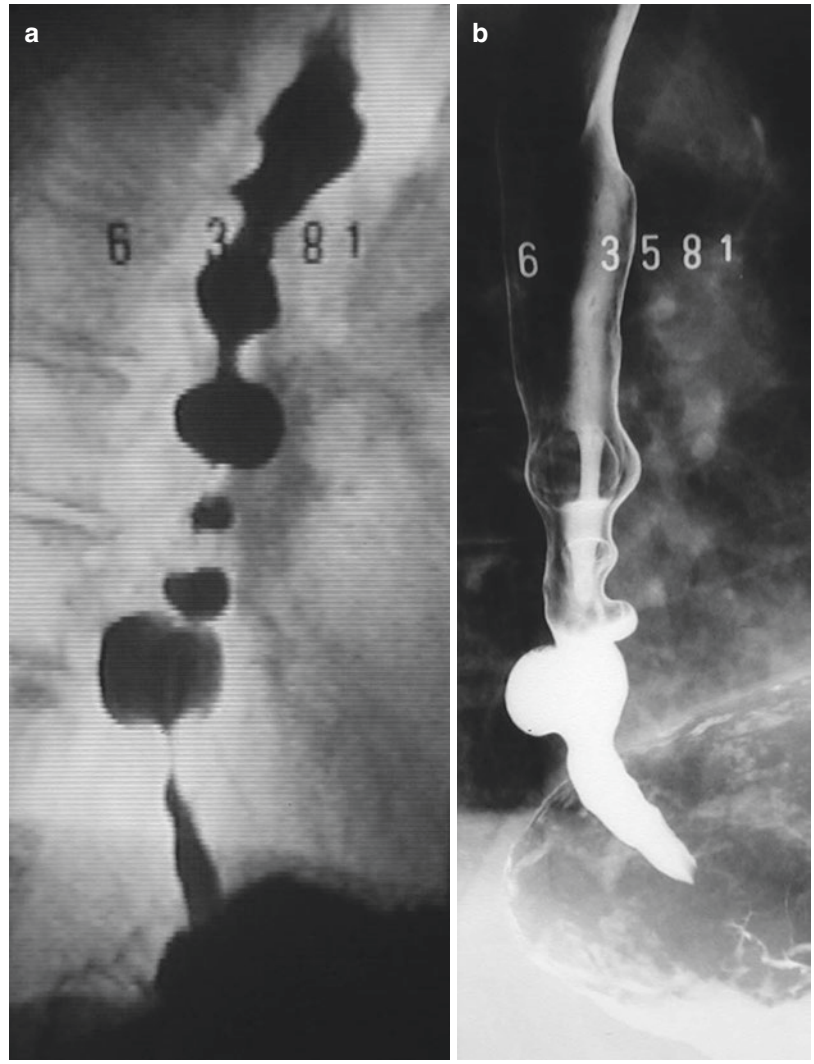


Fig. 7 Diffuse esophageal spasm. (**a**) Videofluoroscopy shows severe non-propulsive contractions, which give the esophagus a corkscrew appearance. (**b**) Barium radiography shows partial relaxation of these transient contractions. There is formation of pseudodiverticulum-like sacculations between the contractions

smooth circumferential wall thickening of the lower esophagus in 21% of patients (Goldberg et al. 2008) and should be included in the differential diagnosis of esophageal wall thickening.

5.4 Jackhammer (or "Nutcracker") Esophagus

As more patients with noncardiac chest pain were studied manometrically, an abnormality clearly different from diffuse spasm was recognized in 1979 (Benjamin et al. 1979). In the so-called "nutcracker esophagus," primary peristalsis is preserved, but there are peristaltic contractions of high amplitude and long duration (Pandolfino and Roman 2011). In the Chicago Classification on motility disorders, now the term Jackhammer esophagus has been used instead.

It is known that approximately 20% of patients admitted to cardiac care units show no abnormality in a detailed cardiac work-up (Bassotti et al. 1998). In a large percentage of these patients with noncardiac chest pain, nutcracker esophagus or diffuse esophageal spasms are present.

Radiologically, the diagnosis is difficult, because peristalsis is preserved. Chobanian et al. found nonspecific abnormalities of

esophageal bolus transit in 36% of patients (Chobanian et al. 1986). These findings were confirmed in a study by Ott et al.: in a series of 170 patients suffering from chest pain, nutcracker esophagus was even more prevalent than diffuse esophageal spasm, but a specific radiologic diagnosis could not be made in any of the patients (Ott et al. 1990).

The pathophysiology of nutcracker esophagus remains unclear. The transition of nutcracker esophagus into achalasia has been shown, suggesting that both diseases lie within the same part of a spectrum of motor disorders (Konturek and Lembo 2008).

5.5 Esophageal Atresia

In infants with esophageal atresia, Vogt's classification is based on the presence and location of an esophago-tracheal fistula (Hasse 1968). After esophageal repair, swallowing difficulties are common. The most common source of postoperative dysphagia is the presence of strictures. However, esophageal dysfunction is also common (Auringer and Sumner 1994). There is absence of swallow-induced primary peristalsis, and secondary peristaltic contractions have lower amplitudes than those seen in normal infants (Daum and Keuerleber 1969).

5.6 Other Primary Motility Disorders

By far the most common esophageal motor disorders are nonspecific contraction abnormalities., being either aperistalsis (categorized as "Major Motility disorder") or weak peristalsis or frequently failed peristalsis (categorized as "Minor Motility disorders") They may be idiopathic (primary) or secondary to a variety of extra-esophageal diseases (Table 1). Manometrically, contraction waves with multiple peaks, peristaltic waves with decreased amplitude, and isolated simultaneous or spontaneous contractions may be found (Gelfand and Botoman 1987; Kahrilas et al. 2015). These contraction abnormalities do not fit into the above-mentioned categories of achalasia, DES, or Jackhammer esophagus.

Radiologically, incomplete or absent peristalsis and non-propulsive contractions can be seen. The sensitivity of radiographic studies is only 46–73%, because intermittent contraction abnormalities may elude radiographic detection (Ott et al. 1987; Schima et al. 1992). Clinically, it is important to search for underlying diseases, such as diabetes, alcoholism, eosinophilic esophagitis, or progressive systemic sclerosis, which may cause esophageal motility disorders (secondary motility disorders). In these cases, therapy is directed at the underlying disorder. Especially, eosinophilic esophagitis may mimic all categories of motor disorders, including nutcracker esophagus and vigorous achalasia (Hejazi et al. 2010). Appropriate treatment may reverse motor abnormalities to normal.

5.7 Presbyesophagus

In 1964, Soergel et al. reported a high incidence of esophageal motor abnormalities in elderly individuals, for which they coined the term "presbyesophagus" (Soergel et al. 1964). In their study on nonagenarians, non-propulsive contractions were prevalent in 10 of 15 patients. However, the existence of such a clinical entity has been much disputed, and it is not included in the Chicago Classification. In another study (Hollis and Castell 1974), esophageal peristalsis was not found to be abnormal in elderly healthy individuals. It has been suggested that the increased prevalence of esophageal motor abnormalities is likely a function of an increased prevalence of underlying diseases, such as diabetes and neuromuscular disorders, which can affect esophageal motility (Ekberg and Feinberg 1991; Price and Castell 1978). Recently, it has been shown that the esophageal transit time of fluid boluses increases significantly with age (Miles et al. 2016). However, it is most important in elderly individuals with newly developed dysphagia to rule out the presence of a tumor or a stricture before making the diagnosis of a motor disorder.

6 Secondary Motility Disorders

6.1 Progressive Systemic Sclerosis (PSS) and other Connective Tissue Diseases

Esophageal dysmotility is a well-known feature of progressive systemic sclerosis (or scleroderma) (Campbell and Schultz 1986) and other connective tissue diseases. PSS often affects the gastrointestinal tract, especially the esophagus and the small bowel, resulting in fibrosis and atrophy of smooth muscle. Esophageal involvement in PSS where the smooth muscle segment is affected results in hypomotility of the distal esophagus with absence of peristalsis and a patulous lower esophageal sphincter. Using esophageal manometry, a motility disorder can be found in 66% of patients with PSS (Luciano et al. 2016). Gastroesophageal reflux is common because of the incompetent sphincter, and refluxed acidic gastric contents are not readily cleared from the esophagus by secondary peristalsis. Esophageal symptoms, especially reflux disease and dysphagia, are common in PSS. Such symptoms are found in 45% and 67% of patients, respectively (Luciano et al. 2016).

In the early stages of esophageal involvement, there is weak peristalsis in the distal esophagus (Montesi et al. 1991). Radiographically, the esophagus may be air-distended for a prolonged period after swallowing, without exhibiting the typical swallowing-induced collapse of the lumen due to a peristaltic contraction. In the prone oblique position, hypomotility is present in the distal esophagus with retention of barium (Fig. 8). With more advanced disease, esophageal dilatation and a patulous lower esophageal sphincter are apparent (Fig. 9). In the prone oblique position, complete aperistalsis with severe retention of barium (and saliva) will be found. Oropharyngeal dysfunction, including pharyngeal retention and aspiration, is found in 26% of patients (Montesi et al. 1991). Patients with an oropharyngeal disorder have a higher incidence of PSS-related pulmonary disease.

As esophageal dysmotility progresses, gastroesophageal reflux and its sequelae will predominate. Severe reflux esophagitis, strictures, and Barrett esophagus develop (Fig. 9). In the

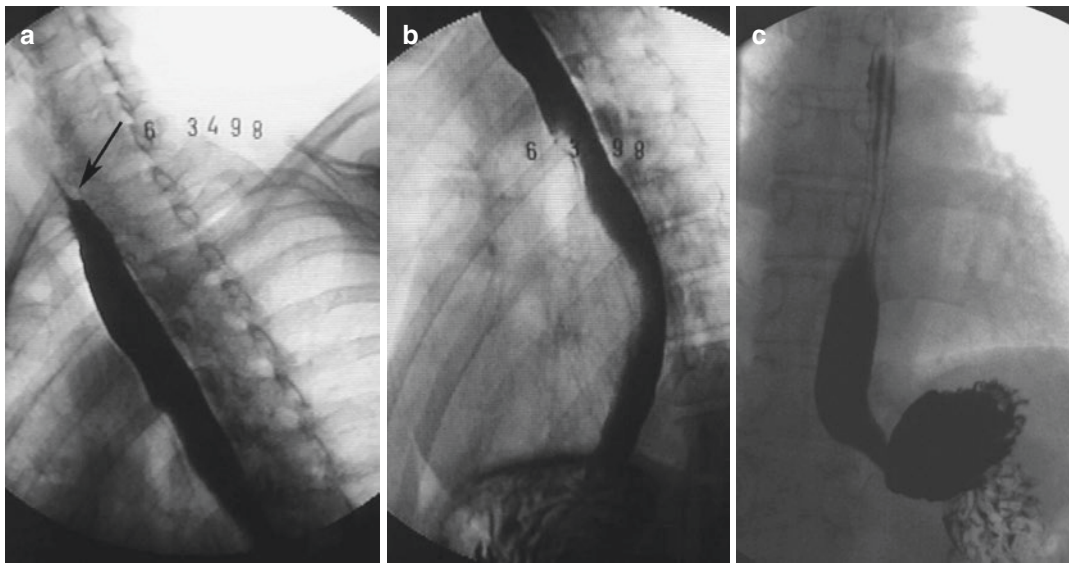


Fig. 8 Progressive systemic sclerosis: early stage. (**a**) Videofluoroscopy in the prone oblique position shows normal peristaltic contraction in the proximal, striated muscle part of the esophagus. (**b**) The peristaltic wave subsides in the middle third of the esophagus with massive retention of barium, indicative of hypomotility. (**c**) There is no evidence of narrowing of the GE junction. Together with clinical history, this is typical of esophageal involvement in PSS

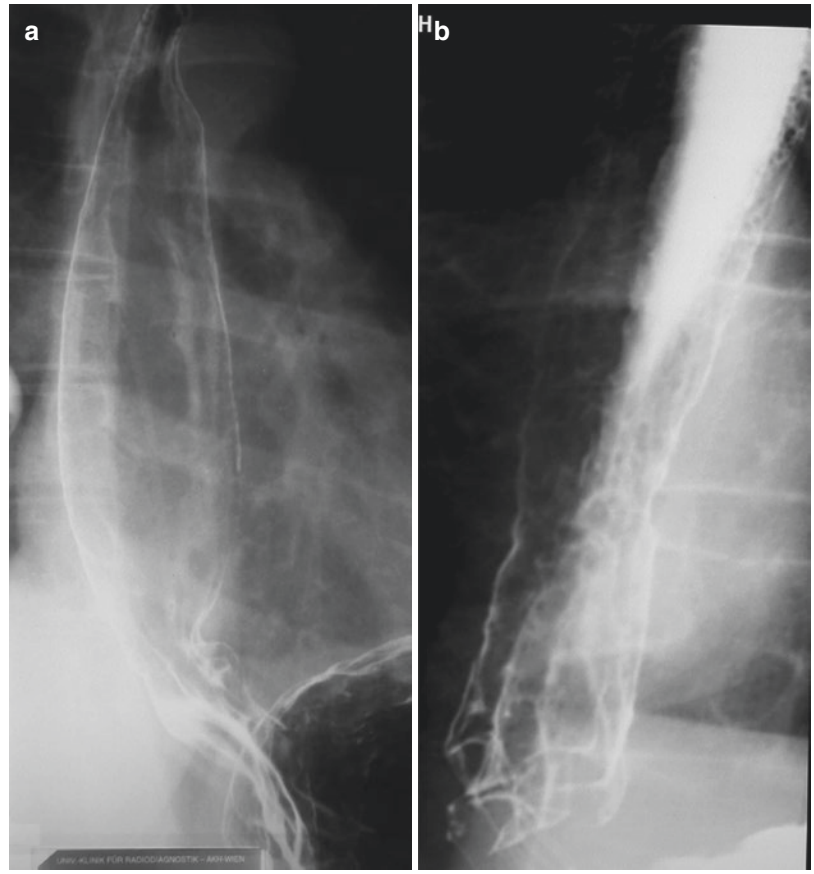


Fig. 9 Progressive systemic sclerosis: advanced disease. (**a**) Barium radiography demonstrates esophageal dilatation and a widely patent gastroesophageal junction (*arrows*). (**b**) In another patient, there is obvious distal fold thickening indicative of reflux esophagitis. Barium radiography also shows a slight peptic stricture in the distal esophagus (*arrow*)

early advanced stages of the disease, differentiation between PSS and achalasia can be made with a high level of certainty. Although aperistalsis and esophageal dilatation is present in both diseases, the shape of the gastroesophageal junction is markedly different. However, the development of distal peptic strictures in PSS may be confusing, although these strictures almost never have the bird beak-like appearance seen in achalasia. PSS patients with severe reflux esophagitis are at increased risk of developing Barrett esophagus and, subsequently, adenocarcinoma. Although barium radiography and videofluoroscopy are very sensitive (67–100%) for the detection of motor dysfunction in PSS (Campbell and Schultz 1986; Schima et al. 1992), these tests are not very accurate in the detection of peptic complications. For this reason, close endoscopic surveillance of PSS patients with reflux esophagitis and peptic strictures is recommended.

Esophageal dysmotility has also been reported to occur in patients with dermatomyositis/polymyositis and mixed connective tissue disease. Findings at radiography are nonspecific, including low-amplitude peristalsis, aperistalsis, and delayed esophageal emptying at scintigraphy (Marshall et al. 1990; Horowitz et al. 1986). In Sjögren's syndrome, dysphagia (65%) and gastroesophageal reflux symptoms (60%) are common, with esophageal dysmotility being found in 80% of patients (Mandl et al. 2007).

6.2 Diabetes mellitus

Esophageal symptoms are common in patients with diabetes, and the likelihood of dysphagia is more than three-fold higher compared to non-diabetic controls (Bytzer et al. 2001). Esophageal motor dysfunction has been demonstrated, characterized by weak peristalsis and increased frequency of non-propulsive contractions (Hollis et al. 1977; Holloway et al. 1999). Esophageal dysmotility is much more prevalent (63%) than gastroparesis (13%) in diabetic patients (Gustafsson et al. 2011). Not surprisingly, a relation between the presence of esophageal dysmotility and diabetic neuropathy has also been reported (Mandelstam et al. 1969; Hollis et al. 1977). It has been suggested that autonomic neuropathy of the vagal nerve supplying the esophagus plays a major role in the development of diabetic dysmotility (Holloway et al. 1999). Radiographically, weak peristalsis or non-propulsive contractions can be observed (Borgström et al. 1988).

6.3 Chagas Disease

Chagas disease (South American trypanosomiasis) is caused by infection with the protozoon *Trypanosoma cruzi* (Dantas et al. 1999). In the chronic phase of the disease, it most often involves the heart, esophagus, and colon, causing cardiomegaly, megaesophagus, and megacolon. Chagas disease and achalasia share the same histopathologic lesion, and the loss of ganglion cells within the esophageal myenteric plexus (Dantas et al. 2001), which are destroyed by the infectious organism in Chagas disease. The clinical and radiological appearance of achalasia and Chagas disease may be identical (Fig. 10). Manometry may help to differentiate the two by identifying a higher resting pressure of the lower esophageal sphincter pressure in Chagas disease. The geographic origin of the patient may also provide a clue to the right diagnosis, and proof of Chagas disease is based on serologic testing.

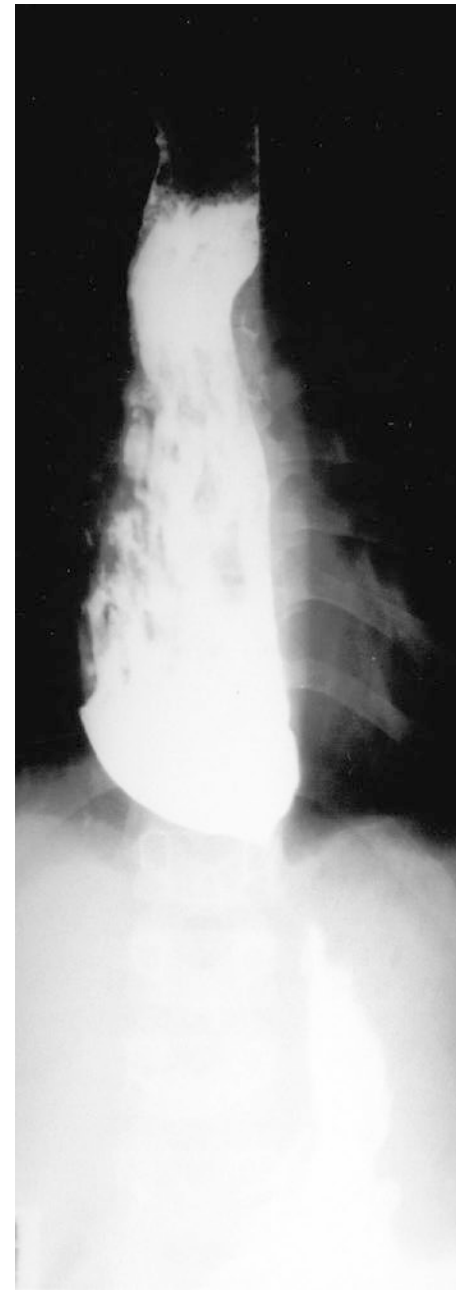


Fig. 10 Megaesophagus in a 14-year-old boy with Chagas disease. Barium radiography reveals esophageal dilation with tapering of the sphincter indistinguishable from idiopathic achalasia (*Image courtesy of Roberto Dantas, Ribeirão Preto, Brazil*)

6.4 Other Secondary Motility Disorders

There are a variety of other diseases and clinical conditions, that may affect the esophagus and cause a secondary motility disorder (Table 1), including amyloidosis (Rubinow et al. 1983; Lefkowitz et al. 1989; Burakoff et al. 1985), alcoholism (Grande et al. 1996), myxedema (Wright and Penner 1981), hyperthyroidism, Parkinsonism (Leopold and Kagel 1997), graft-versus-host disease (Schima et al. 1994), Sjögren syndrome (Kjellén et al. 1986; Palma et al. 1994), and eosinophilic esophagitis (Hejazi et al. 2010). In all these diseases, except progressive systemic sclerosis and Chagas disease, which give a typical radiographic appearance, nonspecific esophageal function abnormalities have been found. Therefore, in all patients with an otherwise unexplained dysphagia and a nonspecific esophageal contraction abnormality, the search should be directed towards the detection and therapy of an underlying disease.

7 Esophageal Diverticula Associated with Motility Disorders

Esophageal diverticula are included in this chapter because they are associated with an esophageal motility disorder in the vast majority of cases. Classification is based in the location: Zenker's diverticulum above the pharyngo-esophageal sphincter (i.e., a pharyngeal diverticulum that will not be covered in this chapter), midesophageal diverticulum just inferior to the level of the aortic arch, and epiphrenic diverticulum just above the diaphragm.

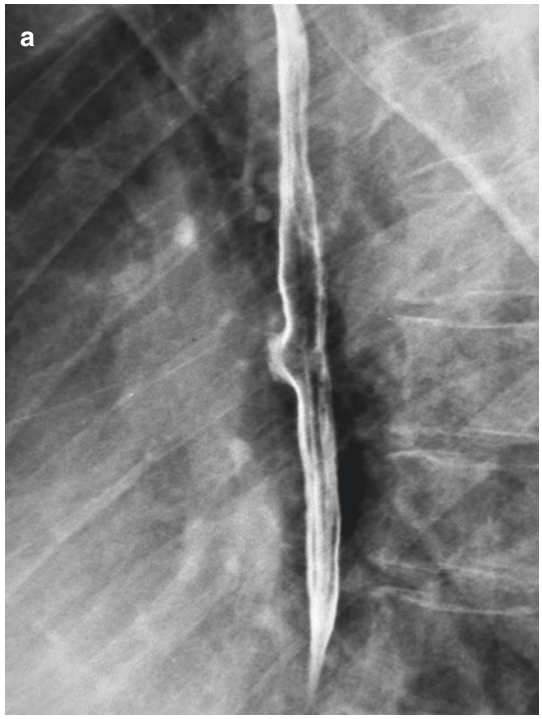
7.1 Midesophageal Diverticula

In the past, midesophageal diverticula have been widely considered to be traction-type diverticula of no clinical significance (Schmidt et al. 1991). Recently, this view has been questioned by some studies, which have shown that these diverticula resemble more the pulsion-type diverticula (Borrie and Wilson 1980; Evander et al. 1986). In 1974, Kaye reported on associated esophageal motor disorders found at manometry (Kaye 1974). In a series of 12 patients, diffuse spasms and nonspecific contraction abnormalities were the most common findings.

Based on radiographic findings, Rivkin et al. pointed out that midesophageal diverticula are likely of the pulsion-type. The pear-shaped configuration of most diverticula and their movement on swallowing resembles the appearance of Zenker's and epiphrenic diverticula (Rivkin et al. 1984). In our study including 30 patients with 33 midesophageal diverticula, 80% were diagnosed as propulsion-type diverticula based on radiographic findings. Diverticula were classified as pulsion-type when they were pear-shaped, when the size and shape changed during bolus passage, and when there was up- and downward movement of the diverticulum of at least 2 cm upon swallowing (Fig. 11) (Schima et al. 1997). In this study, 88% of patients with a pulsion diverticulum suffered from an esophageal motor disorder, and 6/20 (30%) cases were diagnosed as achalasia upon videofluoroscopy and manometry (Schima et al. 1997). In conclusion, midesophageal diverticula in symptomatic patients are primarily of the pulsion-type and tend to be associated with esophageal motor disorders.

7.2 Epiphrenic Diverticula

Epiphrenic diverticula are generally associated with and probably caused by an underlying esophageal motor dysfunction. Approximately two-thirds of patients will have specific motor disorders, with achalasia the most common (Bruggeman and Seaman 1973; Debas et al. 1980) (Fig. 12). The high percentage of motor abnormalities in association with epiphrenic diverticula determines the therapeutic and especially the surgical approach. Patients should always be referred for manometry to search for a curable manometric disorder before



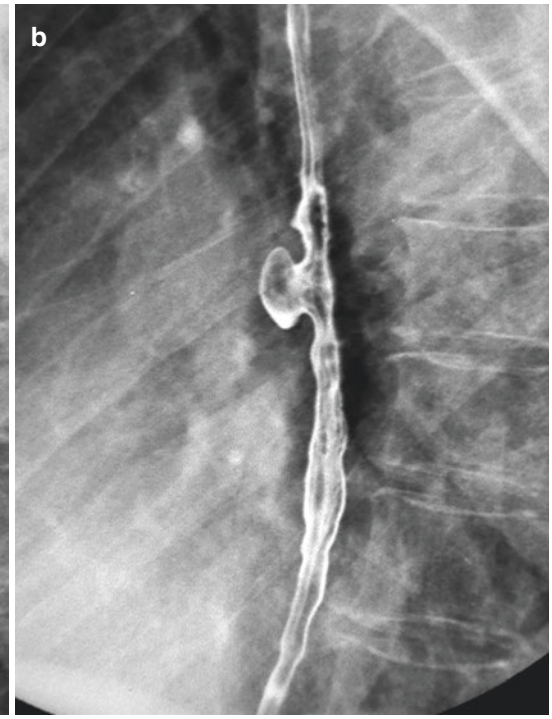


Fig. 11 Midesophageal pulsion diverticulum in a patient with nonspecific motor disorder. (**a**) Spot-film of the esophagus taken during deglutition is normal. (**b**) Another spot-film taken approximately 2 s later shows outpouching of a pulsion diverticulum in the mid-esophagus (*arrow*). A nonspecific motor disorder was found at videofluoroscopy

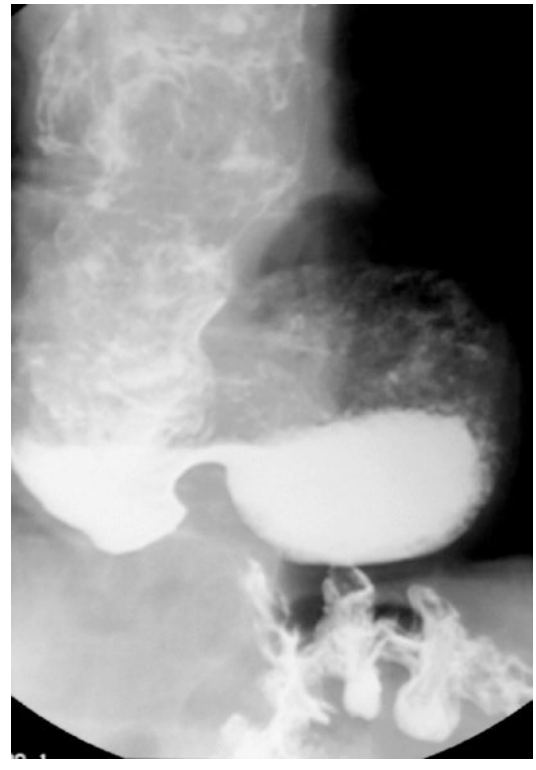


Fig. 12 Giant epiphrenic diverticulum in a patient with achalasia. Barium radiography demonstrates massive esophageal dilatation and a severe narrowing of the gastroesophageal junction, indicative of achalasia (*black arrow*). At videofluoroscopy, there was only a minimal transient opening of the sphincter with passage of only small amounts of barium. There is a giant epiphrenic diverticulum (*white arrows*) located above the sphincter

surgical resection of a "symptomatic" midesophageal diverticulum (Fig. 11). In these cases, diverticulectomy alone carries the risk of postoperative suture breakdown and predisposes the patient to recurrence of the diverticulum (Rivkin et al. 1984). Myotomy of the lower esophageal sphincter is now a routine part of the operation (Evander et al. 1986).

8 Gastroesophageal Reflux Disease (GERD) and Esophageal Function

The term GERD covers the entire spectrum of clinical conditions and histologic esophageal alterations that result from gastroesophageal reflux (Dodds 1988). GERD is by far the most common cause of esophagitis in the general population. In the last 15–20 years, our knowledge about the etiology and pathogenesis of gastroesophageal reflux and the development of esophagitis has considerably broadened. The pathogenesis is multifactorial and the factors believed to be important include (1) inadequate antireflux mechanisms, (2) chemical consistency of refluxed material, (3) esophageal clearance of refluxed material, (4) esophageal mucosal resistance, and (5) volume of gastric contents and efficacy of gastric emptying (Dodds et al. 1981; Dodds 1988). Most recently three dominant mechanisms have been identified: (1) transient LES relaxations without anatomic abnormality, (2) LES hypotension without anatomic abnormality, or (3) anatomic distortion of the esophagogastric junction inclusive of (but not limited to) hiatal hernia (Pandolfino and Roman 2011).

8.1 Hiatal Hernia and Reflux

In the past, the finding of a hiatal hernia has been considered the most important predisposing factor for the development of reflux. The exact prevalence of hiatal hernia in the general population remains unknown, largely because of the differences in examination techniques and diagnostic criteria (Fransson et al. 1989; Ott et al. 1985; Kahrilas et al. 1999). The relationship between the presence of a hiatal hernia and reflux disease remains controversial. Several studies have found that a hiatal hernia is much more common in patients with symptomatic reflux or abnormal findings at pH testing than in patients without reflux disease (prevalence, 80–94% vs. 59–60%) (Chen et al. 1992; Ott et al. 1985). Moreover, the presence of a hiatal hernia reduces lower esophageal sphincter pressure, which may increase the susceptibility to reflux events (Kahrilas et al. 1999). However, severe reflux esophagitis can also be found in patients without hiatal hernia (Kaul et al. 1986). Thus, hiatal hernia is a nonspecific radiologic finding with a poor predictive value: the presence of a hiatal hernia does not predict the presence of GERD (Ott et al. 1995). Conversely, the absence of a hiatal hernia does not exclude severe reflux esophagitis (Kaul et al. 1986).

8.2 Gastroesophageal Reflux and Esophageal Function

Effective esophageal peristalsis is a prerequisite for appropriate esophageal clearance of refluxed gastric contents. In normal subjects, a secondary peristaltic contraction is triggered by gastric contents refluxed into the esophagus, which rapidly clears the esophagus of the irritating agent. In patients with GERD, abnormalities of esophageal function are a common finding (Stein et al. 1990; Schoeman and Holloway 1995). Motor function deteriorates with increasing severity of mucosal injury

(Fibbe et al. 2001). Swallow-induced primary peristalsis is impaired in GERD patients. It has also been shown that patients with reflux disease exhibit a defect in the triggering of secondary peristalsis (Schoeman and Holloway 1995). Instillation of water boluses or distension of the esophagus by air frequently fails to elicit a peristaltic contraction in reflux patients.

Interestingly, Timmer et al. demonstrated that impairment of esophageal peristalsis remained unchanged after healing of esophagitis (Howard et al. 1994; Timmer and Breumelhof 1994). Likewise, esophageal motility did not recover after fundoplication despite significant improvement in clinical symptoms and endoscopic signs of esophagitis (Fibbe et al. 2001). These results can be interpreted in two ways: first, deterioration of esophageal motility is irreversible in GERD; or, second, esophageal motility dysfunction is a preexisting factor in the pathogenesis of reflux disease (Timmer and Breumelhof 1994). The lack of improvement of esophageal motility with healing of esophagitis explains the high recurrence of esophagitis (50%) at two months after discontinuation of omeprazole therapy (Howard et al. 1994). These facts support the hypothesis that dysmotility is rather induced by irreversible inflammatory changes of the esophagus. However, a conclusive answer to this question will require a large prospective study of reflux patients with normal motility to determine whether motility deteriorates over time.

Both the barium swallow and radionuclide transit studies are useful in detecting motor disorders in GERD patients. Abnormalities seen in reflux disease include weak or even absent primary peristalsis and nonperistaltic contractions (Ott 1994). Patients with absent peristalsis have the most severe impairment in esophageal clearance and thus are likely to have the most severe GERD (Pandolfino and Roman 2011). Radiologically, clearance of barium that has refluxed from the stomach can be best assessed in the recumbent position. At present, 24-h pH monitoring is the gold standard in the detection and quantitation of gastroesophageal reflux (Thompson et al. 1994). However, abnormal results at 24-h pH monitoring do not necessarily mean that the patient has clinical symptoms or endoscopic signs of esophagitis and vice versa. Results of several studies evaluating the role of radiology in patients with GERD have been disappointing (Chen et al. 1992; Kaul et al. 1986; Johnston et al. 1996). A major reason for the poor performance of radiology is that there is only limited time for fluoroscopic observation of barium. Meta-analysis of nine studies on radiographic detection of gastroesophageal reflux revealed an average sensitivity of 39% (Ott 1994). In a study by Thompson et al., the diagnostic yield of spontaneous and provoked gastroesophageal reflux during barium radiography was assessed. The detection of spontaneous reflux revealed a sensitivity of 26% and a specificity of 94%. Using provocative tests, including cough/Valsalva maneuver, rolling, and the water-siphon test, increased the sensitivity of radiography to 31%, 44%, and 70%, respectively (Thompson et al. 1994). However, with increasing sensitivity, the specificity dropped to 74%. Thus, prolonged observation and the use of provocative maneuvers increases the sensitivity of barium radiography in the detection of reflux (Fig. 13). The absence of a reflux episode during fluoroscopy does not exclude the presence of GERD. Barium radiography is not accurate enough to be used as a the sole screening test in GERD patients: However, it is inexpensive, noninvasive, and widely accessible and may be used as the initial test for GERD (Levine et al. 2016).

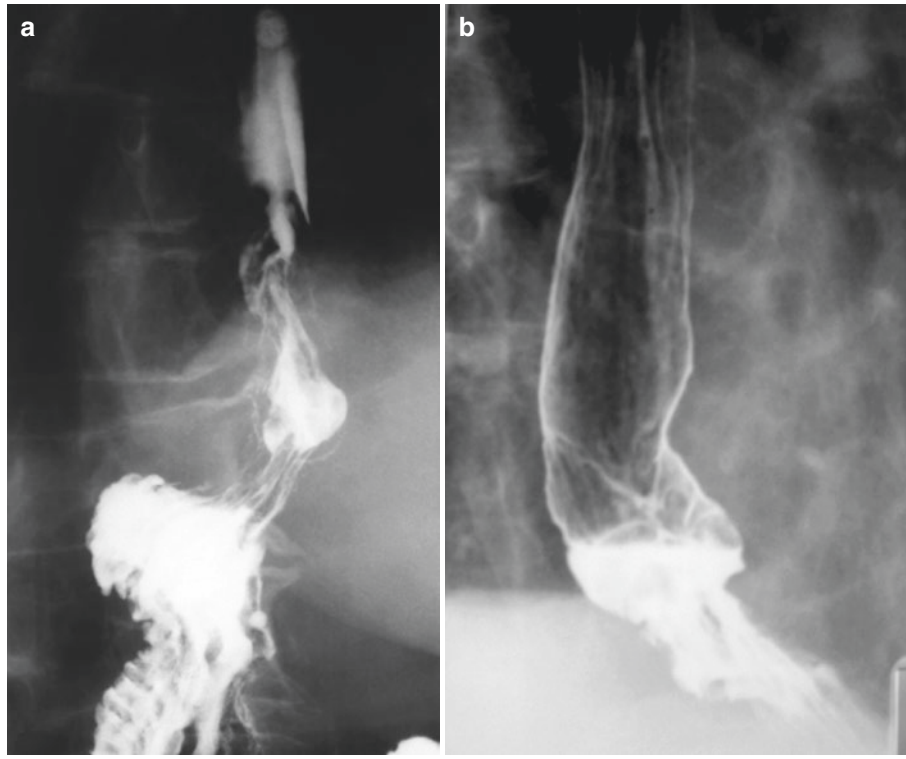


Fig. 13 Gastroesophageal reflux and reflux esophagitis. (**a**) In this patient with severe heartburn, there is spontaneous reflux of liquid barium and barium tablet in the right lateral position. (**b**) Double-contrast esophagram shows signs of severe reflux esophagitis in the distal esophagus with linear ulcerations (*arrow*)

8.3 Esophageal Motility Disorders After Antireflux or Bariatric Surgery

Studies have shown that patients after fundoplication are at increased risk for developing esophageal motility disorders including secondary achalasia due to a tight gastric wrap or diffuse esophageal spasm (Wehrli et al. 2007). Patients with obesity demonstrate more often incidence of an ineffective esophageal motility including hiatal hernias, LES dysfunction, and increased distal esophageal acid exposure than nonobese patients (Tolone et al. 2017). After bariatric surgery, esophageal function seems to be affected by adjustable gastric banding or sleeve gastrectomy (Shiroky et al. 2013; Naef et al. 2011). Beside specific surgery-related complications such as gastric band slippage, radiology may show esophageal dilation and narrowing of the esophagogastric junction, in severe cases signs of pseudoachalasia.

9 Dynamic MR Imaging to Assess Esophageal Motor Function

To avoid exposure to ionizing radiation, dynamic MR imaging protocols have been developed for assessing esophageal function and the gastroesophageal junction. Boluses of buttermilk or other test meals spiked with gadolinium chelates and ferric ammonium citrate have been used as contrast materials (Kulinna-Cosentini et al. 2007; Manabe et al. 2009; Curcic et al. 2010). Steady-state free precession MR pulse sequences (B-FFE, Philips) with parallel imaging allow a time resolution of 1 image/s, enough to assess esophageal function and the gastroesophageal region. Dynamic MR imaging can reliably depict normal peristaltic contractions as well as gastroesophageal reflux (Figs. 14 and 15), as evidenced by manometry (Curcic et al. 2010). Another advantage is the lack of radiation, which allows repeated acquisitions to assess swallowing

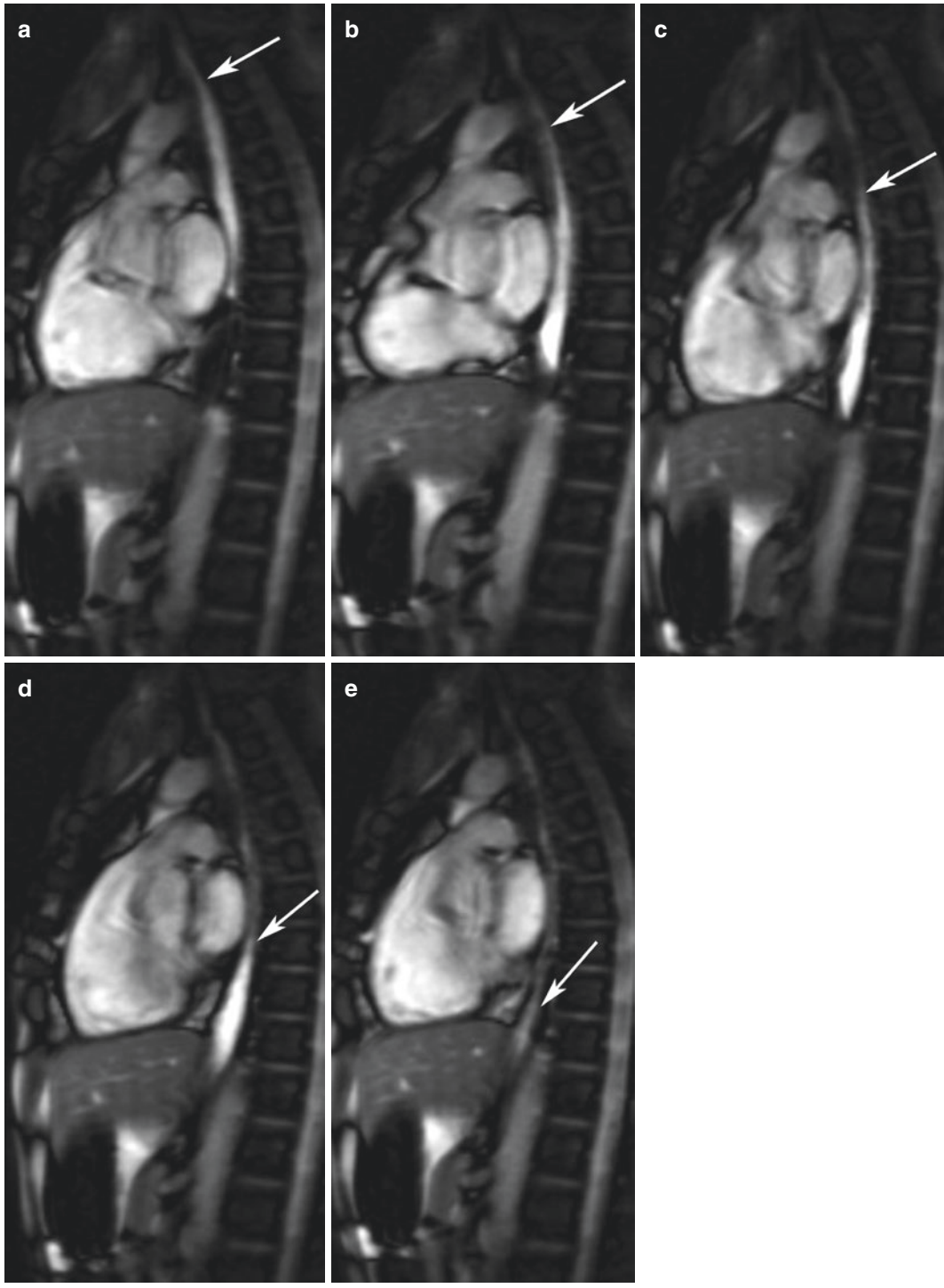


Fig. 14 (**a–e**) Dynamic MRI (sagittal view) at a frame rate of 1/s using a bolus of buttermilk spiked with gadolinium shows normal esophageal peristalsis. There is distal propagation of the peristaltic contraction wave (*arrows*)

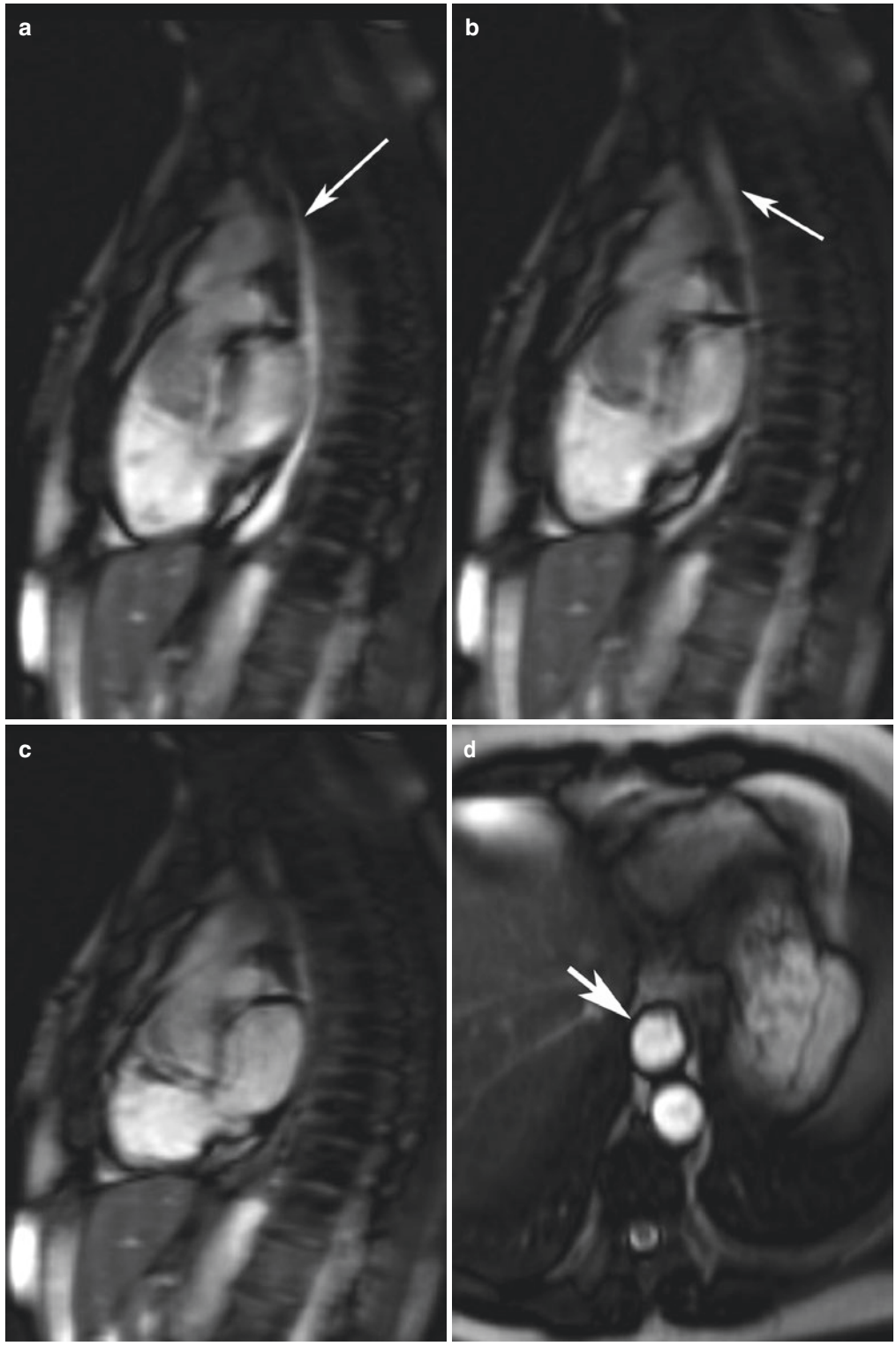


Fig. 15 Dynamic MRI of gastroesophageal reflux and hiatal hernia. (**a**, **b**) Sagittal view shows proximal propagation of bolus in the esophagus (*arrows*) and (**c**) delayed clearance of the esophagus. (**d**) Axial view shows a hiatal hernia (*arrow*) anterior to the aorta

function. However, this technique is not without limitations. The time resolution is inferior to videofluoroscopy. Moreover, swallowing in the recumbent position is not physiologic, and the reflux of small volumes may escape detection (Manabe et al. 2009). Dynamic MR imaging of esophageal function is still a research tool, but it may provide new insights in esophageal function, which we could not make with fluoroscopy.

10 Summary

In patients with dysphagia, radiographic studies evaluate both esophageal morphology and esophageal function. Videofluoroscopy accurately diagnoses achalasia and diffuses esophageal spasm and progressive systemic sclerosis (scleroderma). Videofluoroscopy is less sensitive for the study of nonspecific motor disorders and gastroesophageal reflux. When accuracy, costs, availability, and patient acceptance are considered (Parkman et al. 1996), videofluoroscopy is the initial diagnostic test for patients with esophageal dysphagia.

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Radiology of the Lower Esophageal Sphincter and Stomach in Patients with Swallowing Disorders

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Contents

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Abstract

The lower esophageal sphincter and gastric fundus are challenging anatomical areas to evaluate radiologically. By visualizing the esophagogastric region and the stomach in mono- and double-contrast technique and recording it on videotape, it is an excellent method for evaluating patients with suspected abnormalities or noncharacteristic swallowing disorders. Additionally, in patients after antireflux procedures or bariatric surgery, swallowing studies and CT have proven to be workhorses for the radiological diagnosis of postoperative complications. Examinations should be tailored according to the individual anatomical situation and the patients' symptoms.

1 Introduction

Diseases of the lower esophageal sphincter and the stomach are common, encompassing a number of symptoms including dysphagia, heartburn, nausea, bloating, belching, and vomiting. Organic causes are most frequently related to gastroesophageal reflux disease, gastritis, and ulceration. But, functional disorders, likely related to motility problems of the distal esophagus and the stomach, are an important differential diagnosis in this patient group (Hammer and Talley 2006). A thorough history-taking is essential to further

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guide the required investigations and to tailor the radiological examination. The role of radiology in investigating diseases of the LES and the stomach has changed, since endoscopic techniques are predominant in the initial diagnosis. However, an upper gastrointestinal swallowing study is not only the test of choice in patients with failed endoscopy, but also often the first imaging modality in patients with unclear complaints, enabling assessment of the entire upper gastrointestinal tract through the observation of structural movement related to swallowing function. The esophagogastric transit is evaluated with a high accuracy, whereas the gastroduodenal passage can only be roughly estimated. Computed tomography is now an established modality in the diagnosis of diseases of the esophagogastric junction and stomach, especially with regard to staging of tumors. The emerging role of PET/CT (and possibly PET/MRI) is still under discussion for their routine clinical use, but already a widely used complementary method for detecting distant metastases and assessing treatment response (Lin et al. 2015).

2 Imaging of the Lower Esophageal Sphincter (LES)

Assessment of the gastroesophageal junction is challenging due to the complex and mobile relationship between the distal esophagus, hiatus, and stomach. Different investigation techniques are used, each with individual strengths and weaknesses, and radiological findings may differ significantly from endoscopic or manometric assessments. Videofluoroscopy has been confirmed as the method of choice for the evaluation of bolus flow related to anatomical structures along the upper digestive tract in real time (Ekberg and Pokieser 1997) and should include mono- and double-contrast views in the supine and prone position, mucosal relief views, and solid food testing with a standardized tablet, or solid food mixed with barium to look for retention or obstruction in dysphagic patients (Scharitzer and Pokieser 2016). Provocation maneuvers, such as rotating the patient around his/her axis or a Valsalva maneuver, may improve the detection of spontaneous gastroesophageal reflux (Thompson et al. 1994). The patient's perception of tablet passage or impaction of the swallowed tablet should be noted and related to the radiological findings, as well as the level of reported dysphagia, which is often referred to the neck if a stenosis at the LES level can be found (Ashraf et al. 2017).

In healthy individuals, the cardia can be seen on double-contrast studies as three to four stellate folds radiating from the center with a slight protrusion of the distal esophagus into the gastric fundus to form the cardiac rosette (Fig. 1a). Videofluoroscopy also enables assessment of the angle of His, the insertion angle between the esophageal axis, and a tangent to the proximal fundus (Fujiwara et al. 1998), since an acute angle, which acts as a flap-valve mechanism, is mandatory for prevention of gastroesophageal reflux (Pandolfino et al. 2004).

2.1 Gastroesophageal Reflux Disease (GERD)

In patients with reflux disease, radiology serves as an established method for diagnosing hiatal incompetence. In 1979, Lindell et al. placed radiopaque contrast material in the stomach to assess gastroesophageal reflux during increased abdominal pressure (Lindell and Sandwark 1979). Multiplanar multidetector computed tomography measurements of the hiatal surface area showed larger mean hiatal areas in patients with hiatal hernia than in controls (Ouyang et al. 2016). The Esophageal Diagnostic Advisory Panel considers a radiological assessment necessary in patients before undergoing antireflux surgery (Jobe et al. 2013). Diaphragmatic incompetence under resting conditions can be assessed radiologically showing a larger diaphragmatic hiatus

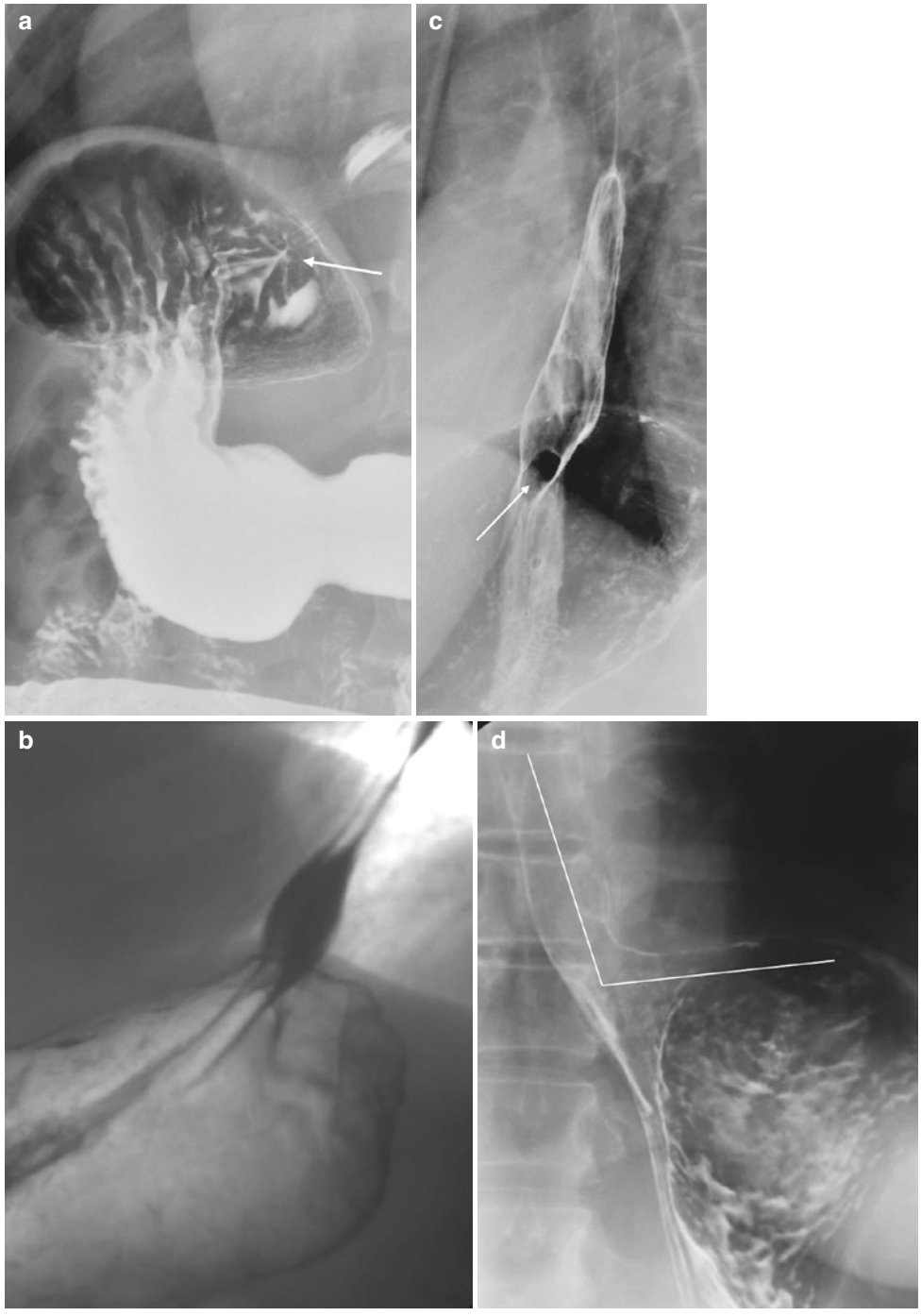


Fig. 1 (**a**) The cardia is anchored by surrounding phrenoesophageal membrane. The cardia is represented by stellate folds, radiating centrally as the cardiac "rosette"—the normal appearance (*arrow*). (**b**) Weakening of the ligaments can cause a funnel-shaped cardia (*arrow*) due to laxity of ligamentous attachments (Herlinger et al. 1980). (**c**) In severe ligamentous laxity a continuous gaping of the EGJ for some seconds can be seen between the swallows. (**d**) The angle of His, first described in 1903, is the angle at which the esophagus enters the stomach. The angle is determined between the esophagus and the top of the fornix. The angle should be acute and not obtuse. After the application of effervescent powder, the His angle can be observed in the upright position

in patients with GERD (Sloan et al. 1994) and severe esophagitis (Jones et al. 2001), as well as a funnel-shaped or gaping cardia combined with widening of the angle of His (Curcic et al. 2014) (Fig. 1b–d). For the diagnosis of reflux-induced esophagitis, endoscopy is the gold standard for the evaluation of morphological pathologies and to exclude Barrett's metaplasia. However, radiological criteria help to classify patients with reflux disease as being at low, intermediate, or high risk for developing Barrett's esophagus (Levine and Rubesin 2005): Midesophageal stricture, ulceration, or a reticular mucosal pattern are findings that indicate high risk, whereas chronic inflammation and scarring or a peptic stricture in the distal esophagus are signs of moderate risk.

2.2 Hiatal Hernia

Accurate assessment of hiatal size is of clinical importance in the preoperative workup for antireflux therapy (Fig. 2). Especially for the diagnosis of smaller hiatal hernias, most imaging modalities have their limitations due to an inadequate distension of the esophagus and the problem of identifying the squamocolumnar junction. The most common type is a sliding hiatal hernia with migration of the esophagogastric junction above the diaphragm and is associated with a laxity of phrenoesophageal membrane. Type II–IV are varieties of paraesophageal hernias, with a clinical potential of mechanical complications. They result from a defect in the phrenoesophageal membrane, but with the esophagogastric junction remaining in its regular position (Kahrilas et al. 2008) (Fig. 2c).

Additionally, ringlike indentations can be observed (Fig. 3): a muscular ring at the superior border of the esophagogastric junction, also called an A-ring; and a mucosal ring, the B-ring, at the level of the squamocolumnar junction. Muscular hypertrophy (A-ring) located at the gastroesophageal junction is covered by squamous epithelium on both sides, can change its diameter with peristalsis, and rarely causes symptoms.

2.3 Stenoses of the LES

Benign and malignant stenoses of the LES are often primarily assessed by a radiological swallowing examination. Ott has shown that radiology may be more sensitive than endoscopy in detecting moderate strictures with a residual diameter of >10 mm (Ott et al. 1986). Lower esophageal rings are thin (2–4 mm axial length) mucosal rings at the gastroesophageal junction, composed of squamous mucosa above and columnar epithelium below, and are also known as a B-ring or, if symptomatically, a Schatzki ring. The caliber of the ringlike lesion does not change during swallowing and is best assessed by optimal distension. These are found in up to 14% of routine radiological swallowing studies, accounting for dysphagia in only 0.5% if the diameter is less than 20 mm (Schatzki and Gary 1956). The cause of these rings is not clear as yet, but most are associated with the presence of a hiatal hernia, and reflux disease has been suggested as an etiology. Tablets with a standardized diameter of 13–14 mm have been proven to accurately allow estimation of residual lumen diameter in these patients (Scharitzer et al. 2017). Mucosal rings may be associated with inflammatory strictures and present as an asymmetric narrowing of the esophageal lumen (Marshall et al. 1990).

Esophagography has reported sensitivities for detecting strictures of 95%, with a high correlation between radiologically diagnosed benign strictures with endoscopic findings (Luedtke et al. 2003). Imaging is also important for staging, assessment of tumor response, and surveillance after neoadjuvant therapies. Cross-sectional imaging, such as CT and PET/CT, is an increasingly used method for improved staging and evaluation of response to therapy (Kim et al. 2009).

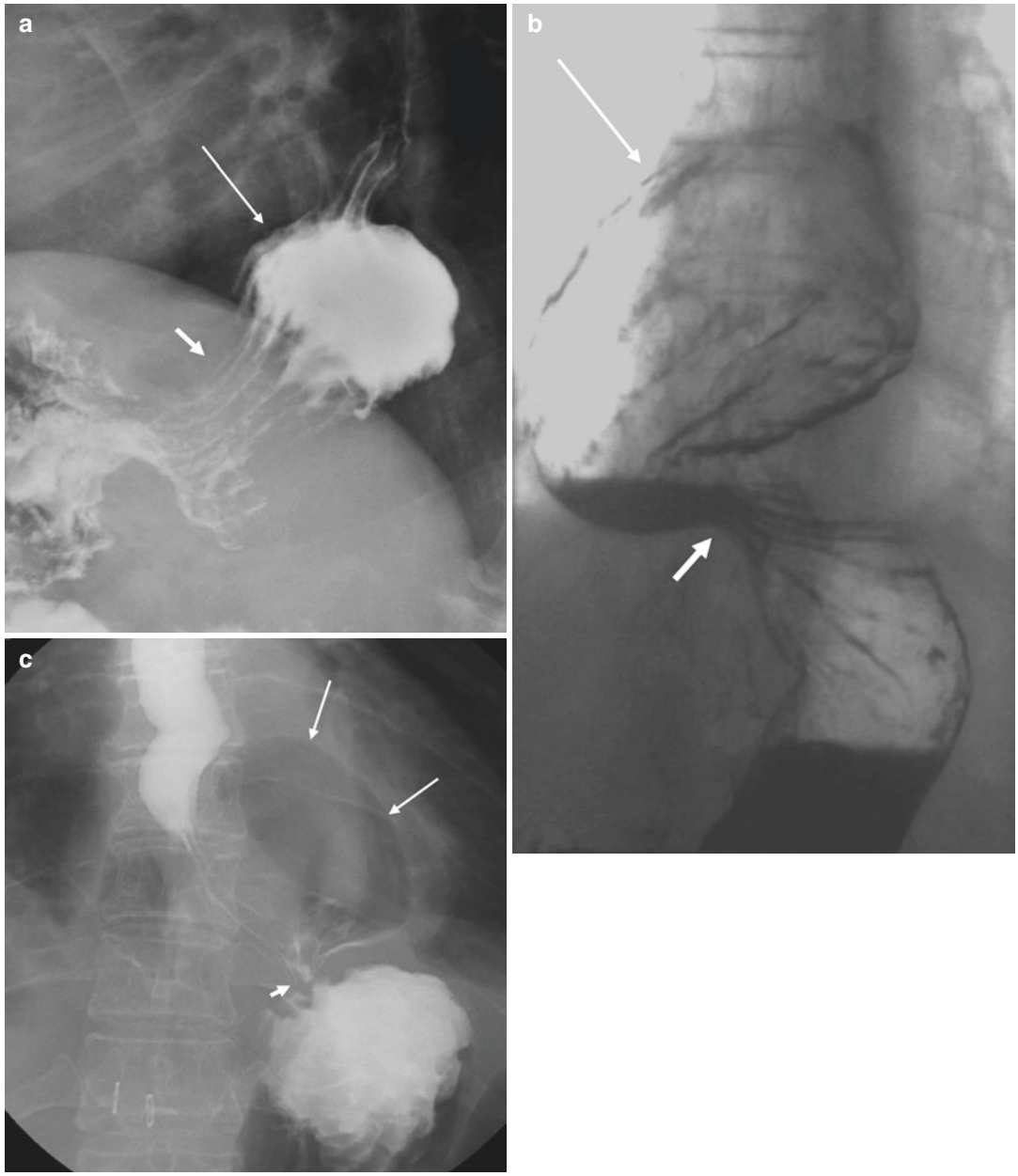


Fig. 2 (**a**) Hiatal hernia (*arrow*), shown in monocontrast and with incomplete distension, and a wide internal diameter of the cardiac esophagus of over 2.5 cm (*short arrow*) might be abnormal. Size estimation of a sliding hiatal hernia largely depends on the time point during swallowing, when the measurement is made. (**b**) Large hiatal hernia (*arrow*) with narrow diameter at the level of the diaphragmatic hiatus (*short arrow*) causing delayed passage of liquid contrast material. (**c**) In this patient with a paraesophageal hernia, the esophagogastric junction remains fixed in regular position (*short arrow*) and the gastric fundus herniates through a localized defect in the phrenoesophageal membrane (*arrows*)

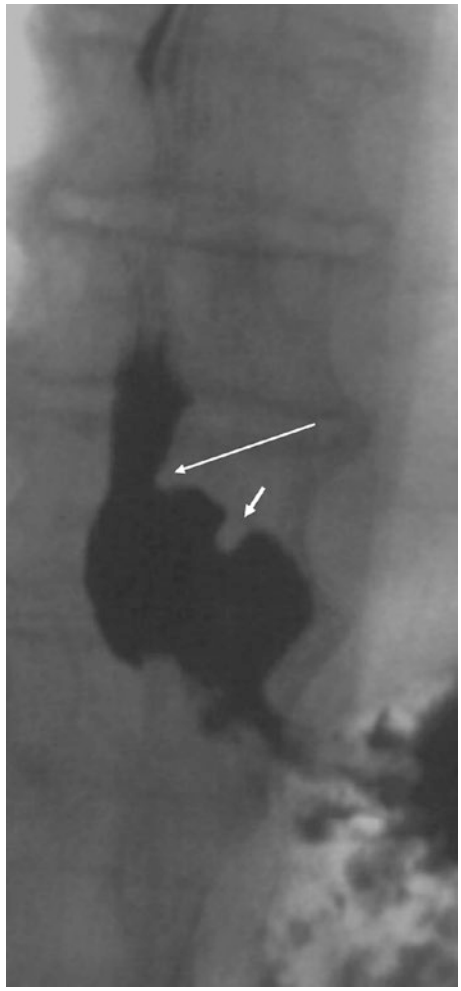


Fig. 3 Mucosal ring or B-ring (*short arrow*) above a small hiatal hernia. The esophageal vestibule, a slight broadening of the gut distal to the muscular A-ring (*arrow*) should end at the level of the diaphragm. A hiatal hernia can be diagnosed when the vestibule ends at least 2 cm above the EGJ. The recess between the vestibule and the EGJ may be diagnosed as a part of the stomach, protruding upward into the thorax

2.4 Eosinophilic Esophagitis

Eosinophilic esophagitis, a chronic immune-mediated inflammatory disease, has been identified only in the past two decades, but is now considered a major cause of dysphagia in children and adults, with a reported prevalence of 10–15% of patients with swallowing disorders (Kidambi et al. 2012). Affected individuals often present with solid food dysphagia or food impactions and have an associated history of atopy or asthma. Although the diagnosis is confirmed by endoscopic biopsy specimens, radiology may suggest this entity by revealing segmental strictures, sometimes with distinctive ringlike indentations, also called the ringed esophagus (Zimmerman et al. 2005). The diagnosis may also be suggested when a small-caliber esophagus is found, which is defined as a long segment of esophageal narrowing with a mean diameter of 20 mm or less (White et al. 2010).

2.5 Esophagogastric Outflow Obstruction

The new Chicago classification has postulated that any functional or mechanical process that impedes the transit across the esophagogastric junction (EGJ) with increased integrated relaxation pressure and intact peristalsis is esophagogastric outflow obstruction (Roman et al. 2014). Dysphagia is reported as the most common symptom, but the manometric criterion defines a heterogeneous clinical group. Anatomic abnormalities are common potential causes of manometrically assessed outflow obstruction, emphasizing the need for ancillary diagnostics, such as barium studies (DeLay et al. 2016). Delayed retention of 10 mL barium suspension in the esophagus for more than 10 s as well as the impaction of a standardized tablet of a diameter of 13–14 mm are considered abnormal. Possible causes include reflux-induced distal esophageal strictures, large nonreducible hiatal hernias, spasm/dysmotility, epiphrenic diverticula, postoperative stenosis after prior Nissen fundoplication, as well as eosinophilic esophagitis with obstructing distal rings (Okeke et al. 2017).

2.6 Achalasia

Achalasia refers to failure of the esophageal peristalsis with impaired relaxation of the lower esophageal sphincter. This results in many patients in marked esophageal dilatation and stasis of ingested food. Radiology may show the typical "bird beak sign," esophageal dilatation, and pooling of barium in an atonic or noncontractile esophagus, typical findings in late-stage disease (Fig. 4).

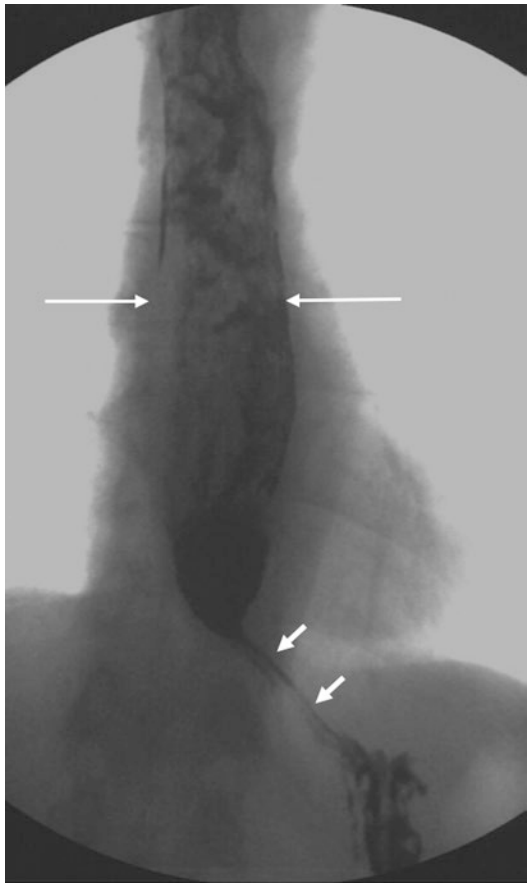


Fig. 4 Achalasia with esophageal dilatation and incomplete lower esophageal sphincter relaxation. Note the inhomogeneous appearance of the material within the dilated esophagus due to undigested food that did not pass into the stomach (*arrows*). In severe achalasia, a support level persists during the entire examination and only small quantities of contrast medium are able to pass through a beak-like esophagogastric junction (*short arrows*)

Early disease may present as uncoordinated nonpropulsive contractions with failure of normal peristalsis as well as repeated short passages of contrast material in the stomach, if the hydrostatic pressure overcomes the lower esophageal sphincter pressure. A fluid level within the esophageal lumen for longer than 10 s in standing position ("support level") is an important sign of failure to clear the esophagus of barium and should be followed by a manometric investigation (Fig. 5).

Pseudoachalasia is an achalasia-like pattern with narrowing of the esophagogastric junction due to causes other than primary denervation including most often malignant tumors (Fig. 6).

3 Imaging of the Stomach

A considerable decline in performing gastrointestinal fluoroscopic procedures of the stomach reflects the improved medication for peptic ulcer disease, the general availability and predominance of endoscopy, and the increased use of cross-sectional imaging of the stomach with considerable advantages of simultaneous imaging outside the intestinal wall (DiSantis 2008). Nevertheless, in a significant number of patients with nonspecific swallowing disorders, a barium examination is the first imaging modality to show gastric pathologies as well. Features that cause alarm, such as dysphagia and weight loss, warrant prompt diagnostic workup and radiology may serve as an initial management strategy. Therefore, high-density and low-viscosity barium sulfate suspensions are used to evaluate the stomach so as to optimally coat the gastric mucosal folds and facilitate double-contrast studies. By administering an effervescent agent, the lumen is distended with gas and the patient is positioned according to anatomy and gravity to ensure optimal double-contrast images. Hypotonic agents, such as glucagon or scopolamine methylbromide (Buscopan), are preferred by some radiologists, whereas in our practice we see no advantage in inducing gastric hypotonia.

3.1 Computed Tomography

CT provides additional information about the stomach in relation to its surrounding structures. Oral contrast agent is used for optimal distension of the stomach. Water as oral contrast agent has widely replaced positive contrast media, because subtle gastric wall thickening or enhancement is not obscured and regular gastric wall layers can be delineated during the arterial or venous phases (Ba-Ssalamah et al. 2003). Intravenous contrast agent is necessary for enhancement of the gastric wall, especially when using neutral intraluminal contrast. Multiplanar reformation enables visualization and correct assessment of gastric pathologies.

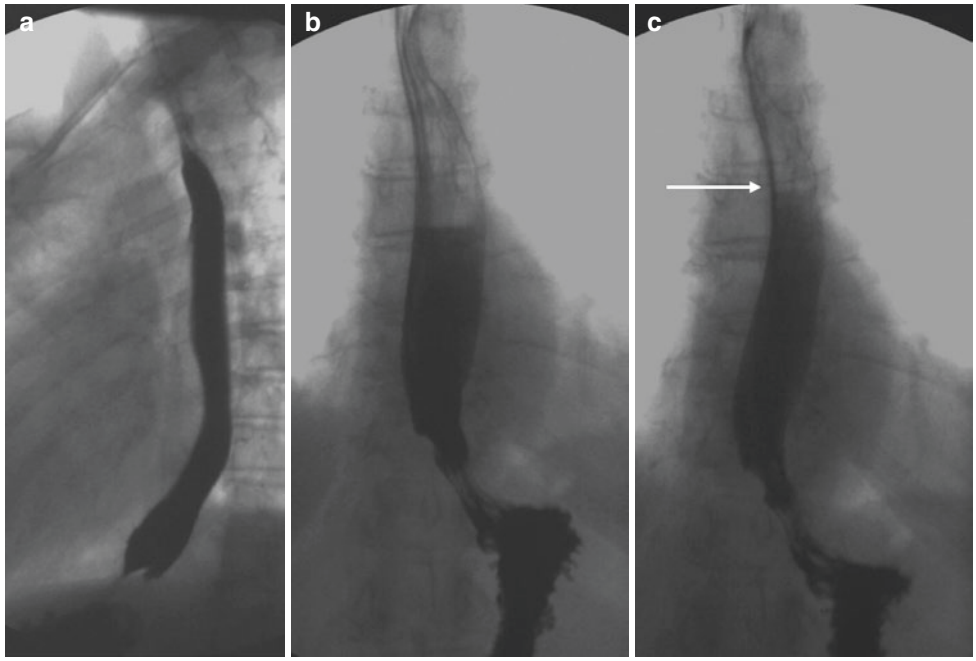


Fig. 5 Achalasia. (**a**) At 2 s after the pharyngeal phase, the bolus reaches the esophagogastric junction. (**b**) At 8 s after the onset of swallowing, a little fluid level remains above the esophagogastric junction. (**c**) The passage of 10 mL of barium takes more than 40 s in this case. The persistent fluid level in the distal esophagus, which is characteristically seen with the patient in standing position, moves up and down without completing the passage, also known as "support level" (*arrow*). This is a typical and important sign in symptomatic patients with and without marked dilatation of the esophagus

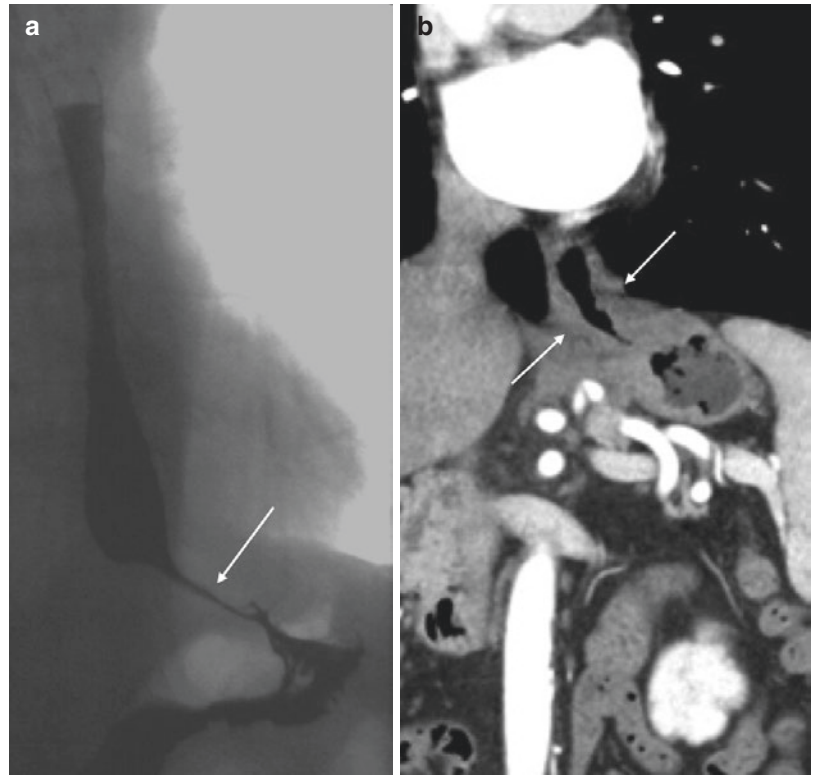


Fig. 6 Pseudoachalasia. (**a**) Patient with dysphagia since 2 months and stenosis at the esophagogastric junction (*arrow*) causing a high support level. (**b**) CT shows tumorous lesion of the cardia (*arrows*), histology proves adenocarcinoma

3.2 Gastric Pathologies that Cause Dysphagia

Inflammatory conditions of the stomach may be asymptomatic or cause vague upper gastrointestinal symptoms, such as epigastric pain, dyspepsia, and upper gastrointestinal symptoms. They may appear radiologically as enlarged areae gastricae and gastric fold thickening, or gastric ulcer formation (Rubesin et al. 2005). Benign or malign gastric tumors may be an incidental finding during a radiological swallowing study, with higher detection rates when using a double-contrast technique (Fig. 7). Most benign tumors are asymptomatic, whereas weight loss, short-term dysphagia, and nausea may suggest malignant disease. But many of the symptoms overlap with more common benign conditions and, often, at the time of diagnosis, patients suffer from advanced disease. Radiological imaging findings may be polypoid, ulcerative, or infiltrative lesions, and CT is ideally suited for further tumor staging. Especially in cases where scirrhous gastric carcinoma is suspected, upper gastrointestinal studies may show decreased distensibility and a rigid appearance (Park et al. 2004) (Figs. 8 and 9).

Gastric outlet obstruction may present with intermittent progressing symptoms, with vomiting as the cardinal symptom and with a better tolerance for liquids than for solid food. Gastric obstruction comprises not a single entity, but varying pathologies that produce a mechanical barrier to gastric emptying. As part of the initial workup, possible functional, nonmechanical causes of obstruction, such as diabetic gastroparesis, should be excluded. Major causes include chronic peptic ulcer disease

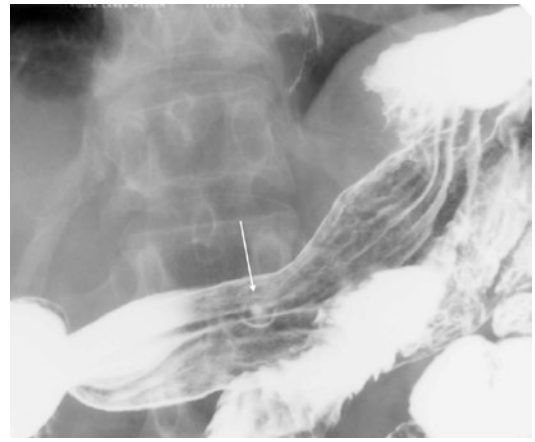


Fig. 7 Patient with GERD symptoms and hoarseness. Upper gastrointestinal imaging shows incidentally detected filling defect on the anterior wall of the stomach, outlined by a barium pool (*arrow*)

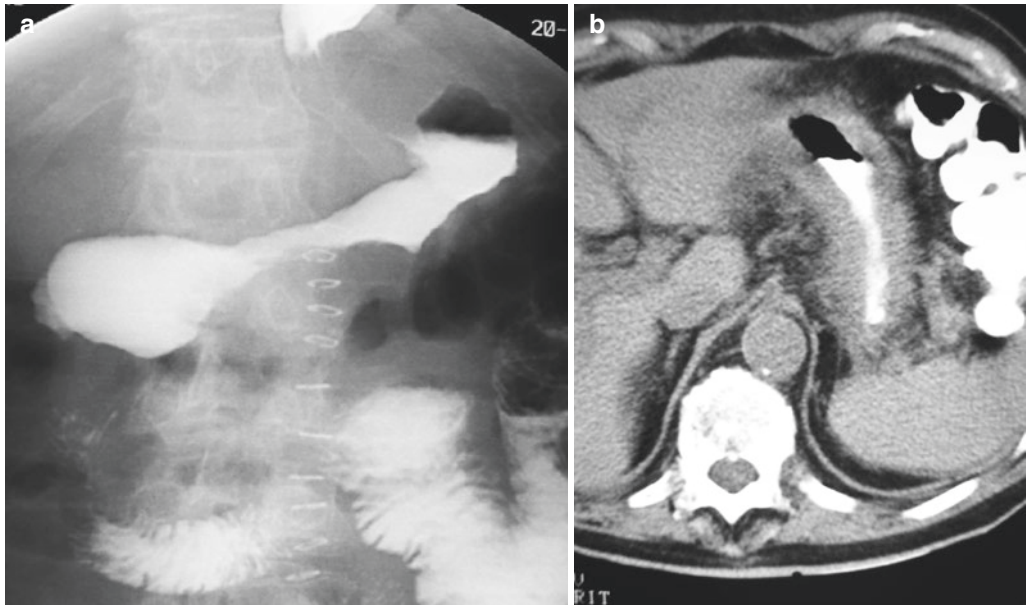


Fig. 8 (**a**) Incomplete distension and luminal narrowing of the stomach with rigidity and lack of peristaltic activity, indicating an infiltrative process of the stomach. (**b**) Computed tomography confirms circumferential gastric wall thickening due to scirrhous carcinoma

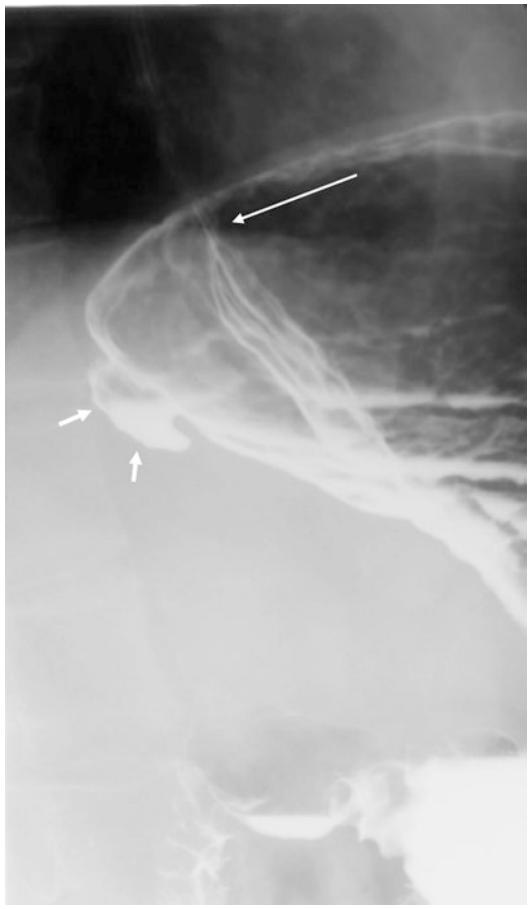


Fig. 9 Patient with vague sensation of fullness immediately after eating. After a regular barium swallow with regular esophagogastric junction (*arrow*), incidentally a diverticulum originating from the gastric fundus could be detected (*short arrow*)

as the main cause for gastroduodenal obstruction, whereas, currently, malignant tumors predominate (Fig. 10), as well as pancreatic pseudocysts, gastric polyps, pyloric stenosis, or congenital webs. Antral webs can be found in rare cases as the cause of symptoms such as refractory gastroesophageal reflux, dysphagia, nausea, and vomiting (Morales et al. 2017) (Fig. 11). Findings of inflammatory changes on swallowing studies include thickened folds, aphtha, antral nodularity, or, rarely, luminal narrowing. The differential diagnosis includes Crohn's disease or MALT lymphoma.

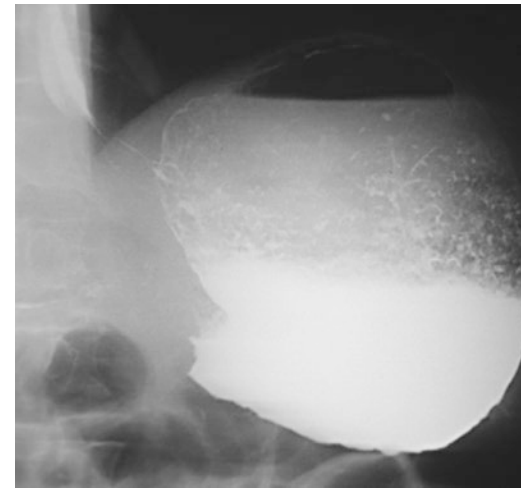


Fig. 10 Gastric outlet obstruction due to mechanical obstruction of stomach emptying with stasis of barium suspension and an irregular stenosis due to adenocarcinoma

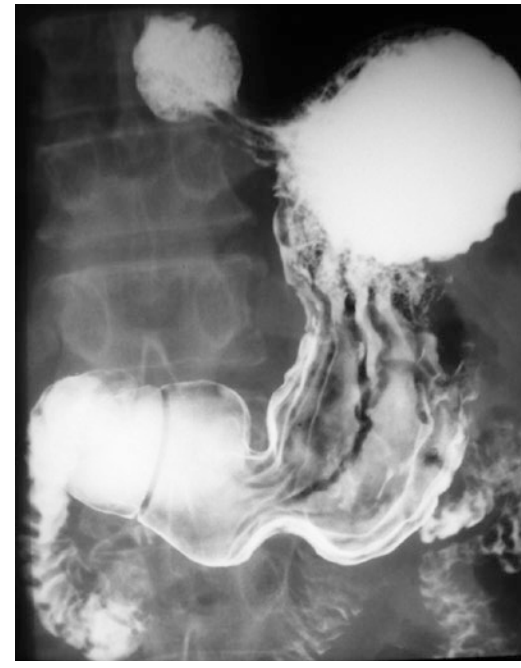


Fig. 11 Patient with unspecific gastrointestinal symptoms such as epigastric fullness, retrosternal pain, and weight loss. Barium examination reveals a smooth thin circumferential indentation of the gastric antrum, also known as "antral web"

4 Dysphagia After Surgical Antireflux Therapies

Despite improved surgical techniques of antireflux procedures, persistent or recurrent symptoms of reflux or postoperative dysphagia remain an important clinical cause of morbidity and the most common indicator of fundoplication failure (Sato et al. 2002). Transient dysphagia after fundoplication is found in approximately 50% of patients 1 week after surgery (Kamolz et al. 2000), owing to edema and esophageal ileus after surgical manipulation, and disappears, in most cases, within a few weeks postoperatively. However, in a significant number of patients, postoperative severe dysphagia may also be found months after surgical therapy, ranging from 4 to 12% (Tian et al. 2015). Causes include a tight wrap, migration of the wrap into the mediastinum due to failure to identify a short esophagus, a slipping of the stomach, or a tight approximation of the crura. The reappearance of GERD symptoms can be found in up to 55–59% (Tian et al. 2015), with weak correlation to pH studies, indicating the need for objective verification of reflux (Thompson et al. 2009).

4.1 Radiological Assessment

Radiological tests may reveal typical signs, such as intrathoracic wrap migration, slipping of the gastric fundus through partial or complete disruption of the fundoplication sutures, or recurrent hiatal hernia, all of which correlate to obstructive or reflux symptoms (Carbo et al. 2014) (Fig. 12). Although the relevance of routinely performed

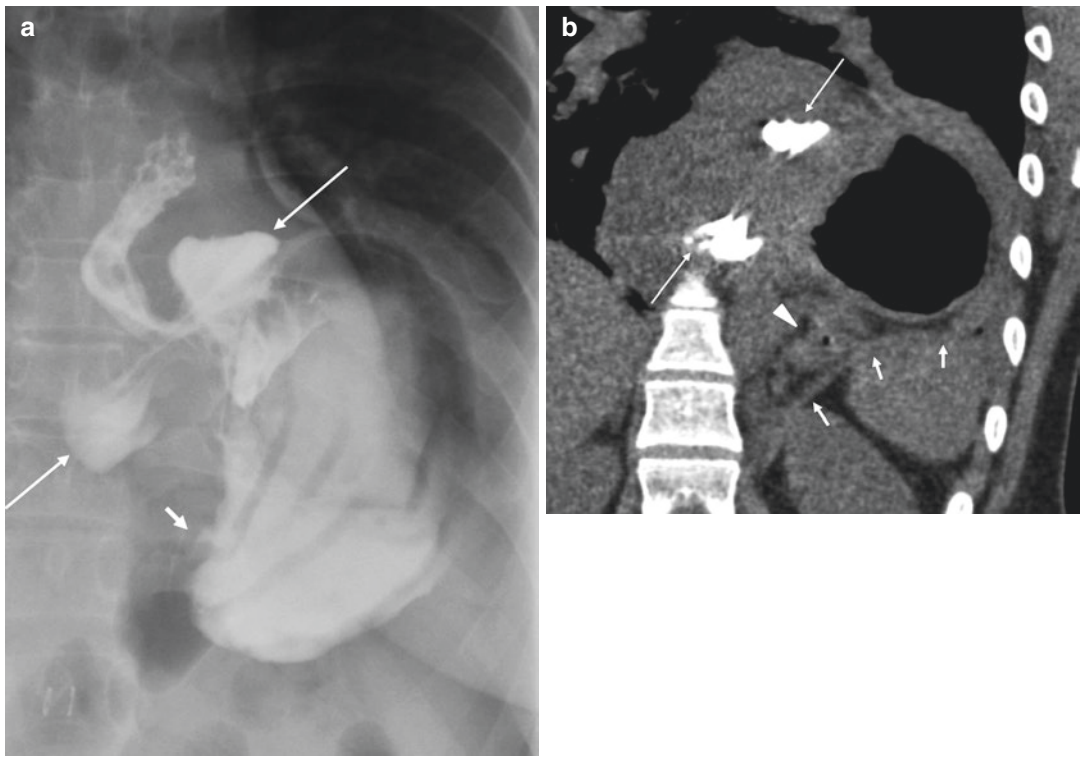


Fig. 12 Complication after fundoplication: patient with recurrent symptoms of obstruction. (**a**) Fluoroscopy shows a transdiaphragmatic wrap herniation with a gastric wrap filled with positive contrast material (*arrows*) located above the diaphragm and slipping of the stomach through the hiatus of the diaphragm with obstruction (*short arrow*). The stomach is compressed by the diaphragmatic hiatus (*short arrow*). (**b**) Then performed CT confirms transdiaphragmatic wrap herniation with a still contrast-filled wrap (*arrows*) above the regular located diaphragm (*short arrows*) and the slipped stomach through the wide diaphragmatic hiatus (*arrowhead*)

postoperative contrast studies is still controversial, they seem beneficial for a significant number of patients without typical symptoms (Tsunoda et al. 2010).

5 Dysphagia After Bariatric Surgery

Bariatric surgery, when accompanied by lifestyle and medical interventions, has been proven to be a successful treatment modality in obese patients. Various surgical strategies have been introduced within the last several decades and the rise of laparoscopic methods was a fundamental step toward a less invasive approach. The detection of postoperative complications is the main goal of radiology in bariatric surgery, and, due to nonspecific clinical symptoms, radiology plays a critical role in postoperative management. Especially in patients with restrictive (gastric banding) or restrictive and malabsorbtive operation techniques (laparoscopic Roux-en-Y gastric bypass), dysphagia is a frequently encountered side effect, with food backing up into the esophagus and concomitant chest pain or tightness in the throat. Postoperative dysfunction of the LES may lead to pseudoachalasia, esophageal dilation, or a new occurrence or worsening of existing GERD (Naik et al. 2016, Altieri and Pryor 2015). Bariatric surgical procedures may also have a deleterious effect on esophageal function (Tolone et al. 2016).

5.1 Radiological Assessment

The upper GI swallowing study and CT have proven to be the workhorses for the assessment of complications after bariatric surgery. For radiological evaluation, the investigator must be familiar with the different surgical procedures and possible complications. The evaluation should start after understanding the operation that has been performed in the patient. In this specific patient group, the physician must carefully follow the instructions for the use of the technical equipment, since extremely obese patients, in particular, can exceed the limits of the fluoroscopic table or CT table. In addition, artifacts are more common in obese patients. The cumulative medical radiation dose from upper gastrointestinal fluoroscopic series and CT scans in the postoperative bariatric population ranges from 4 to 156 mSv (Oei et al. 2010), which emphasizes the need for appropriate technical factors and a short and focused examination in order to minimize patient dose.

5.2 General Complications

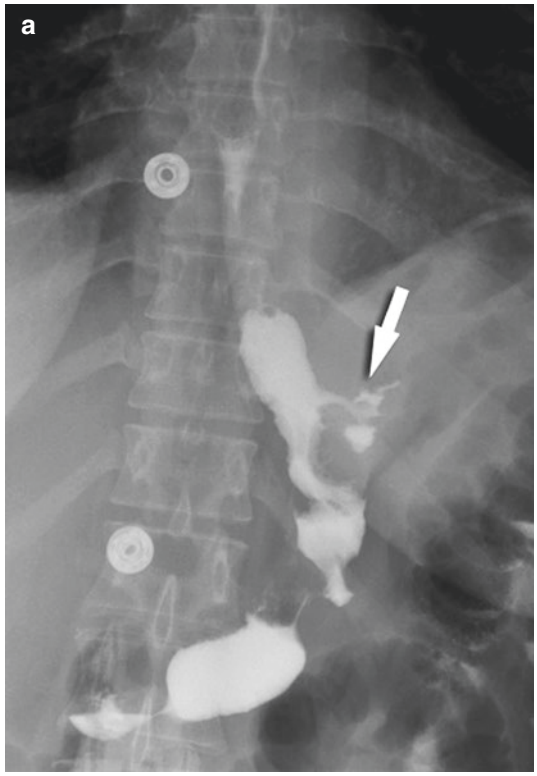
Early general complications include anastomotic leak, hemorrhage, staple line dehiscence, and bowel obstruction. They can be assessed using radiological and endoscopic methods (Shah et al. 2011). Complications in the late postoperative period (more than 1 month postoperatively) include obstruction, dehiscence, stomal stenosis, and marginal ulcers.

Pseudoachalasia results from the creation of a potential high-pressure zone at the level of the esophagogastric junction by sleeve gastrectomy, gastric banding, or bypass surgery, leading to severe dysphagia and motility disorders (Ravi et al. 2016). Esophageal dilation after gastric banding is observed more frequently, with a reported prevalence as high as 15% in long-term studies (Mittermair et al. 2009). But defining esophageal dilation remains difficult. Milone stated that a diameter greater than 35 mm was considered dilation (Milone et al. 2008) and Naef et al. found, in their long-term study, radiographically esophageal dysmotility in 108 of 167 patients after gastric banding, as well as esophageal dilatation in 25.5%, with a mean diameter of 47 mm (Naef et al. 2011). Radiologists should be aware of this condition in the postoperative follow-up.

5.3 Specific Complications

5.3.1 Gastric Bypass

For postoperative upper GI series after the performance of a gastric bypass, complications can be expected in about 10% of patients. A delayed emptying of the pouch has been reported in 4.5%, an anastomotic leak in 3%, a gastrogastric fistula in 1.7%, and an outlet obstruction of the gastric pouch in 1% (Podnos et al. 2003) (Fig. 13).



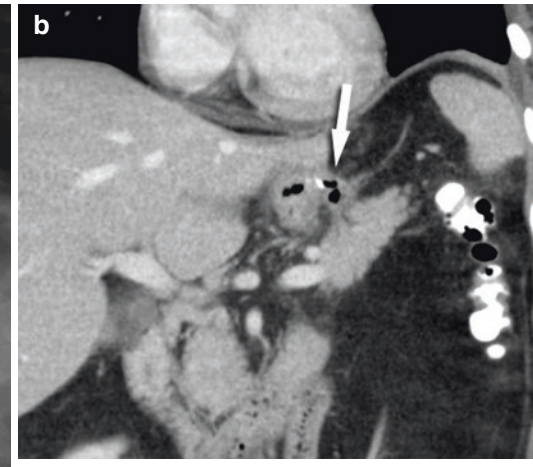


Fig. 13 (**a**) GI series in this patient after gastric bypass surgery shows an extraluminal collection of contrast material (*arrow*) near the gastroenteric anastomosis. (**b**) CT confirmed extravasation of contrast material (*arrow*) located adjacent to the perisplenic area and the left subphrenic area (**b**)

Strictures, adhesions, internal hernias, volvulus, and intussusception represent the wide spectrum of underlying pathologic conditions causing gastrointestinal obstructions in the later postoperative course, found in about 5% of patients (Scheirey et al. 2006). Strictures of the gastrojejunostomy are relatively common and are manifested with vomiting and postprandial pain. In the early postoperative phase, a delayed emptying of the esophagus and the pouch is often due to edema of the anastomosis. Obstructions are more common after laparoscopic operations and are the most frequent cause for acute obstruction secondary to internal hernias (Yu et al. 2004). They are reported with an incidence of 4–5%, with an increased prevalence of internal hernia formation (Blachar et al. 2004). Due to stenosis or kinking of the enteroenteric anastomosis, the biliopancreatic limb and the excluded stomach can be dilated. In patients with a retrocolic roux limb, a stenosis can develop at the opening of the mesocolon; radiographs can show a dilated jejunal limb, as can CT with oral contrast (Fig. 14). The whirl sign, mesenteric fat haziness, a mushroomlike appearance of the herniated gut, and intestinal distension are typical features of internal hernias on cross-sectional imaging (Yoshikawa et al. 2014). These typical signs are not always present. The diagnosis of internal hernias can be very difficult and requires experienced radiologists. The successful radiologist cooperates closely with the responsible surgeon and communicates the results of the examinations best in front of the images, to share morphological findings and the clinical information.

As a late complication, degradation of pouch restriction may be the result of a widened gastrojejunostomy or a dilated pouch. The radiologic report should describe the size of the pouch with diameters to approximate the volume. With the use of effervescent granules and barium suspension, the pouch volume and the diameter of the anastomosis can be measured in order to visualize

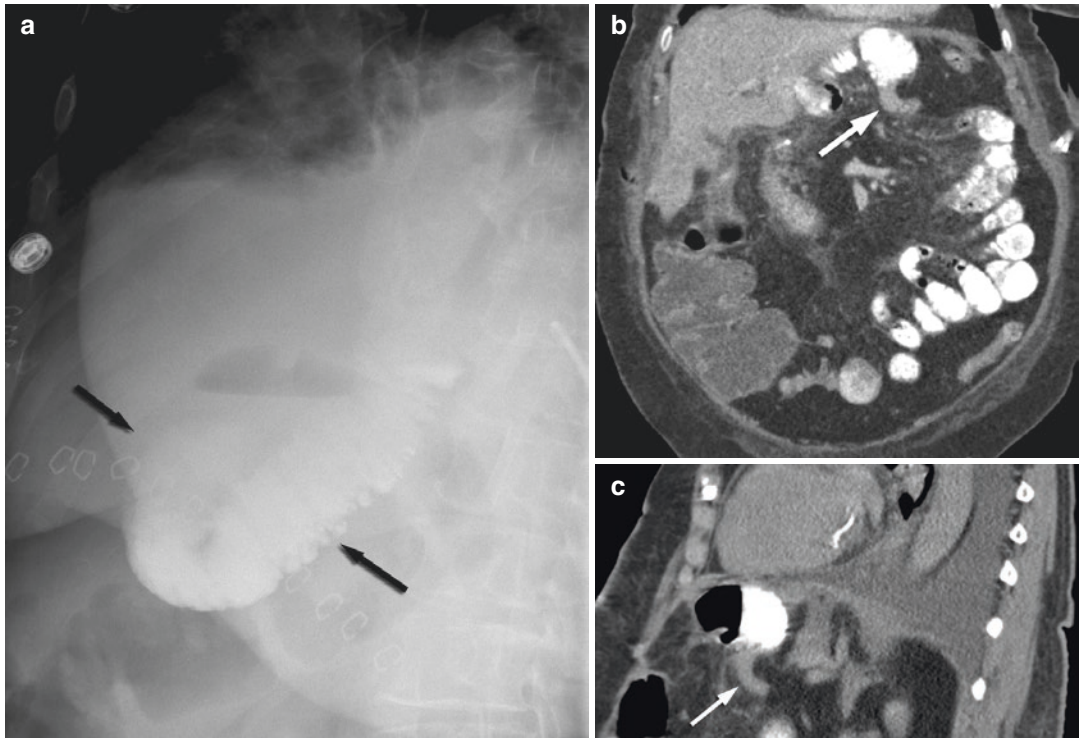


Fig. 14 Images of a 73-year-old patient who presented with vomiting and abdominal pain 6 months after gastric bypass surgery. (**a**) After an unhindered passage of contrast media through the gastroenteric anastomoses, an upper GI series shows a dilated bowel segment (*arrows*) in the left upper abdomen, suggesting small bowel obstruction. MSCT scan in the coronal (**b**) and sagittal (**c**) reformations confirmed the presence of a dilated bowel segment and a transition zone (*arrows*) from the dilated to the collapsed bowel at the level of the mesocolic window

pouch capacity. This showed strong correlation to weight loss (Blanchet et al. 2010). A gastrogastric fistula into the excluded part of the stomach can be found in about 4% of patients (Fig. 15), may heal spontaneously if it occurs directly postoperatively, and serves as an additional functional increase of gastroenteric communication, inducing weight gain as a late postoperative complication (Carucci et al. 2008).

5.3.2 Gastric Banding

A considerable decline in the number of gastric banding procedures within the last few years has been observed in many centers due to the refinements of the technique of laparoscopic Roux-en-Y gastric bypass during the last decade and the larger fraction of patients who fail to lose weight compared to other bariatric operations (Kizy et al. 2017). The most common complications of the LAGB technique are stomal stenosis, acute concentric pouch dilatation, band slippage, intraluminal band penetration, and esophageal widening (Prosch et al. 2006). Clinically, these complications present with pain or abdominal/retrosternal discomfort during or after meals, vomiting, and symptomatic reflux episodes. Postoperative mucosal swelling at the initial examination may lead to a narrow stoma, not reflective of the actual functional width of the passage and necessitating a second radiographic examination in persistent postoperative dysphagia. Iatrogenic overfilling of the band or postoperative stomal edema can be the cause of the narrowing, easily detected fluoroscopically by a narrowed stoma, concentric enlarged pouch, and a delayed passage of contrast material (Fig. 16). Prompt decompression is the best treatment in the early stages in these patients. In 3–8% of cases, a chronic concentric pouch dilation is reported (Wiesner et al. 2000; Mortele et al. 2001) and is

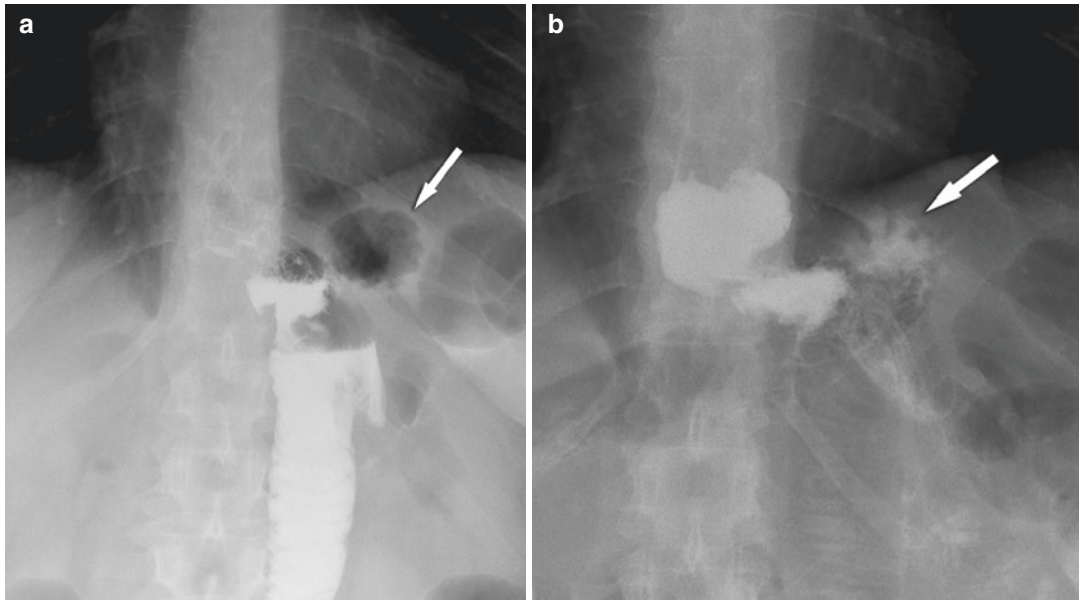


Fig. 15 Gastrogastric fistula in a 38-year-old woman with weight gain 2 years after gastric bypass surgery. (**a**) UGI image shows rapid passage of contrast media through the gastroenteric anastomosis and air within the gastric fundus (*arrow*). (**b**) Image performed shortly afterward shows oral contrast material in the fundus of the excluded stomach (*arrow*) without contrast material in the gastric body, which excludes reflux through the biliopancreatic limb and verifies gastrogastric fistula

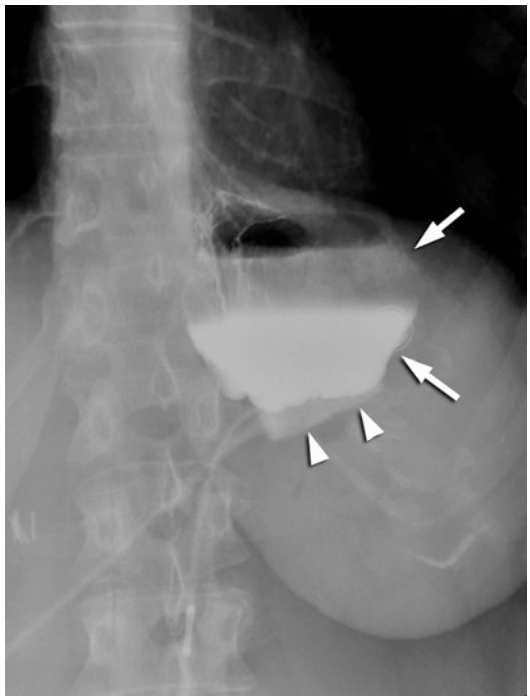


Fig. 16 Fluoroscopic a.p. view shows concentric pouch dilatation (*arrows*) due to a too narrow stoma caused by overinflation of the gastric band (*arrowheads*)

usually due to overeating, with a recurrence of binge-eating behavior. In these cases, the pouch dilation is combined with a normal width of the stoma. A massive progression of this condition can be observed when the chronic concentric pouch dilation aggravates to a megaesophagus.

Independently of the compliance of the patient, band slippage may occur in 3–13% of the patients (Wiesner et al. 2001). Despite correct band placement, the stomach herniates superiorly to the band, producing a pouch prolapse (Fig. 17). The modification of the operative technique leads to a decrease of band slippage by placement of the band out of the lesser sac and creating a fundoplication stitch to reduce herniation of the stomach (Fielding and Allen 2002). The slippage occurs far more commonly anteriorly and presents as an eccentric pouch enlargement, which leads to a more horizontal orientation of the band projection with a phi angle over 58%. In the anterior prolapse, the projected right and upper end drops downward, increasing the phi angle (angle formed by the vertical axis of the spine and the longitudinal axis of the band tubing), while the

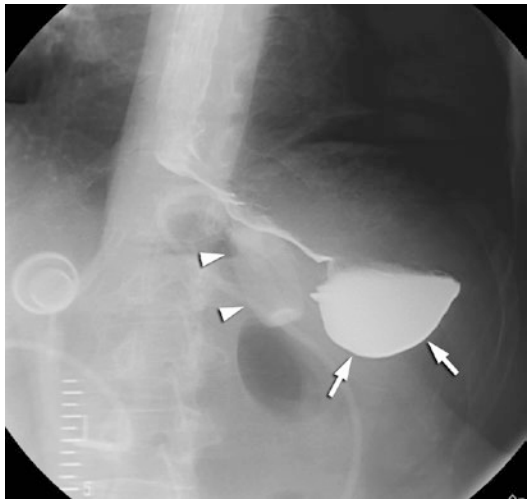


Fig. 17 GI study performed in this 46-year-old patient using water-soluble contrast material shows an abnormally oriented band (*arrowheads*), indicating anterior slippage associated with eccentric pouch dilatation (*arrows*) caused by a herniation of the greater curvature of the stomach and complete stomal obstruction

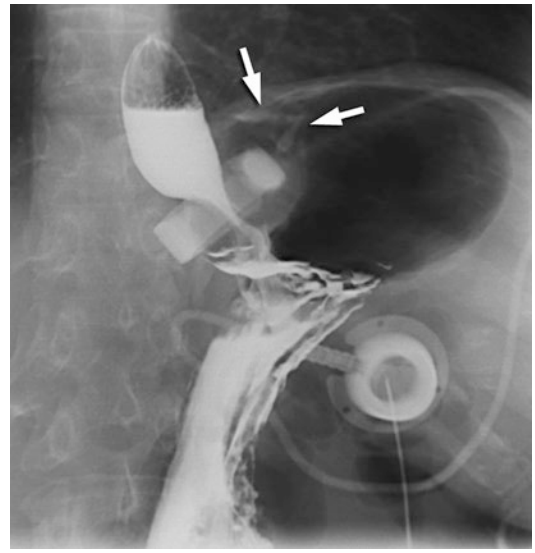


Fig. 18 GI investigation after gastric banding shows regular position of the implanted band and regular flow of contrast material through the band. After injection of water-soluble contrast material through the port during fluoroscopy, an extravasation could be diagnosed (*arrows*) indicative of a connecting tube complication, a leak between the tube and the port

prolapse tends to take on a lateral position. The posterior slippage results in a more medial prolapse with a vertical band orientation with a phi angle of <4°. The "O-sign" is a relevant observation (Pieroni et al. 2010) and is present when the misplaced band after slippage loses the rectangular appearance of the band, due to the rotation of the horizontal axis of the band.

Other less common complications are problems with the port system or the band itself, including leakage, infection, and band erosion. Leakage of the system can occur at the level of the port, the tube, or the band balloon (Figs. 18 and 19). Clinical signs are insufficient weight loss and evident loss of eating restriction. With contrast injection, the site of the leak can be diagnosed fluoroscopically. A rare complication is intragastric band erosion, usually caused by ischemia, with intraluminal migration of the band (Fig. 20).

5.3.3 Sleeve Gastrectomy

In patients with sleeve gastrectomy, unhindered flow through the sleeve to the antrum or filling of the proximal sleeve with a delay of flow distally toward the duodenum can be observed (Gotein et al. 2013). In some patients, a transient retention of contrast medium within the proximal end of the pouch may be seen, caused by the loss of peristalsis in the early postoperative period (Levine and Carucci 2014). Specific complications of sleeve resections include stenosis of the sleeve with postprandial abdominal pain. In turn, dilation of the tubelike stomach is caused most often by overeating and causes weight gain to obesity, necessitating surgical revision in about 4.5% of patients (Gumbs et al. 2007). The tubelike resection includes the fundus of the stomach and affects the patency of the lower esophageal sphincter. However, pathological reflux is a common complication in patients after sleeve resection, found in as many as 20% of patients 1 year after surgery (Himpens et al. 2006).

5.3.4 Biliopancreatic Diversion

The biliopancreatic diversion, a surgical technique, with the creation of what is often called a duodenal switch, is a combined restrictive and malabsorptive method. The restrictive part involves a pylorus-sparing vertical or sleeve gastrectomy and the malabsorptive part the exclusion

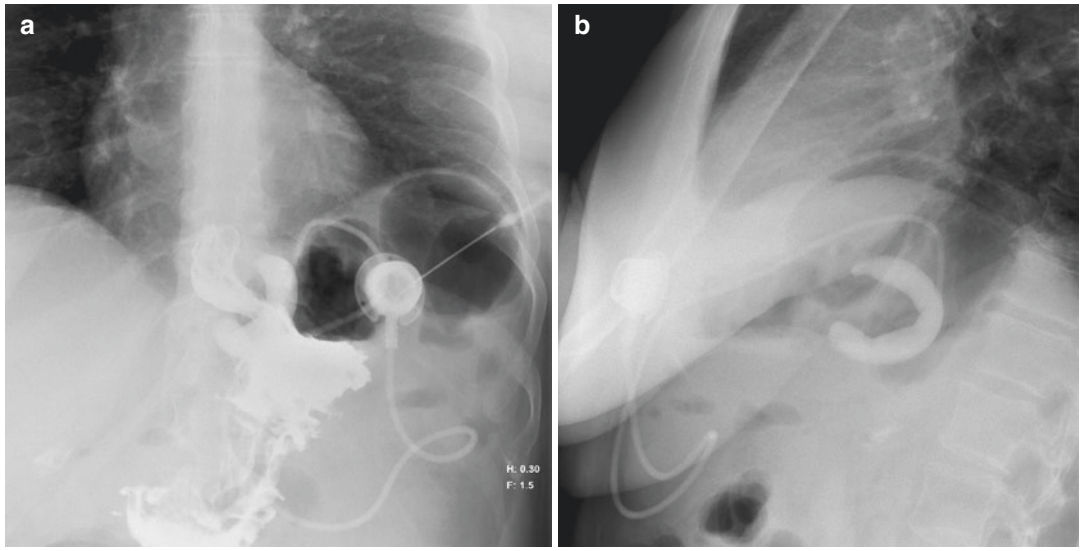


Fig. 19 Fluoroscopy in this 49-year-old patient 5 years after gastric banding performed due to weight gain. Anteroposterior (**a**) and lateral (**b**) views show a defective device with rupture of the locking device of the band system

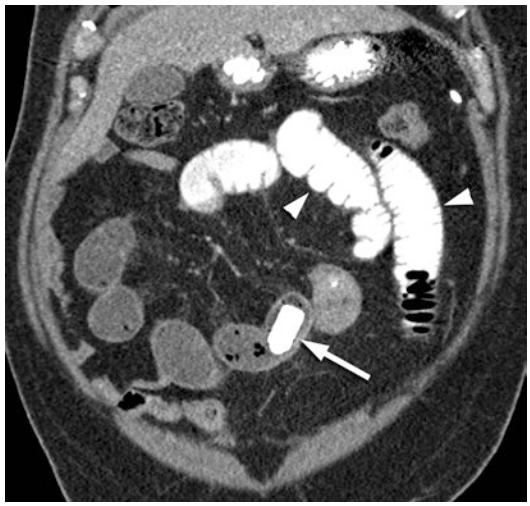


Fig. 20 A 51-year-old patient 5 years after gastric banding who presented with severe abdominal pain and clinical signs of bowel obstruction. CT showed complete intragastral band erosion with dislocation of the gastric band into the distal jejunum (*arrow*), causing small bowel obstruction with dilated pre-stenotic jejunal loops (*arrowheads*)

of the duodenum, jejunum, and proximal ileum by formation of a digestive loop, a biliopancreatic loop, and a common channel. Preservation of the pyloric valve reduces the risk of development of a dumping syndrome. The complications of this procedure are leaks, small bowel obstruction, and malnutrition (Carucci and Turner 2012). Although in superobese patients this procedure provides superior weight loss, gastric bypass surgery is the preferred method among bariatric surgeons (Alverdy et al. 2009).

6 Summary

Pathologies of the esophagogastric junction and the stomach are common, and, for optimal individual workup, various diagnostic modalities have their specific role. The radiological swallowing study remains a relevant and efficient diagnostic evaluation for the management of patients with functional or morphological abnormalities of the LES and the stomach, including dysphagic patients after surgical procedures of the stomach. In particular, videofluoroscopy offers the advantage of simultaneous evaluation of the morphology and function of the LES and the stomach, an attribute not shared by other single clinical tests. It illustrates motility in real time, accurately detects leaks in patients after surgery, and provides targeted investigations tailored to the individual patient. The main goal of

radiology in the postoperative patient requires specific knowledge about the postoperative pathophysiology and the associated radiologic findings and pitfalls.

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Neuroimaging in Patients with Dysphagia

Kasim Abul-Kasim

Contents

Abstract

With increasing availability of computed tomography (CT) and magnetic resonance imaging (MRI), patients with dysphagia are nowadays often investigated with these modalities in order to localize a possible site of injury causing dysphagia. However, these radiological modalities often reveal some abnormalities especially in elderly patients, and the correlation of these findings with clinical symptoms needs therefore a good knowledge about the anatomy of different structures involved in swallowing. Beside description of these different anatomical structures and the most common pathological conditions that cause dysphagia, this chapter is also enriched with illustrative radiological images, often at the axial plane that radiologists are familiar with.

1 Neuroanatomy of Swallowing

Different structures in the central nervous system (CNS) are responsible for coordination of the three sequential phases of swallowing, namely, the oral, the pharyngeal, and the esophageal phases. There are sensory and motor structures in the CNS that play an important role in swallowing. The three most important locations that are involved in processing information related to swallowing are the cerebral cortex, the medulla

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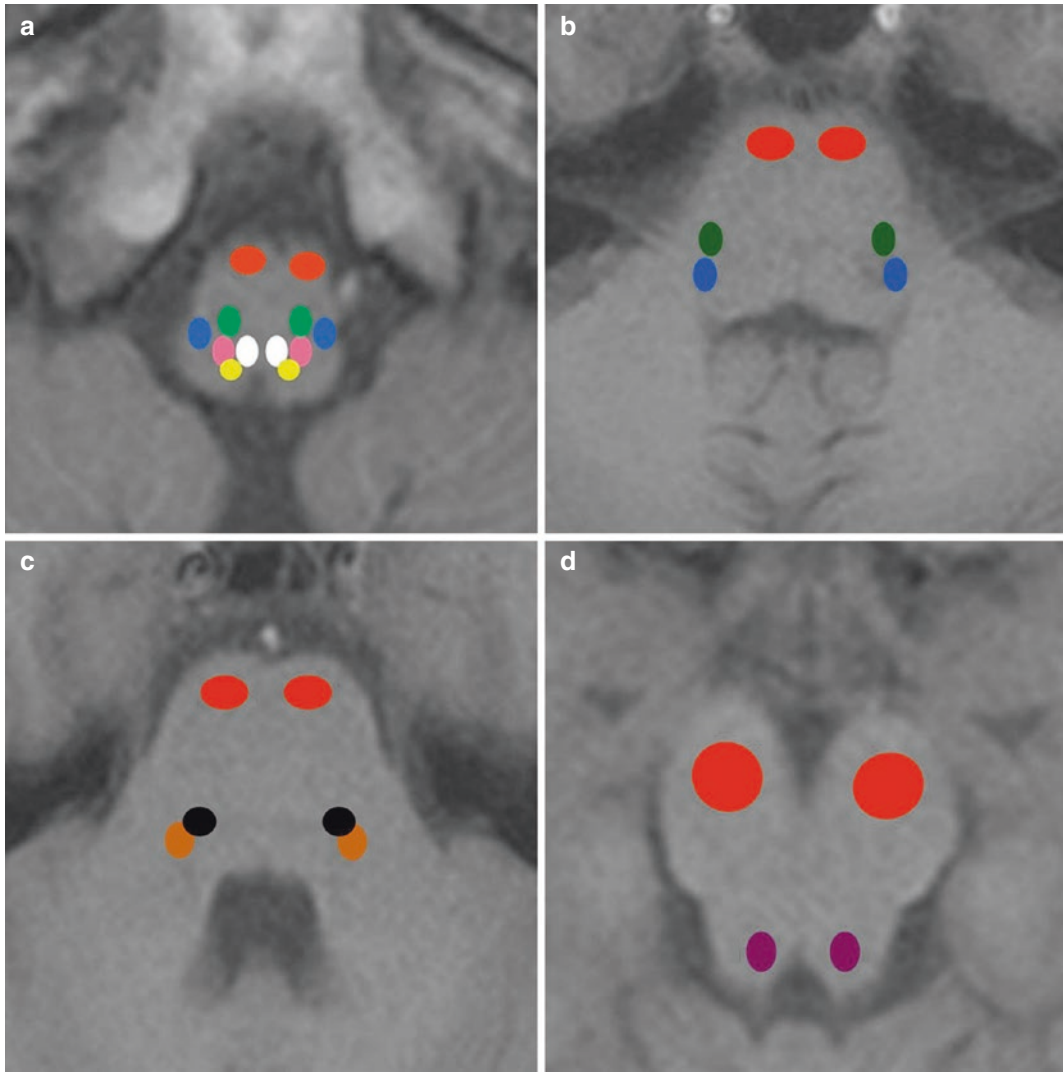

Fig. 1 Axial T1-weighted magnetic resonance imaging (MRI) showing the location of cranial nerve nuclei in the brain stem that are involved in the swallowing process. (**a**) At the level of the medulla oblongata: corticospinal tract (pyramidal tract) in *red*, ambiguous nucleus in *green*, spinal nucleus of trigeminal nerve in *blue*, dorsal nucleus of vagus nerve in *pink*, hypoglossal nerve nucleus in *white*, and solitary nucleus/solitary tract in *yellow*. (**b**) At the level of the lower pons: corticospinal tract (pyramidal tract) in *red*, facial nerve nucleus in *green*, and spinal nucleus of trigeminal nerve in *blue*. (**c**) At the level of the upper pons: corticospinal tract (pyramidal tract) in *red*, motor nucleus of trigeminal nerve in *black*, and sensory nucleus of trigeminal nerve in *brown*. (**d**) At the level of the mesencephalon: corticospinal tract (pyramidal tract) in *red* and mesencephalic nucleus of trigeminal nerve in *purple*

oblongata, and the cranial nerves and their nuclei located in different parts of the brain stem.

The sensory nerves and cranial nerve nuclei involved in swallowing are as follows (Figs. 1 and 2):

1. Trigeminal nerve (V): the main sensory nucleus, the mesencephalic nucleus, and the spinal nucleus extending in the spinal cord.
2. Facial nerve (VII).
3. Glossopharyngeal nerve (IX).
4. Vagus nerve (X).

The motor nerves and cranial nerve nuclei involved in swallowing are as follows (Figs. 1, 2, and 3):

1. Motor nucleus of trigeminal nerve.
2. Motor nucleus of facial nerve.

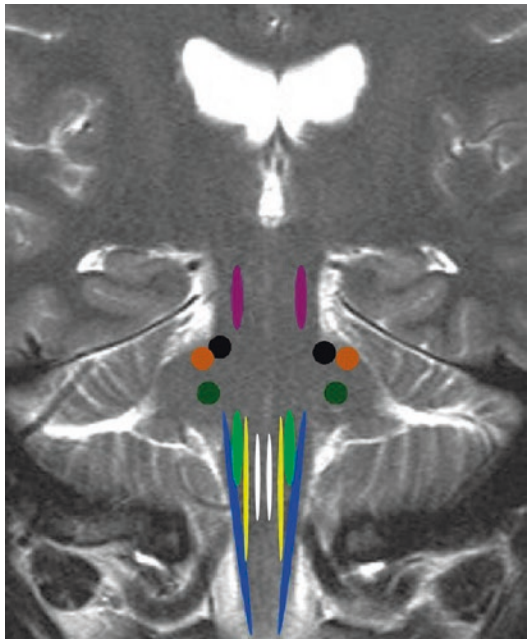

Fig. 2 Coronal T2-weighted MRI showing the distribution of different cranial nerve nuclei in the brain stem: The *lower part* (medulla oblongata): spinal nucleus of trigeminal nerve in *blue*, ambiguous nucleus in *light green*, solitary nucleus/solitary tract in *yellow*, and hypoglossal nerve nucleus in *white*. The *middle part* (pons): facial nerve nucleus in *dark green*, motor nucleus of trigeminal nerve in *black*, and sensory nucleus of trigeminal nerve in *brown*. The *upper part* (mesencephalon): mesencephalic nucleus of trigeminal nerve in *purple*

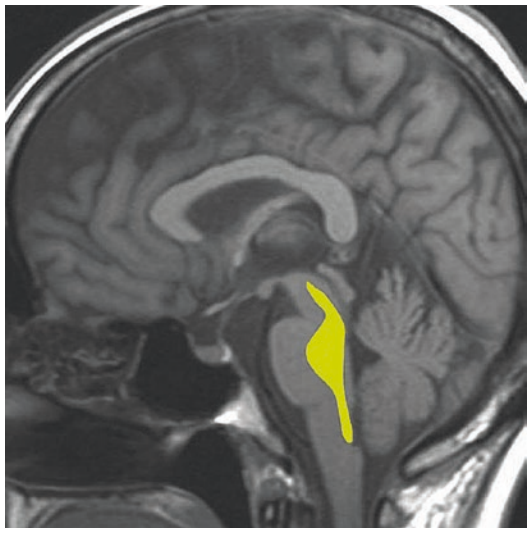

Fig. 3 Sagittal T1-weighted MRI showing the distribution of the reticular formation of the brain stem (marked in *yellow*)

3. Ambiguous nucleus of the vagus and glossopharyngeal nerves.
4. Dorsal motor nucleus of the vagus nerve.
5. Hypoglossal nerve nucleus (XII).
6. Solitary nucleus and solitary tract with contribution from glossopharyngeal, vagus, and hypoglossal nerves.
7. Reticular formation representing an interconnecting pathway between the motor nuclei of the trigeminal, facial, and hypoglossal nerves and the ambiguous nucleus.

The supratentorial structures involved in swallowing are as follows (Daniels and Foundas 1997; Miller 1999; Fig. 4):

1. Premotor cortex (Brodmann's area 6) located anterior to the primary motor cortex.
2. The primary motor cortical representation of swallowing is located at the level of the frontoparietal operculum at the lower part of the precentral gyrus (M1, Brodmann's area 4).
3. The primary somatosensory cortical representation of swallowing is located at the level of the frontoparietal operculum at the lower part of the postcentral gyrus (S1, Brodmann's areas 3, 2, and 1).
4. Anterior part of the insular cortex.

Generally, esophageal cortical representation is located cranial to the pharyngeal cortical representation; the latter is located cranial to the oral cortical representation (Hamdy et al. 1996). Swallowing centers are usually present bilaterally but one center, independent of the language-dominant hemisphere, is usually larger than the other one (Barritt and Smithard 2009). The fibers connecting the supratentorial motor areas involved in swallowing to the brain stem constitute the corticobulbar tracts. The cerebellum is usually involved in modulating the movements required to accomplish the swallowing.

2 Neurological Disorders Causing Dysphagia

Many neurological disorders can cause dysphagia. Neurological causes of dysphagia can be classified simply into degenerative and nondegenerative disorders (Daniels 2006). Stroke is the most common cause of the nondegenerative

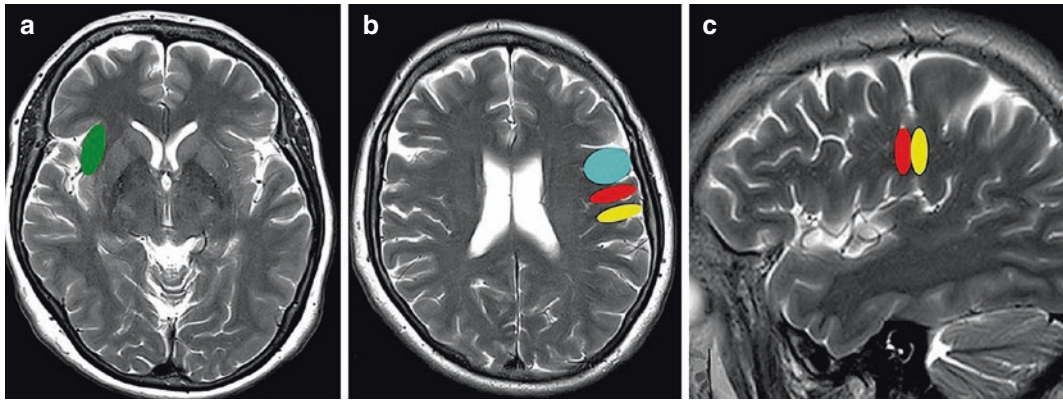

Fig. 4 (**a**, **b**) Axial T2-weighted images and (**c**) sagittal T2-weighted image showing the anterior part of the insular cortex (marked in *green* in **a**), primary sensory cortical representation (marked in *yellow* in **b** and **c**), primary motor cortical representation (marked in *red* in **b** and **c**), and premotor cortex (marked in *blue* in **b**) at the level of the frontoparietal operculum. The cortical representation is usually present on both sides

type of dysphagia, followed by trauma. Among other causes are multiple sclerosis (MS), cerebral palsy, brain tumors, and iatrogenic lesions (following cervical spine surgery, carotid artery surgery, and head and neck surgery). Degenerative disorders include different types of dementia, movement disorders, e.g., Parkinson's disease, Huntington's disease, Wilson's disease, progressive supranuclear palsy, and pontocerebellar atrophy. Amyotrophic lateral sclerosis (ALS) is a progressive and eventually fatal disorder affecting both the upper and the lower motor neurons involving predominantly the corticobulbar or corticospinal tracts. Limb weakness and spasticity is the dominating feature of the disease, whereas dysphagia and dysarthria are among the most common features of the bulbar palsy associated with ALS. Other causes of dysphagia include myasthenia gravis and different types of myopathy, e.g., dermatomyositis and myotonic dystrophy.

The workup of patients with dysphagia is based on a thorough medical history and clinical examination. Videofluoroscopy is the method of choice to study the dynamics of swallowing. Fiber endoscopic evaluation of swallowing may also be used.

The course and the prognosis of dysphagia differ widely depending on the cause of dysphagia. Dysphagia in stroke, traumatic brain injury, and following neck surgery has an acute presentation but in many patients is reversible, with spontaneous recovery or successive improvement. However, radiological abnormalities of swallowing may still be evident even in patients receiving an oral diet months after the stroke (Logemann et al. 1999). Dysphagia in other neurological disorders such as MS and ALS is progressive. In ALS the progression of dysphagia is usually rapid, whereas dysphagia among patients with MS is slowly progressive.

3 Neuroimaging in Dysphagia

Neuroimaging is usually included in the workup of patients with dysphagia following stroke and trauma and is usually performed before videofluoroscopy. Neuroimaging is also routine in patients with MS, brain tumors, and Wilson's disease suffering from dysphagia. Although the diagnosis of conditions such as dementia and Parkinson's disease is not primarily radiological, in the last 20 years the different radiological modalities have been increasingly used during the course of events of these diseases as well. Computed tomography (CT) is the method of choice in the workup of acute supratentorial stroke and trauma, whereas magnetic resonance imaging (MRI) is preferred in infratentorial stroke, MS, and degenerative disorders. CT is

cheaper, less time-consuming (both in performing and in evaluating the examination), and more widely available than MRI. The disadvantages of CT are the radiation exposure and the lower sensitivity in detecting lesions in the brain stem, where different cranial nerve nuclei involved in the swallowing are located. MRI provides more detailed anatomical and morphological information than CT especially in pathological conditions of the skull base and posterior cranial fossa, including the brain stem. In the last decade, new MRI modalities have been introduced enabling functional evaluation of different CNS structures involved in swallowing using functional MRI. Structural evaluation of different tracts involved in the swallowing connecting the motor cortex with swallowing centers of the brain stem is now possible by using diffusion tensor imaging and tractography.

4 Dysphagia Following Stroke

Stroke affects 2000 people per million worldwide each year (Thorvaldsen et al. 1995); 80–85% of strokes are ischemic and 15–20% are hemorrhagic. Up to 35–50% of patients with stroke develop dysphagia (Paciaroni et al. 2004; Gordon et al. 1987). In a systematic review of published literature concerning dysphagia after stroke, the incidence of stroke was about 50% using clinical testing and about 75% using instrumental testing. Dysphagia tends to be less severe compared with brain stem stroke (Martino et al. 2005). Among patients with middle cerebral artery ischemic stroke, the size of the infarct plays a more important role than the location of the ischemic injury (Paciaroni et al. 2004; Fig. 5). Cortical and subcortical supratentorial lacunar infarcts as well as brain stem infarcts may result in dysphagia (Fig. 6). Cerebral

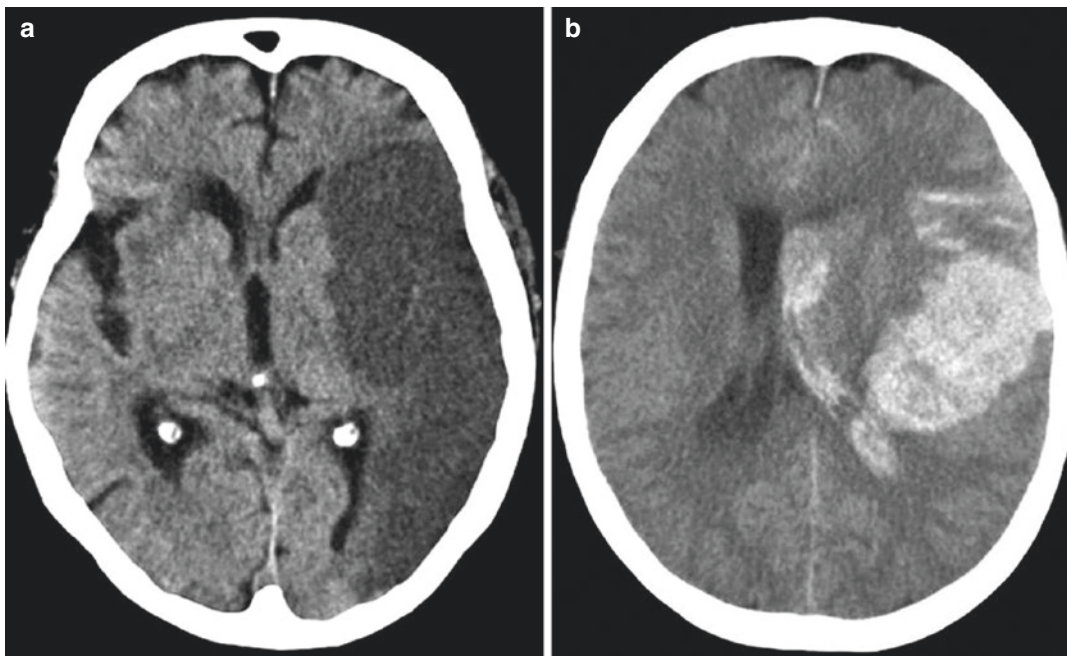

Fig. 5 Axial computed tomography images of two different patients. (**a**) A large cerebral infarct (*dark area*) involving the whole left middle cerebral artery territory. The patient complained of aphasia, hemianopia, right-sided hemiplegia, and sensory loss. (**b**) A large cerebral hemorrhage in the left frontal and parietal lobes with blood in the subarachnoid space and the left lateral ventricle. The patient complained of aphasia and sensory and motor deficit. The hemorrhage affects the cortical representation of the face and the tongue, resulting in swallowing difficulties primarily due to impairment of the oral phase of swallowing. Both patients needed long-standing tube feeding

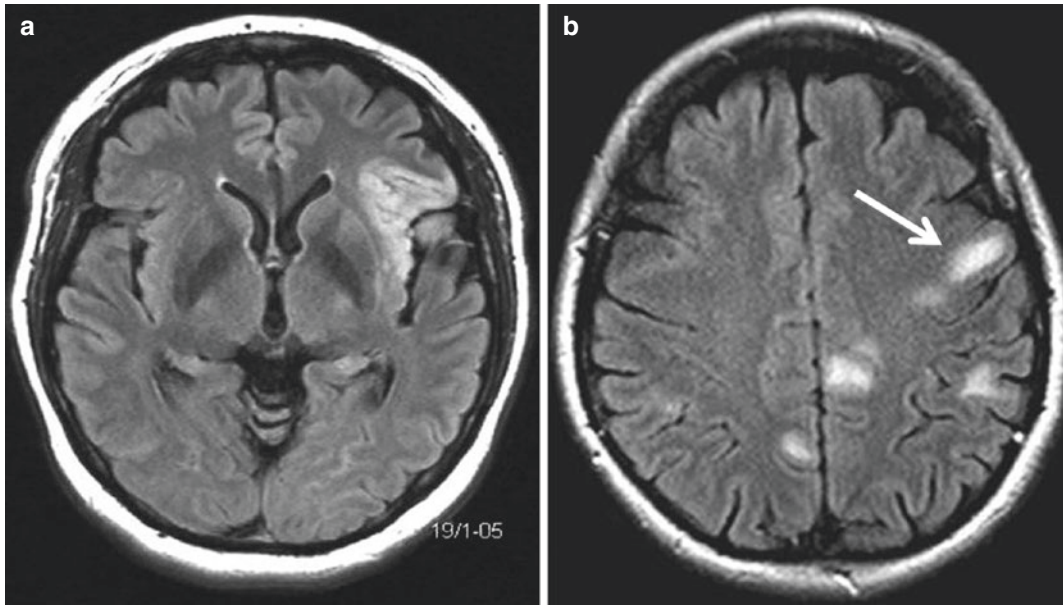

Fig. 6 Axial T2 fluid-attenuated inversion recovery (FLAIR) MRI of two different patients. (**a**) A small infarct affecting the frontal lobe operculum responsible for speech and the anterior part of the insular cortex. The patient had complained of expressive aphasia and swallowing difficulties. (**b**) Multiple lacunar cortical and subcortical infarcts. The infarct marked with an *arrow* affects the precentral gyrus

infarctions affect all three phases of swallowing with subsequently increased risk of aspiration of liquid or solid food and development of pneumonia, which is one of the life-threatening complications of stroke (Miller 1999). Cerebral infarctions may be classified as either large-vessel infarcts or small-vessel infarcts. Patients with large-vessel infarcts affecting the middle cerebral artery territory present with hemiplegia, sensory loss, aphasia, neglect, and visual disturbance (hemianopia). Patients with bilateral infarcts involving the frontoparietal operculum develop severe dysphagia (Foix–Chavany–Marie syndrome). The clinical presentation of large-vessel infarcts affecting the brain stem differs depending on the structures affected, often with evidence of involvement of different cranial nerves, dysarthria, dysphagia, syncope, and ataxia as well as motor and sensory deficit (Fig. 7). Large-vessel infarcts affecting the middle cerebral artery territory induce dysphagia by affecting the cortical structures responsible for the processing of the swallowing, whereas large-vessel infarcts affecting the vertebrobasilar

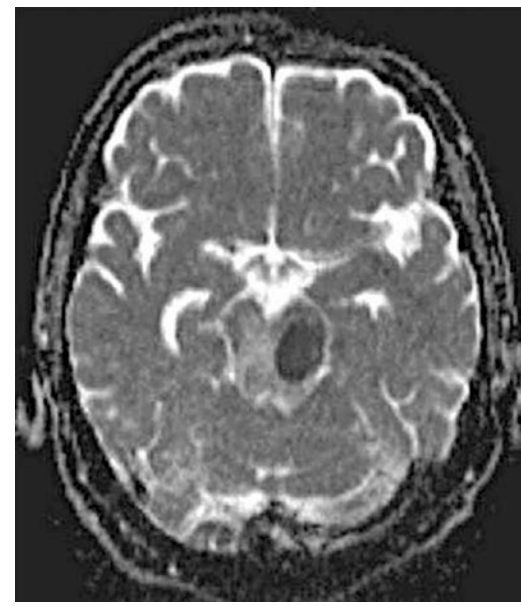

Fig. 7 Apparent diffusion coefficient of magnetic resonance diffusion showing a large infarct of the left side of the upper pons and mesencephalon (*dark area* of restricted diffusion indicating acute infarction). Among other neurological deficits, the patient complained of dysphagia due to affection of cranial nerve nuclei, primarily those of the trigeminal nerve

circulation result in infarcts affecting different cranial nerve nuclei and fibers as well as the reticular formation and solitary tract. There are several vascular syndromes affecting different parts of the brain stem and medulla oblongata that can potentially result in dysphagia. One specific syndrome is Wallenberg's syndrome (posterolateral medullary syndrome). Patients with this syndrome present with Horner's syndrome (ptosis, mitosis, and anhydrosis of the ipsilateral side of the face), sensory loss of temperature, and pain in the ipsilateral side of the face and in the contralateral side of the extremities. Dysphagia is always present due to involvement of the solitary tract (vagus and glossopharyngeal nerve nuclei) (Fig. 8).

In the acute phase of the stroke, CT is the method of choice to detect early signs of large-vessel infarcts and cerebral hemorrhage. When the CT findings are normal on admission of the patient and when the patient complains of dysphagia and/or the presence of other neurological deficits, MRI is usually performed to visualize small supratentorial cortical and subcortical infarcts as well as brain stem infarcts that have failed to be detected by CT. Special attention should be paid to small infarcts in the medulla oblongata, brain stem, anterior insula, lateral portion of the precentral gyrus, posterior portion of the inferior frontal gyrus, basal ganglia, and internal capsule. MRI enables detection of small infarcts and helps to determine their age by demonstrating restricted diffusion on diffusion-weighted images in the acute phase of ischemia and showing contrast enhancement in the subacute stage. Evidence of chronic ischemic changes in the white matter of the brain stem or the supratentorial white matter as in cases of vascular dementia may explain the occurrence of dysphagia among these patients (Fig. 9).

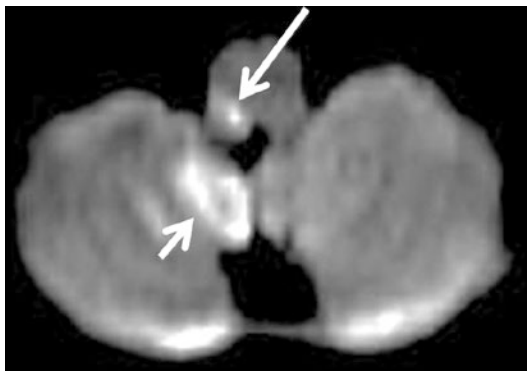

Fig. 8 MRI diffusion showing a small infarct (*bright lesion* marked with a *long arrow*) in the right posterolateral part of the medulla oblongata. The patient presented with symptoms and signs consistent with Wallenberg's syndrome. Dysphagia was primarily caused by involvement of the solitary tract. The image shows also a larger infarct in the right adjacent part of the cerebellum (marked with a *short arrow*)

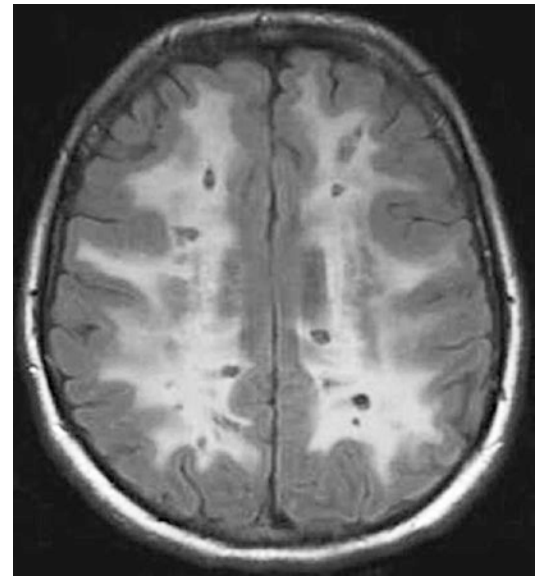

Fig. 9 Axial T2 FLAIR MRI of a patient with vascular dementia with widespread signal abnormalities in the white matter (confluent *bright area*) and multiple small infarcts (*black lesions*). The patient had hypertension, cognitive impairment, and dysphagia

5 Other Neurological Disorders Causing Dysphagia

In trauma, CT is the method of choice as it can detect brain contusions, hemorrhages, and brain swelling. However, small cortical and subcortical hemorrhages, brain stem hemorrhages, and non-hemorrhagic lesions that usually occur in patients with deep axonal injury are not commonly detected by CT. These patients usually have

dysphagia, and the establishment of this diagnosis by performing MRI is essential from a therapeutic and prognostic point of view.

MS is believed to be an autoimmune disease resulting in inflammation of the myelin sheaths around the axons of the brain and spinal cord with subsequent demyelination, damage, and scarring of the affected brain tissue. MS often affects young adults, is more common in women than in men, and has a prevalence ranging between 2 and 150 per 100,000 individuals (Rosati 2001). The clinical presentation of MS differs depending on the site of the MS lesions. Optic neuritis is a common clinical presentation and in many patients is the presenting feature. MS has the predilection to affect the brain stem, the cerebellar peduncles, the corpus callosum, and the periventricular white matter (Fig. 10). However, at least one subcortical lesion should be present to establish the diagnosis according to McDonald's four radiological criteria for the diagnosis of MS. Lesions affecting the brain stem and the subcortical white matter may produce dysphagia in patients with MS. In advanced and late-stage MS, dysphagia and the requirement of tube feeding are not uncommon. In patients with MS, MRI is the method of choice to establish the diagnosis, help the clinicoradiological correlation, and depict lesions with ongoing activity by showing restricted diffusion and/or contrast enhancement. Patients with MS might exhibit plenty of lesions in their white matter, and MRI helps to detect lesions that are responsible for the symptoms, including dysphagia.

In patients with brain tumors, both CT and MRI are suitable methods in the workup of these diseases, although MRI is more sensitive to show the accurate extent of the tumor (Fig. 11), the perifocal edema, or to detect subtle contrast enhancement that might affect regions responsible for swallowing not depicted by CT.

MRI is also the method of choice in the workup of diseases such as ALS (showing increased signal along the corticospinal tract; Fig. 12), Wilson's disease (showing bilateral symmetrical low T1 signal and high T2 signal in basal ganglia, especially putamen), and pontocerebellar atrophy.

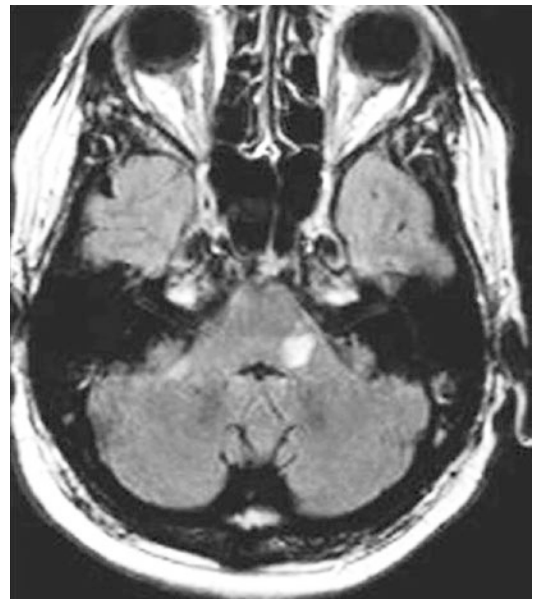

Fig. 10 Axial T2 FLAIR MRI showing a small bright lesion in the lateral dorsal pons. Dysphagia in this case was due to involvement of motor and sensory nuclei of the trigeminal nerve

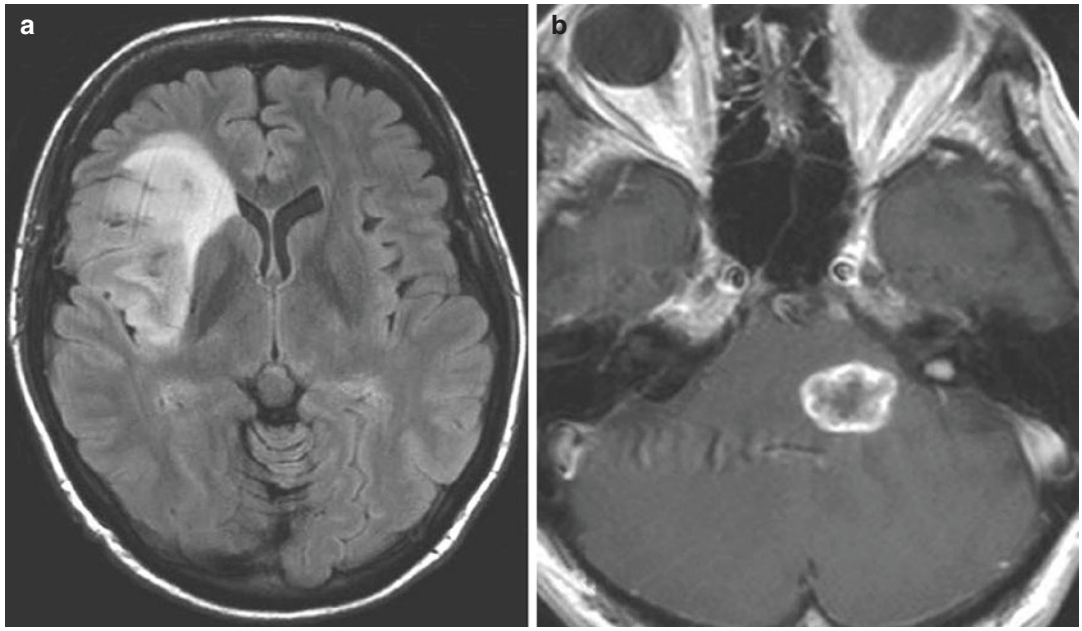

Fig. 11 Axial T2 FLAIR and postcontrast T1-weighted MRI, respectively. (**a**) A large glial tumor (histopathologically proven to be grade II astrocytoma) in the right frontal lobe in a patient with epilepsy and slowly progressive speech and swallowing difficulties. (**b**) Contrast-enhanced tumor in the left side of the pons in a patient with right-sided sensory loss and dysphagia due to involvement of the lateral spinothalamic tract and trigeminal and facial nerve nuclei

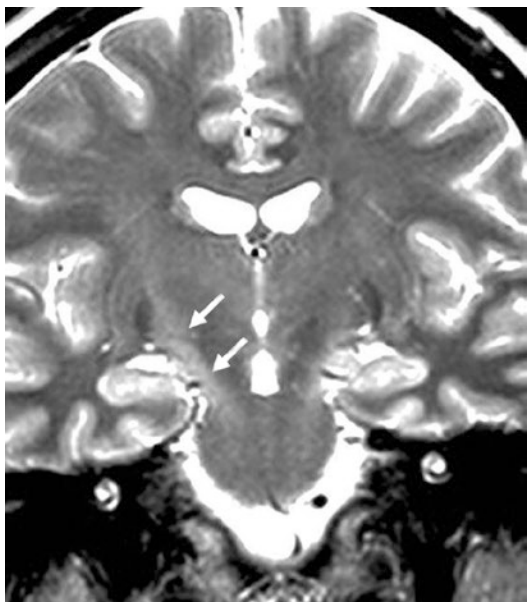

Fig. 12 Coronal T2-weighted MRI of a patient with amyotrophic lateral sclerosis showing high signal intensity along the corticospinal tract (*arrows*)

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Cross-Sectional Imaging of the Oesophagus Using CT and PET/Techniques

Ahmed Ba-Ssalamah

Contents

Abstract

Multidetector computed tomograpy (MDCT) is the most frequent imaging modality in the diagnostic workup of oncologic diseases of the abdomen. Although CT has been used for preoperative evaluation of oesophageal cancer, the major role of CT has been the depiction of lymph nodes, distant metastases, or both, rather than the evaluation of the local status of oesophageal cancer. The sensitivity of conventional or helical CT protocols for the localisation of oesophageal cancer, especially early-stage cancer, is not satisfactory. This may be attributed to the fact that conventional or helical CT cannot offer optimal conspicuity of oesophageal cancers against the normal oesophageal wall, or because the oesophagus is too long to be imaged entirely using thin slices during a single breath hold on conventional or helical CT scans, especially in the absence of lumen distension, since inadequately distended hollow viscera on CT may hide small lesions and may even mimic pseudolesions. Thus, optimal distension of the oesophagus and stomach is important to overcome this limitation. The combination of the MDCT technique with thin-slice sections and the possibility to obtain high-quality, isotropic, multiplanar reconstructions and the water filling, or the application of gas-producing effervescent granules to distend the stomach and the oesophagus, are important factors that may increase the efficacy of CT for local

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staging of oesophageal cancer. Using this technique is not only useful for a complete preoperative staging of oesophageal malignancies according to TNM classification but also clinically relevant for evaluation of a broad spectrum of inflammatory and traumatic diseases. The introduction of FDG PET in combination with MDCT resulted in further optimizing the diagnostic workup of oesophageal cancer and other malignant diseases rendering this technique to be the modality of choice depending on its availability. In this book chapter we review the value of the hydro-MDCT technique and hydro-FDG-PET-CT technique in the diagnostic workup of oesophageal diseases.

1 Introduction

Cross-sectional imaging of the oesophagus is challenging due to its pathoanatomical morphology. The oesophagus is a long tube, and poorly distensible, with a close relationship to many vital organs. These factors make the detection and staging of oesophageal cancer difficult using the cross-sectional modalities. In addition, the lack of a serosal layer of the oesophagus facilitates the spread of the tumour into surrounding organs (Ludeman and Shepherd 2005). Furthermore, the first symptom of oesophageal cancer is often dysphagia, which is a late manifestation, and, at that point, a direct invasion of some vital organs is almost always present, which renders these patients inoperable (Smithers et al. 2010).

Using the multi-detector computer tomography (MDCT) technology covering a large anatomic volume with thin collimation, imaging of the entire oesophagus in a single breath hold becomes possible with high-quality multiplanar reformation and three-dimensional visualisation (Panebianco et al. 2006; Ba-Ssalamah et al. 2009). Adequate distension of the oesophagus and stomach, using water and effervescent granulate as a negative contrast agent, is a prerequisite for assessing the oesophageal wall and gastro-oesophageal junction (Ba-Ssalamah et al. 2003, 2009). Proper contrast material injection techniques (Mani et al. 2001) enhance further the differentiation of pathologic tissue from normal mucosa. Compared to endosonography, multi-detector CT is able to demonstrate not only the immediate vicinity of the oesophagus but also the infiltration of the adjacent organs and the involvement of lymph node regions or distant metastases (Choi et al. 2010). The introduction of FDG-PET in combination with MDCT resulted in further optimising the diagnostic workup of oesophageal cancer (Flamen et al. 2000; Kobori et al. 1999). Therefore, it can be expected that PET/hydro-MDCT will further increase the sensitivity and accuracy in patients with oesophageal cancer for the initial diagnosis, stratifying patients in the proper therapeutic options, monitoring during neoadjuvant chemotherapy and for search of possible recurrence after treatment (Sharma et al. 2011; Jeganathan et al. 2011; Bradley et al. 2012; Krause et al. 2009). Therefore, FDG-PET/HYDRO-MDCT can be considered as the primary modality of choice if available.

2 CT and PET/CT Technique

CT examinations of oesophagus should be performed on at least a 16-detector row CT with a 0.5 s tube rotation. To acquire a near-isotropic data set, primary sub-millimetre (0.75–0.63 mm) thin collimation raw data should be performed (Ba-Ssalamah et al. 2009). For diagnostic viewing, reconstructions of 3–4 mm thick axial sections directly from the scanning raw data using the multiplanar reformation function of the scanner console can be obtained. In addition, routinely coronal and sagittal reformation (with 3–5 mm slice thickness) along the entire oesophagus and the stomach is performed (Panebianco et al. 2006; Ba-Ssalamah et al. 2003). Contrast material injection for the oesophagus and stomach is timed in a manner that ensures capture of the arterial phase for imaging of the oesophageal and gastric mucosa and evaluation of possible associated hypervascular focal liver lesions (Mani et al. 2001; Umeoka et al. 2010; Prokop 2005). An additional portal venous phase examination of the whole abdomen is performed for

complete staging purposes as well. In this protocol, the scanning range includes the cervical region, chest, and the whole abdomen.

For preparation either for hydro-MDCT or for fused FDG-PET/hydro-MDCT, patients are instructed to fast for at least 4–6 h prior to the examination (Ba-Ssalamah et al. 2003). Additionally, in case of combined FDG-PET/hydro-MDCT blood glucose levels are measured before the injection of the FDG tracer (Skehan et al. 2000; Haley et al. 2009). The scanning starts after a resting period of at least 45 min post-injection of the tracer (Kobori et al. 1999; Weber et al. 2001). During this time period, patients are encouraged to drink 1.0–1.5 L of tap water in order to distend the stomach and oesophagus. Hydro-MDCT scanning starts immediately after the ingestion of the last portion of tap water (250 mL) and effervescent gas-producing granules. Adequate distension of the oesophagus and stomach, using water and effervescent granulate as a negative contrast agent, is a prerequisite for assessing the wall of these organs (Ba-Ssalamah et al. 2009, 2011; Ulla et al. 2010).

In case of simultaneous FDG-PET/hydro-MDCT examinations, the patient remains on the examination table for both scans. Emission PET scans last between 3 and 5 min per bed position depending on the body weight (Halpern et al. 2004; Nagaki et al. 2011; Talanow and Shrikanthan 2010). Scans are corrected for decay, scatter, and randoms. There are various reconstruction algorithms for PET images. The most popular algorithm, ordered subset expected maximisation (OSEM), uses CT-derived attenuation correction (Boellaard et al. 2001; Kontaxakis et al. 2002). Axial and coronal reformatted scans of iodine contrast-enhanced hydro-MDCT are performed to match the PET section thickness. The examination of hydro-MDCT and fused FDG-PET is performed in the supine position from the top of the head to the mid-thigh.

The use of FDG-PET yields physiologic information that provides a means for diagnosing cancer based on altered tissue metabolism enabling co-registration of both anatomic and functional information obtained by hydro-MDCT (Bar-Shalom et al. 2005; Rampin et al. 2005). FDG-PET takes advantage of the principle that biochemical changes often precede or are more specific than the structural changes associated with any given disease process (Luketich et al. 1997; Hsu et al. 2009). Therefore, fused FDG-PET/MDCT offers the potential to show early oesophageal cancer or small lymph node metastases before any structural abnormality is detectable, or to exclude the presence of tumour in an anatomically altered structure. The tumour uptake of FDG, measured as the maximal standardised uptake value (SUVmax) in FDG-PET, even provides a quantitative estimate of tumour aggressiveness (Cerfolio and Bryant 2006).

Recent studies demonstrate that FDG-PET can be used not only for pretreatment staging, but also for the assessment of treatment response, detection of recurrence, and prediction of survival in patients with adenocarcinoma of the oesophagus (Hsu et al. 2009; Cerfolio and Bryant 2006). FDG-PET/CT more accurately shows the extent of disease than do other imaging methods, and this frequently leads to a radical change in patient management.

3 Oesophageal Cancer

Oesophageal cancer is one of deadliest cancers worldwide and is the sixth leading cause of death from malignancies (Edwards et al. 2002). Recent advances in the diagnosis, staging, and treatment of this neoplastic condition have led to small but significant improvements in survival. The lifetime risk of developing this cancer is 0.8% for men and 0.3% for women. The risk increases with age, and the mean age at diagnosis is 67 years (Edwards et al. 2002; Daly et al. 2000). More than 90% of oesophageal cancers are either squamous cell carcinomas or adenocarcinomas (Edwards et al. 2002). Rarely, carcinomas of other histologic types, including melanomas, gastrointestinal stroma tumours, carcinoids, and lymphomas, may develop in the oesophagus as well (Barr 2011). Smoking is associated with an increased risk of both squamous cell carcinoma and adenocarcinoma of the oesophagus (Wu et al. 2001; Brown et al. 2001). Individuals with recurrent symptoms of reflux have an eightfold increase in risk for oesophageal adenocarcinoma (Lagergren et al. 1999). Barrett's oesophagus

develops in approximately 5–8% of patients with gastrooesophageal reflux disease (Csikos et al. 1985). The relatively low incidence of oesophageal cancer, the absence of early symptoms, and the rarity of a hereditary cause of the disease (Romero et al. 2002) make prevention, surveillance, and evaluation-based screening untenable except in certain high-risk areas (Lagergren et al. 2000) of the world. Patients who are found to have Barrett's oesophagus, however, may be candidates for regular endoscopic surveillance (Yang et al. 2002).

Over the past 25 years, the nature of oesophageal cancer has changed from primarily a squamous cell neoplasm involving the mid-thoracic oesophagus in 50% of patients to adenocarcinoma of the gastrooesophageal junction in nearly two-thirds of cases (Daly et al. 2000; Siewert et al. 2001; Parfitt et al. 2006). Once cancer develops, it may spread rapidly. Only 2% of T1 cancers, but 38–60% of T2 cancers, are associated with extension of the disease to lymph nodes (Siewert et al. 2001; Stein et al. 2005). Therefore an accurate local staging in terms of (T staging) has a great impact on the therapeutic management (Ba-Ssalamah et al. 2011). At the time of the diagnosis of oesophageal cancer, more than 50% of patients have either locally unresectable tumours or radiographically detectable metastases (Pennathur and Luketich 2008). Thus, hydro-MDCT and even better combined PET/hydro-MDCT (if available) help to obtain an accurate staging and consequently to choose the most appropriate treatment option for those patients in a single examination (Wolf et al. 2011).

4 CT, PET/CT Imaging of the Oesophagus

4.1 Tumour Detection and Classification

From a morphological point of view, oesophageal carcinoma may manifest as a focal area of mural thickening with or without ulceration, as a flat or polypoid lesion, or as generalised mural thickening.

Since the thickness of individual layers of the normal oesophageal wall cannot be determined using CT with certainty because of the variable distensibility of its lumen, we use 3 mm as the upper limit of normal (Fig. 1); any increase beyond this is considered abnormal. Therefore, the following criteria, taken from the literature (Umeoka et al. 2010; Halvorsen and Thompson 1984; Moss et al. 1981; Lea et al. 1984; Picus et al. 1983; Quint et al. 1985; Thompson and Halvorsen 1994) and recently modified by Ba-Ssalamah et al. (Ba-Ssalamah et al. 2011), are used to determine the CT-T stage, according to

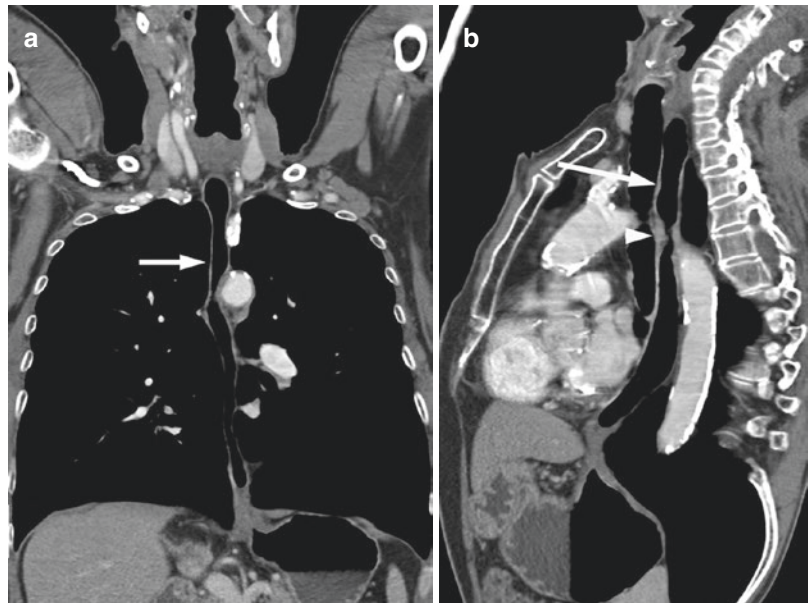

Fig. 1 Hydro-MDCT of the oesophagus in coronal (**a**) and sagittal (**b**) reformations to follow the course of the oesophagus, demonstrating the normal wall thickening of the oesophagus (≤3 mm) and homogeneous enhancement (*arrows*). *Note*: On the sagittal reformation, the physiologic angulation caused by the aortic arch with pseudothickening (partial volume) of the oesophageal wall (*arrowhead*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

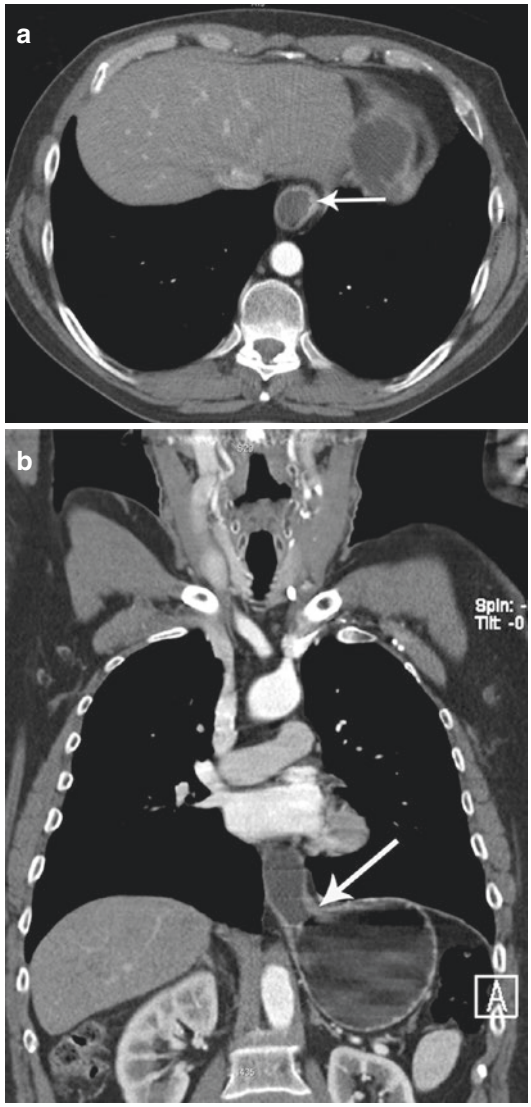

Fig. 2 Hydro-MDCT of the oesophagus in axial (**a**) and coronal (**b**) reformations shows a small focal polypoid lesion in the distal third of the oesophagus, with homogeneous enhancement in terms of the T1 tumour (*arrows*). The outer borders are smooth. Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

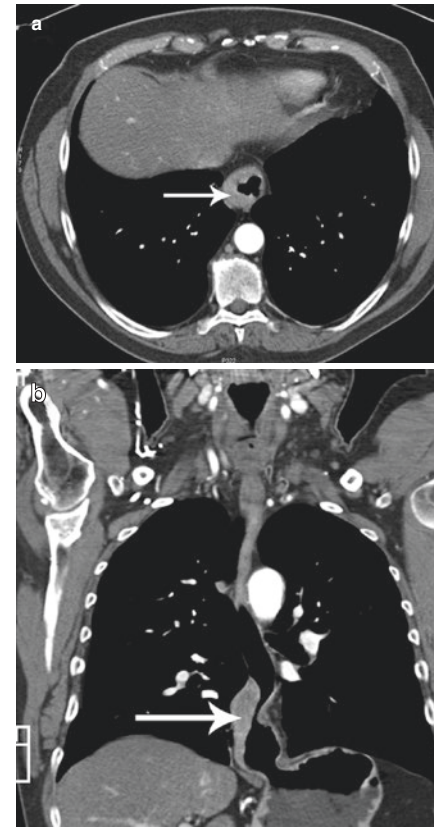

Fig. 3 Hydro-MDCT of the oesophagus in axial (**a**) and coronal (**b**) reformations shows a circumferential wall thickening 10 mm in depth in the middle third of the oesophagus, with homogeneous enhancement and smooth outer borders in terms of the T2 tumour (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

the TNM classification (pT) adapted by the AJCC 7th edition (Greene et al. 2002; Sobin and Wittekind 2002; Rice et al. 2010).

T1: Focal or circumferential wall thickening of >3 and ≤10 mm and/or intense enhancement of the oesophageal wall, without stenosis. The outer borders of the tumour are smooth (Fig. 2).

T2: Focal, polypoid, or diffuse circumferential thickening of the oesophageal wall >10 and ≤15 mm, with the possible presence of a mild stenosis. The outer borders of the tumour are either smooth or show stranding for less than one-third of the tumour extension (Fig. 3).

T3: Tumour appears symmetric or asymmetric, markedly diffuse or circumferential wall thickening of ≥15 mm, with mild-to-severe stenosis, and marked stranding for over one-third of the tumour extension, or extensive blurring of the outer border (Fig. 4).

T4: Tumour shows invasion into one of the adjacent structures, such as the pericardium, the diaphragm, the pleura (T4a), the tracheobronchial tree, or the aorta and spine (T4b), using the criteria described in the literature (Thompson and Halvorsen 1994) (Fig. 5).

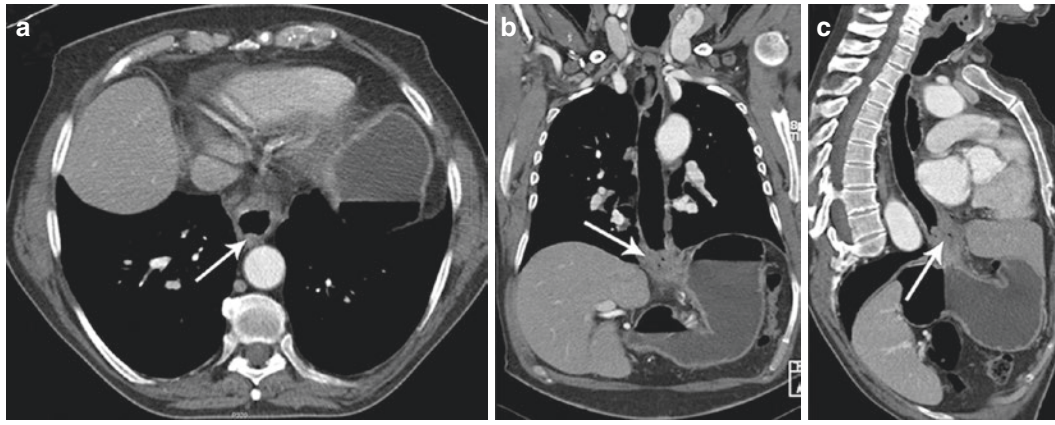

Fig. 4 Hydro-MDCT of the oesophagus in axial (**a**), coronal (**b**), and sagittal (**c**) reformations shows a markedly diffuse oesophageal wall thickening 18 mm in depth in the distal third of the oesophagus, with inhomogeneous enhancement and blurred outer borders in terms of the T3 tumour (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

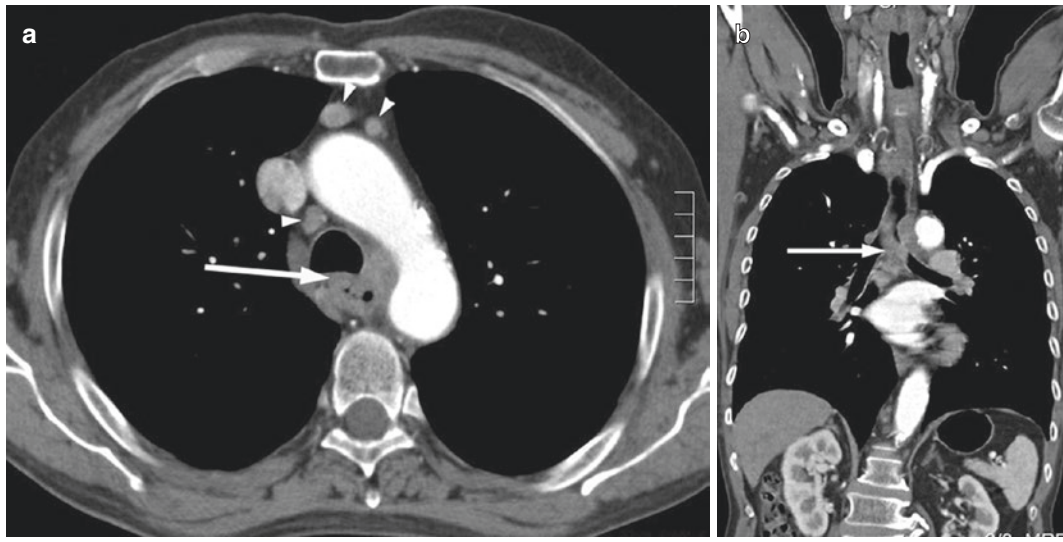

Fig. 5 Hydro-MDCT of the oesophagus in axial (**a**), and coronal (**b**), reformations shows a huge mass with inhomogeneous enhancement in the mediastinum arising from the oesophageal wall, with infiltration of the trachea (**a**, *arrow*), in terms of the T4 tumour; note the enlarged pathologic lymph node as stage N2 (**a**, *arrowheads*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

These structures may be invaded by contiguous tumour spread. However, it is often difficult to distinguish infiltration into these adjacent organs (T4) from a broad contact without infiltration. Evaluation for direct invasion by oesophageal cancer into adjacent vital structures by CT is based on two criteria: mass effect and loss of fat planes. When the trachea or bronchial wall is indented or displaced away from the spine by a tumour mass, then mass effect is present and invasion is presumed (Lagergren et al. 2000). Coronal or sagittal reformatted images are best suited for this purpose and seem to be helpful. The cardia is directly involved by carcinoma of the distal oesophagus in about 60% of patients according to the Siewert classification (AEG I–III) (Fig. 6) (Siewert 2007). The depiction of the anatomic location of the tumour and assessment of the degree of cardia involvement are crucial for the surgical strategy. This is a key factor to define gastric fundus involvement, since the stomach is the organ usually used as the first choice for reconstruction after esophagectomy.

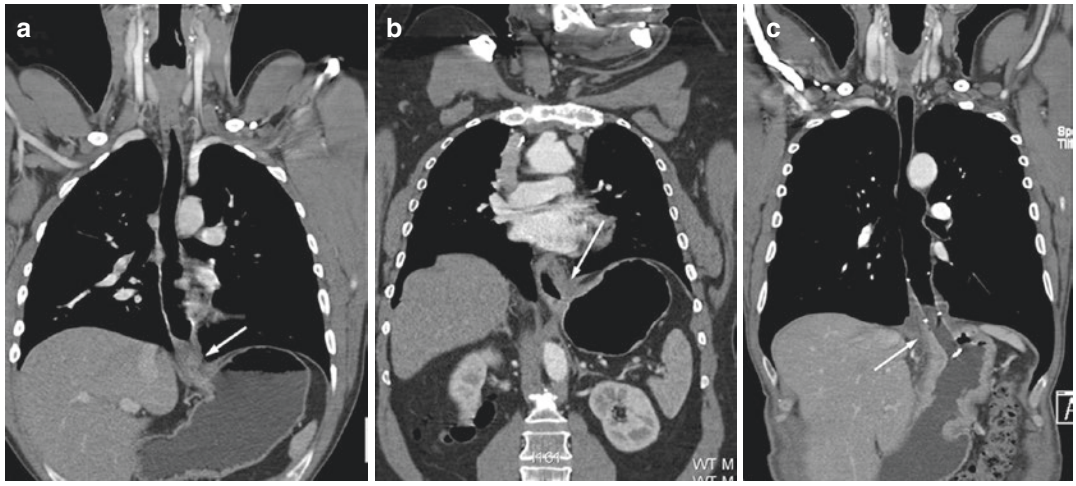

Fig. 6 Hydro-MDCT of the oesophagus in coronal reformations showing examples of large cancer in the lower third of the oesophagus at the gastroesophageal junction, with AEG I (**a**), AEG II (**b**), and AEG III (**c**). The differentiation between distal oesophageal cancer and gastric cancer located in the cardia is difficult in some cases. Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

In case of using fused FDG-PET/hydro-MDCT, tracer uptake is markedly helpful in the detection of even a small primary tumour and may be better in the estimation of its local staging and response to therapy (Fig. 7).

The sensitivity of FDG-PET for detecting primary oesophageal tumours has been reported to be 91–95% in prospective studies. Lowe et al. (2005) and Meyers et al. (2007) reported that 75 patients with oesophageal cancer PET correctly assessed T stage in 43%, understaged in 29%, and overstaged in 29%. Since PET scanners have a limited spatial resolution of about 5–8 mm, lesions smaller than 1 cm might not be detected; however, the combination of PET/CT and hydro technique may improve its efficiency.

N Staging. Lymphatic spread is found in 74–88% of patients with oesophageal carcinoma because of the abundant lymphatic vessels in the oesophagus (Siewert 2007). The frequency of lymphatic metastases is related to the T local staging including the size and depth of penetration of the tumour (Stein et al. 2005). The extensive mediastinal lymphatic drainage of the oesophagus, which communicates with abdominal and cervical collateral vessels, is responsible for the findings of mediastinal, supraclavicular, celiac lymph node metastases in at least 75% of patients (Thompson et al. 1983). According to the American Joint Committee on Cancer (Suga et al. 2005), N staging depends on the presence of positive locoregional or perioesophageal lymph nodes (affected lymph nodes) (Fig. 8). The N staging is explained according to the 7th edition (AJCC Cancer Staging Manual, 7th edition) as follows:

- N0 no regional lymph node metastasis
- N1 1–2 positive regional lymph nodes
- N2 3–6 positive regional lymph nodes
- N3 ≥7 positive regional lymph nodes

Lymph node assessment for metastatic spread remains a challenge, even with PET/MDCT. However, improved evaluation appears possible if morphology including size and shape, contrast enhancement pattern, as well as tracer uptake of lymph nodes are used (Blom et al. 2011; Okada et al. 2009). On CT perioesophageal lymph nodes are considered positive if they are ≥6 mm in diameter, and rounded in shape, and show marked or in homogenous contrast enhancement (Ba-Ssalamah et al. 2003). In case of FDG-PET there is no established SUV cutoff for lymph node metastases, although single institutions have their own cutoffs (Yu et al. 2011; Kato et al. 2009). However, in general, lymph nodes are considered involved if they show an FDG uptake that is higher than the background. A meta-analysis of 12 studies (n = 490) examined the diagnostic accuracy of FDG-PET in preoperative staging of oesophageal cancer and reported sensitivity and specificity for detecting

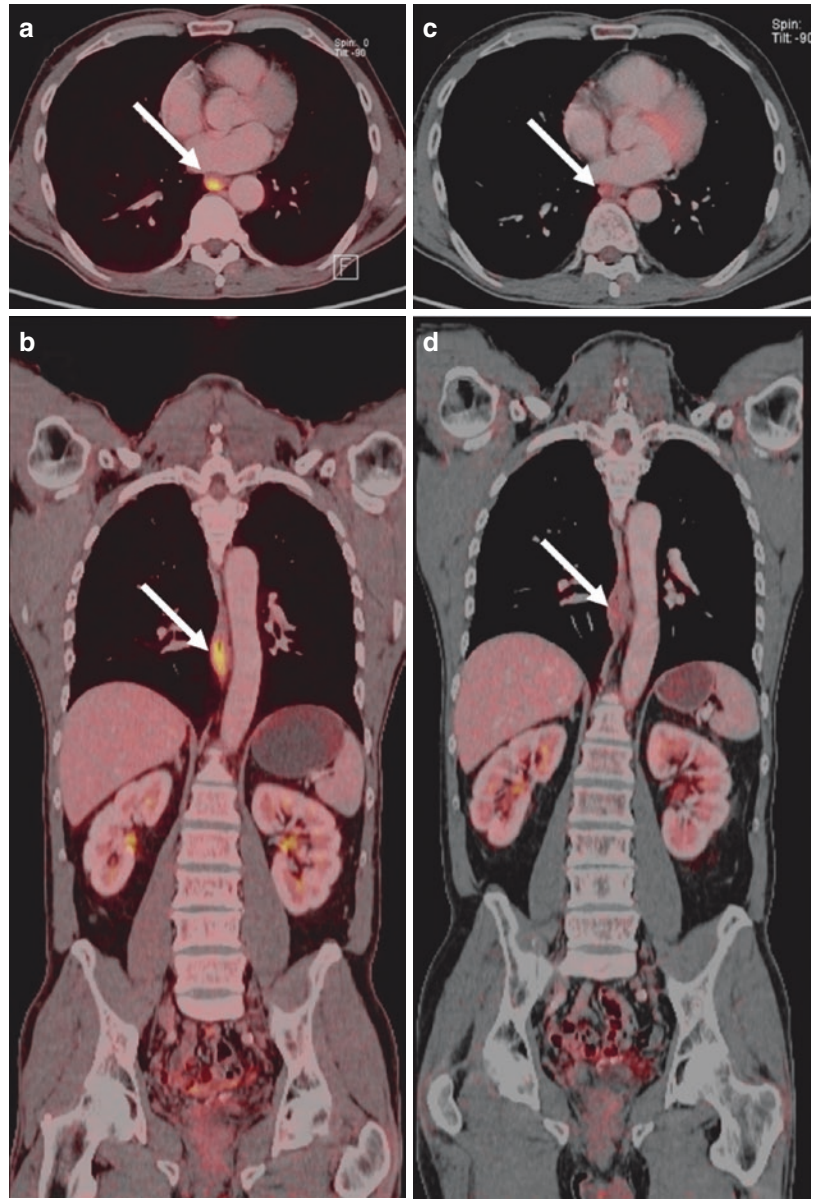

Fig. 7 FDG-PET/CT of a patient with oesophageal cancer in axial and coronal reformations. The area of the untreated tumour shows intense FDG uptake (**a**, **b**, *arrows*). After treatment no FDG uptake is appreciated (**c**, **d**, *arrows*). Histopathological workup after resection confirmed no viable tumour tissue. Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

locoregional lymph node involvement of 51% and 84%, respectively (van Westreenen et al. 2004).

M Staging. Hematogenous metastases from oesophageal carcinoma most commonly involve the liver because the oesophagus is drained by the portal vein (Fig. 8). Other less common sites of hematogenous spread include the lungs, adrenal glands, kidneys, bones, and brain. Lymph node involvement outside a perioesophageal location is considered M1 disease (Nomura et al. 2012). Advanced distal cancers can develop peritoneal metastases (Fig. 9).

FDG-PET is most helpful in distinguishing potentially resectable, locally advanced disease (T3–4, N0, M0) from distant disease (M1). In prospective studies M1 disease was detected by FDG-PET and missed by CT (with or without EUS) in 5–7% of cases (Meyers et al. 2007; Heeren et al. 2004). M1 disease was detected by FDG-PET and missed by CT in 6–15% of patients (Flamen et al. 2000; Meyers et al. 2007; Heeren et al. 2004).

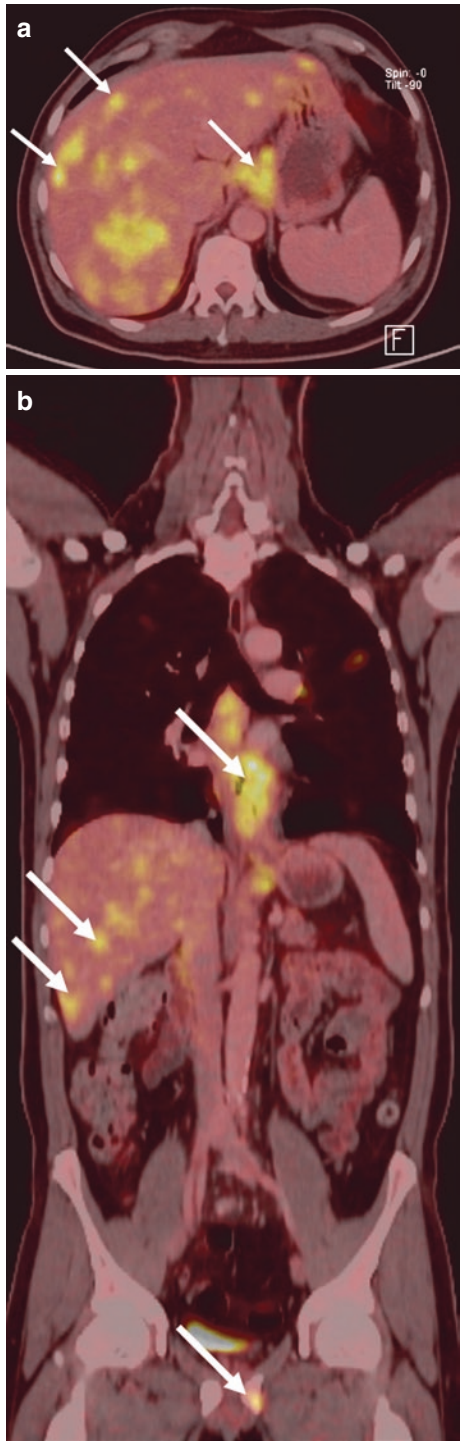

Fig. 8 FDG-PET/CT of a patient with distal oesophageal cancer in axial and coronal reformations. There is an intense FDG uptake in the area of primary tumour as well as in the liver and left pubic bone indicating distant metastases (**a**, **b**, *arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

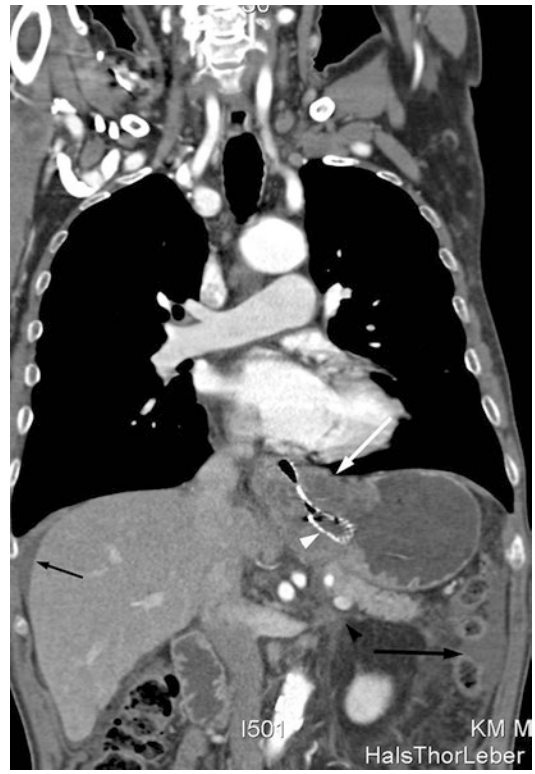

Fig. 9 Hydro-MDCT of the oesophagus in coronal reformations shows a distal oesophageal cancer (*white arrow*) with marked ascites (*small black arrow*), and diffuse stranding of the mesenteric root (*black arrowhead*) indicative of peritoneal carcinomatosis (*large black arrow*). Note the oesophageal stent (*white arrowhead*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

4.2 Follow-Up After Oesophagectomy

Tumour recurrence of oesophageal cancer can be divided into locoregional recurrence and distant metastatic disease. The rate of recurrence of oesophageal cancer even after curative surgery was found to be high in most reports (AJCC 2009). In the detection of tumour recurrence, the selected imaging modalities are important in many regards. First of all, the imaging modality must be suitable and cost effective, and able to detect the pathology in the early stages. After oesophagectomy and gastric excision, the anatomy of the posterior mediastinum is markedly changed. This makes assessment of possible local tumour recurrence difficult. Wall thickening or adjacent mass and suspicious lymph

nodes are highly predictive for recurrent disease (AJCC 2009). Hydro technique in combination with FDG-PET/MDCT is again the modality of choice in early detection of recurrent tumour (Guo et al. 2007).

4.2.1 CT Findings

Locoregional recurrent oesophageal tumour is well demonstrated by CT. A smooth or spiculated area of extrinsic mass effect on the mediastinal border can be visualised by CT. Furthermore, MDCT with multiplanar reformations is accurate in detecting masses after oesophageal surgery and superior for distant metastatic disease, and can accurately delineate the neoesophagus and its surroundings (Fig. 10). However, differentiating between fibrosis and tumour tissue at CT is based on indirect signs and may be difficult or even impossible in some cases. FDG-PET/MDCT can overcome this limitation (Sun et al. 2009; Carlisle et al. 1993; Tunaci 2002). Early postoperative cases with possible inflammatory reactions or early post-radiation changes, in particular, must be interpreted with caution.

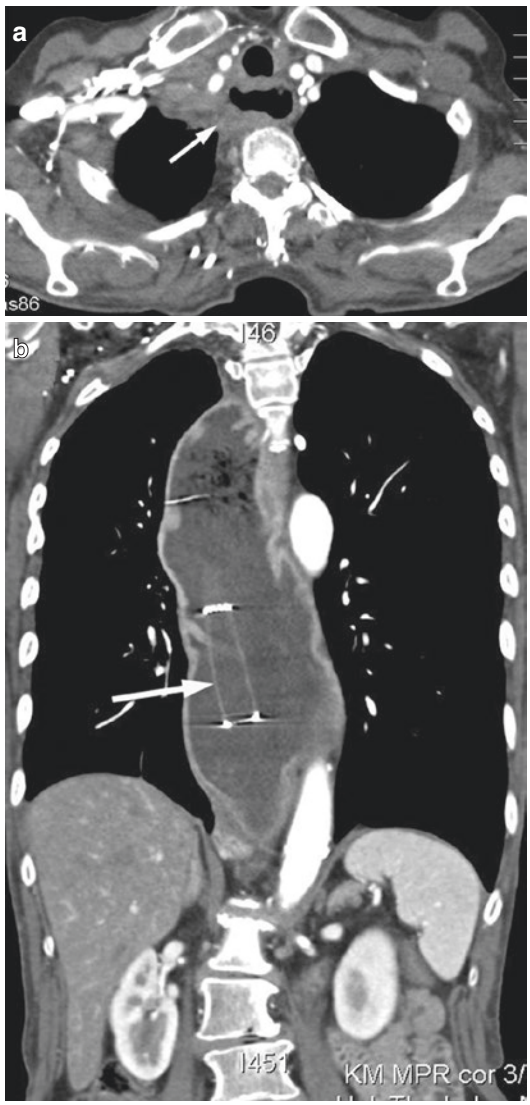

Fig. 10 Hydro-MDCT of the oesophagus in axial (**a**) and coronal (**b**) reformations in a patient with a clinical history of oesophageal cancer and esophagectomy and gastric transposition. We can detect a recurrence demonstrated as a solid mass with inhomogeneous enhancement at the anastomosis site (*right side cervical*, **a**, *arrow*). Note the stent dislocation (**b**, *arrow*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

5 Other Oesophageal Malignancies

5.1 Oesophageal Lymphoma

The oesophagus is the alimentary organ least commonly involved with lymphoma; therefore lymphoma of the oesophagus is rare. Any histologic variety of lymphoma may affect the oesophagus (Mendelson and Fermoyle 2005). To diagnose primary oesophageal lymphoma, the following criteria have been proposed: (a) predominantly oesophageal involvement with only regional lymph node involvement; (b) no definite enlargement of mediastinal lymph nodes; (c) no involvement of liver and spleen; and (d) no superficial lymphadenopathy (Kaplan 2004).

5.1.1 CT and PET/CT Findings

CT may demonstrate a homogeneously enhancing mass with irregular borders or sharply delineated, pronounced, polypoid wall thickening in any part of the oesophagus (Fig. 11), with or without associated lymphadenopathy. Lymphoma may infiltrate the entire oesophagus diffusely. While splenic involvement is suggestive of lymphoma, hepatic metastases are characteristic of oesophageal cancer. There is no specific CT finding for oesophageal lymphoma. PET/CT scans can also be used in staging patients with primary oesophageal lymphoma, as well as for monitoring these tumours

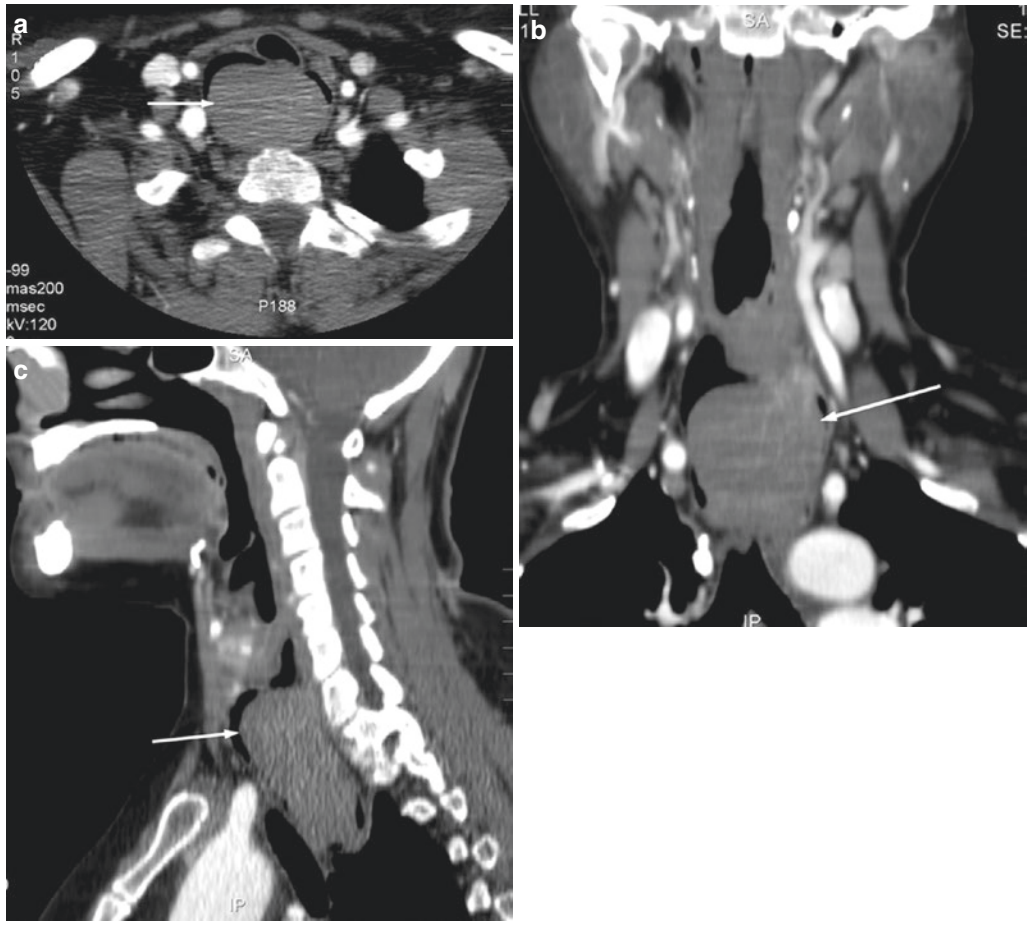

Fig. 11 Hydro-MDCT of the oesophagus in (**a**), coronal (**b**), and sagittal (**c**) reformations in a patient with surgically proven lymphoma shows a large polypoid mass in the cervical oesophagus (*arrows*) without infiltration of the oesophageal wall. Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

after therapy (Suga et al. 2009). However, the availability of FDG/PET and, in particular, FDG-PET/CT, is still limited and expensive.

5.2 Leiomyoma and GIST

Leiomyoma accounts for 60–70% of all benign oesophageal neoplasms and is the most common benign tumour of the oesophagus while rare in the remaining gastrointestinal tract (Hatch et al. 2000; Seremetis et al. 1976; Simmang et al. 1989). The tumour is present more often in male patients (2:1) at a median age of 30–35 years. Usually, leiomyomas are between 2 and 8 cm in diameter. They are multiple in less than 3% of cases. More than half of the patients with oesophageal leiomyoma are asymptomatic. Typical complaints are either dysphagia or substernal chest pain due to obstruction of oesophageal bolus transit. Gastrointestinal stromal tumours (GISTs) are the most common nonepithelial tumours of the gastrointestinal tract, although they are rare in the oesophagus (Monges et al. 2010).

5.2.1 CT Findings

Enhanced CT scans reveal a smooth or lobulated tumour margin, with either iso- or homogeneously low attenuation. Leiomyoma and GIST may appear as a well-circumscribed, intensely enhancing mass or may be a sessile (Fig. 12), pedunculated, polypoidal, exophytic intraluminal solid mass, sometimes with secondary ulceration. Leiomyomas are the only tumours that may contain calcification (Fig. 13). Absence of infiltration

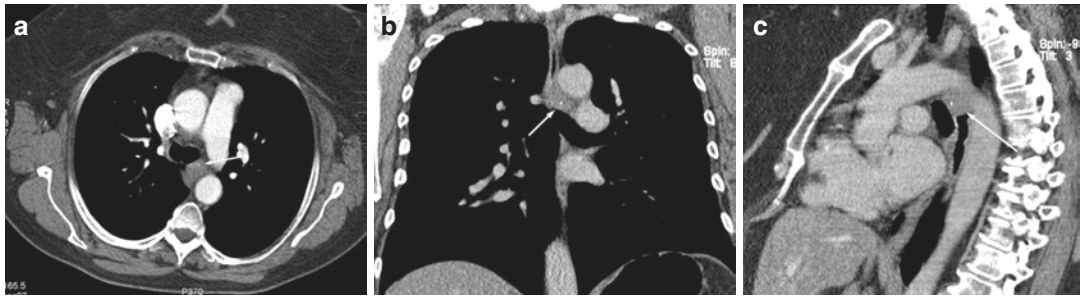

Fig. 12 Hydro-MDCT of the oesophagus in axial (**a**), coronal (**b**), and sagittal (**c**) reformations in a patient with leiomyoma, demonstrated as a small soft-tissue mass with slight calcifications in thoracic area of the oesophagus (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved)

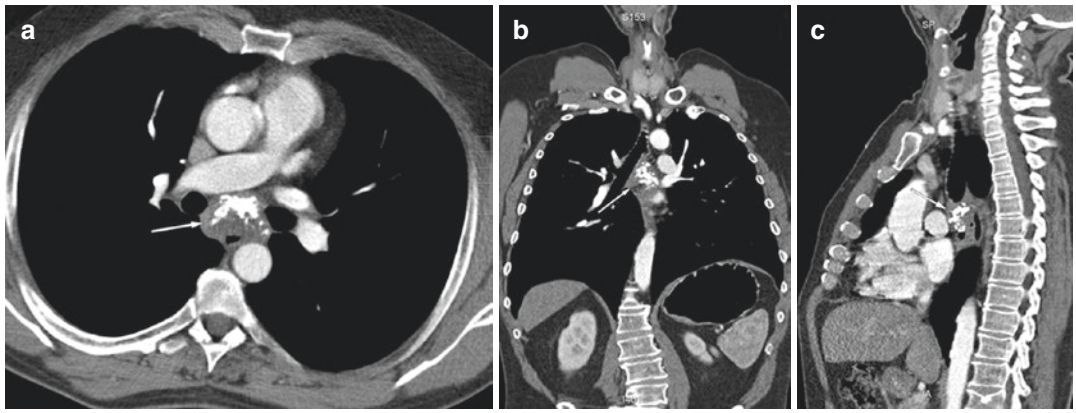

Fig. 13 Hydro-MDCT of the oesophagus in axial (**a**), coronal (**b**), and sagittal (**c**) reformations in a patient with biopsy-proven leiomyoma, demonstrated as a large tumour-like mass with marked calcifications invading the oesophagus in the thoracic area (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

of the oesophageal wall or the absence of the typical circumferential growth pattern enables differentiation from oesophageal cancer. GISTs may not change in size or may even enlarge during therapy, but show a decrease in CT attenuation values (Hounsfield units, HU) (Choi et al. 2004). PET/CT is able to show early effects in patients undergoing treatment. Functional imaging proved significantly more accurate than CT alone when assessing GIST response to therapy. Combined PET/CT imaging is, therefore, a valuable diagnostic tool for the primary diagnosis of GISTs or for the assessment of therapeutic response (Suga et al. 2009; Antoch et al. 2004).

5.3 Fibrovascular Polyps

Fibrovascular polyps of the oesophagus are rare benign tumours, comprising about 1% of all benign oesophageal tumours. However they are the most common intraluminal benign tumours of the oesophagus (Sargent and Hood 2006). Giant fibrovascular polyps are defined as polyps larger than 5 cm in maximum diameter. Even though they are benign, they may be lethal due to either bleeding or, rarely, asphyxiation if a large polyp is regurgitated. Patients commonly present with dysphagia or hematemesis.

5.3.1 CT Findings

The polyps may not be well visualised on endoscopy and imaging plays a vital role in aiding diagnosis as well as providing important information for preoperative planning, such as the location of the pedicle, the vascularity of the polyp, and the tissue elements of the mass. These polyps contain predominantly fibrovascular and fatty tissue, which gives them their typical CT appearance of a pedunculated intraluminal mass of fat density, which expands the oesophagus (Ascenti et al. 1999).

5.4 Oesophageal Fistula

Oesophageal fistulas can be classified according to their anatomic relationship into oesophageal-airway, oesophago-pleural, aorto-oesophageal, and oesophago-pericardial fistulas. Oesophageal-airway fistulas can be either congenital (so-called tracheo-oesophageal fistulas) or acquired. The development of an oesophageal-airway fistula is a life-threatening complication of oesophageal cancer or secondary to oesophageal trauma, infection, or radiochemotherapy. Initial symptoms most often include cough, aspiration, and fever, frequently culminating in pneumonia. More than half such fistulas involve the trachea; alternatively, a connection with the left or right main or lower lobe bronchus may be formed. Patients with oesophageal-airway fistulas are treated with covered stents to seal off the leak. CT may be necessary to localise the fistula and to aid in treatment planning. CT can also be used to detect pleuro-plumonary or mediastinal inflammatory reactions to oesophageal fistulae (Peyrin-Biroulet et al. 2006; Liu et al. 2006).

5.4.1 CT Findings

CT can demonstrate a fistulous connection between the oesophagus and the tracheobronchial system, pleura, pericardium, or mediastinal fat if the fistulous tract is of sufficient size and contains air or oral contrast medium. Oral administration of dilute iodine contrast material (contrast material:water 1:100) can help to delineate the fistula. CT can also detect perifocal reactions in the form of empyema, pneumonia, or mediastinitis (Fig. 14).

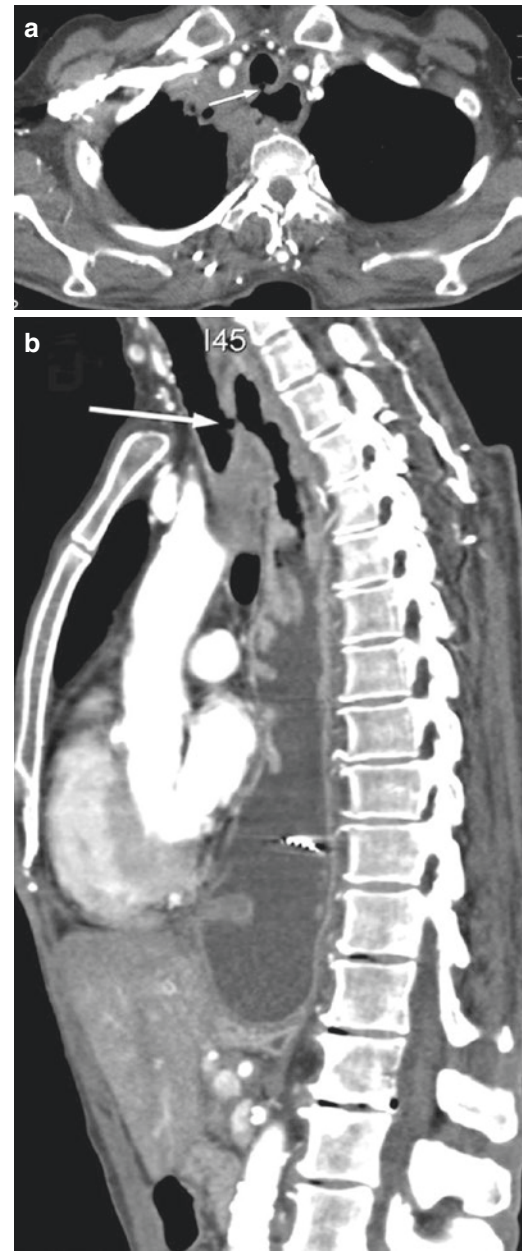

Fig. 14 Hydro-MDCT of the oesophagus in axial (**a**) and sagittal (**b**) reformations in a patient with a clinical history of oesophageal cancer with symptoms suspicious for fistula, due to continuous coughing and recurrent pneumonia, shows a fistula tract between the tumour and the trachea (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

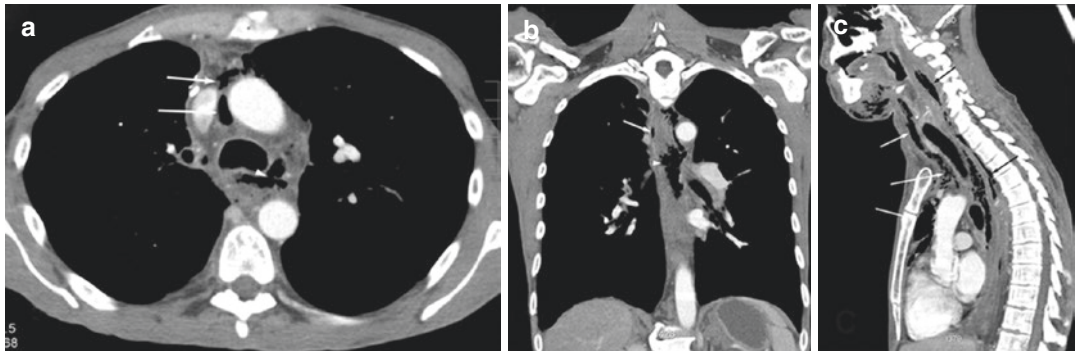

Fig. 15 Hydro-MDCT of the oesophagus in axial (**a**), coronal (**b**), and sagittal (**c**) reformations in a patient with oesophageal perforation after dilation of tumour stenosis. CT scan shows pneumomediastinum, and air bubbles in the mediastinum (**a**, **b**, *arrows*), as well as a tissue defect of the oesophageal wall (*arrows*), and extensive soft-tissue emphysema in the cervical region (**c**). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved.

5.5 Oesophageal Perforation

Oesophageal injuries include penetrating injuries, blunt traumatic perforation, iatrogenic perforation, as well as spontaneous perforation due to a sudden rise in intraluminal pressure during vomiting (so-called Boerhaave syndrome). Most often, oesophageal perforation occurs during endoscopic investigation of malignant disease and presents a difficult problem. Oesophageal diseases, such as strictures, achalasia, and tumours, predispose the oesophagus to perforation. Oesophageal perforation is associated with high mortality, and postoperative leaks occur frequently after primary surgical repair (Chao et al. 2005). Early and accurate diagnosis of oesophageal perforation is critical, because the consequences of missed oesophageal injury are devastating, with potential progression to fulminate mediastinitis and septic shock. Delay in treatment beyond 24 h after onset may adversely affect prognosis. Contrast studies are the method of choice to demonstrate oesophageal rupture. CT has been increasingly used for the diagnosis of oesophageal injuries (LeBlang and Nunez 1999).

5.5.1 CT Findings

Radiographic detection of oesophageal injuries relies on the presence of indirect radiological signs, including subcutaneous or muscular, thoracic or cervical emphysema, a widened mediastinum, pneumomediastinum, pneumopericardium, left-sided pneumothorax, pleural effusion, an abnormal course of a nasogastric tube when it is inserted, and a left lower lobe atelectasis. CT can also display subtle signs such as localised oesophageal wall thickening, mucosal hyperemia, mucosal dissection, and oesophageal hematoma, as well as oedema (De Lutio di Castelguidone et al. 2005). CT also allows the visualisation of very small collections of mediastinal air in cases with small tears (Fig. 15).

6 Other Conditions

6.1 Achalasia

Achalasia is a primary rare motor disorder of the oesophagus, with an incidence of about 1/100,000. Symptoms usually become manifest in early adult age, but even children may be

affected. Achalasia is characterised by incomplete relaxation of the lower oesophageal sphincter (LES) on swallowing and aperistalsis of the oesophageal body (Gelfand and Botoman 1987). In 1947, Ogilvie recognised the syndrome of neoplastic involvement of the distal oesophagus that mimicked idiopathic achalasia, with submucosal infiltration of the lower oesophagus and cardia by carcinoma, which is now commonly referred to as pseudoachalasia (Carter et al. 1997). Therefore, CT can be helpful in differentiating between achalasia and pseudoachalasia of malignancy. Usually endoscopy and biopsy are used to detect tumour spread in pseudoachalasia. However, CT may be used in suspect cases, when submucosal tumour growth escaped endoscopic detection. Moreover, CT may delineate the presence of other tumour manifestations (Carter et al. 1997).

6.1.1 CT Findings

CT shows uniform dilatation that affects a long segment of the oesophagus, with no wall thickening and with normal-appearing boundary surfaces and mediastinal fat. The oesophagus narrows abruptly at the oesophagogastric junction with no evidence of an intramural or extrinsic obstructive lesion (Fig. 16). In contrast to a stricture, the oesophageal wall is not thinned at the site of the narrowing, and the wall is not thickened as it is with the oesophageal tumour or oesophagitis. Most pseudoachalasia patients have CT findings of oesophageal dilation, more marked and/or asymmetric wall thickening, or mass. In this group, asymmetric or marked thickening (>10 mm) indicates pseudoachalasia.

6.2 Diverticula

Oesophageal diverticula are divided into the pulsion or traction type. The two predominant locations of oesophageal diverticula are the mid-oesophagus (at the level of the tracheal bifurcation) and the distal oesophagus (so-called epiphrenic diverticula). Diverticula are incidental findings at CT (Pearlberg et al. 1983).

6.2.1 CT Findings

Diverticula appear as an air-, water-, or contrast-filled bulge. Mid-oesophageal and epiphrenic diverticula are better visualised on coronal or sagittal (Fig. 17) reformations on hydro-MDCT. The most frequent location is posteroinferior to the cricoid cartilage, the so-called Zenker's diverticulum, which actually is a pharyngeal diverticulum (Fig. 18).

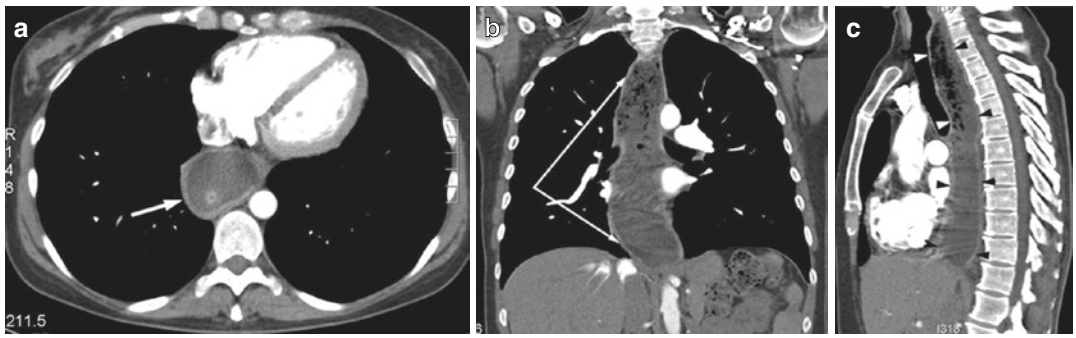

Fig. 16 Hydro-MDCT of the oesophagus in a patient with primary achalasia shows a marked diffuse dilatation of the entire oesophagus, which is filled with fluid and food without wall thickening and malignancy (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

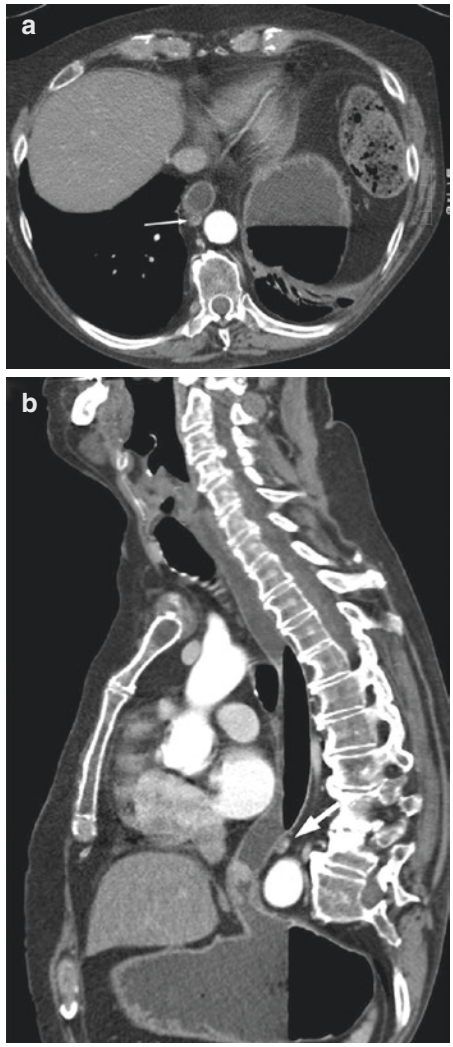

Fig. 17 Hydro-MDCT of the oesophagus in axial (**a**) and sagittal (**b**) reformations shows a small, circumscribed bulge at the gastroesophageal junction, representing a small diverticulum (*arrow*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

6.3 Duplication Cyst

Duplication cysts of the oesophagus are rare congenital anomalies that may be noted incidentally on conventional chest radiographs as an indeterminate mediastinal mass and require further investigation by CT (Kuhlman et al. 1985).

6.3.1 CT Findings

Duplication cysts are smoothly marginated, homogeneous masses with water-equivalent attenuation that most commonly occur in the lower oesophagus (60%). They are intimately related to the oesophagus but rarely communicate with it. The cyst may have a paraoesophageal or an intramural location (Fig. 18).

6.4 Hiatal Hernia

Oesophageal hiatal hernias comprise two types: sliding axial hernia and paraoesophageal hernia (Eren and Ciris 2005). Sliding hiatal hernia is a displacement of the upper stomach with the cardioesophageal junction upward into the posterior mediastinum. In the paraoesophageal type, all or part of the stomach herniates into the thorax with an undisplaced gastrooesophageal junction. Haemorrhage, incarceration, obstruction, and strangulation of the stomach and intestine are the most common complications.

6.4.1 CT Findings

Axial herniation of the stomach results in a large retrocardiac mass and the cardia is displaced into the thoracic cavity. With CT, the demonstration

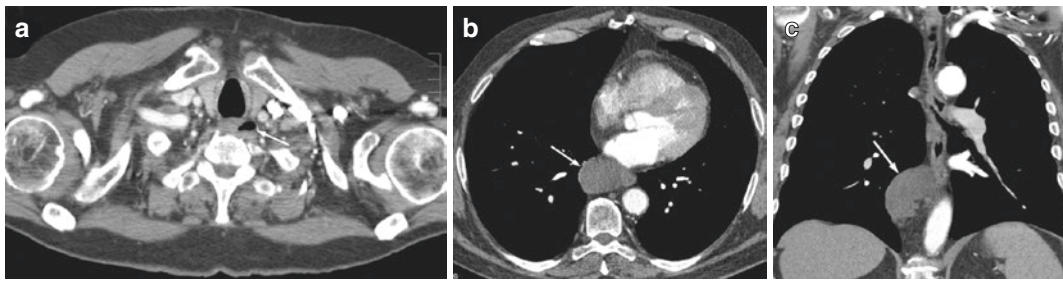

Fig. 18 Hydro-MDCT of the oesophagus in axial (**a**, **b**) and coronal (**c**) reformations in a patient with a small Zenker's diverticulum, lateroposterior to the upper oesophagus filled with air (**a**, *arrow*), and a duplication cyst, which appears as a smoothly marginated homogeneous mass with water-equivalent attenuation in the lower oesophagus (**b**, **c**, *arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

of gastric folds is frequent and pathognomonic. A good distension of the stomach and oesophagus is very helpful in the differential diagnosis. A paraoesophageal hernia is associated with fixation of the gastric cardia and portions of the stomach herniated alongside the oesophagus. "Upside-down stomach" is an extreme form of hernia, in which all of the stomach has herniated into the thoracic cavity and no portions of the stomach can be detected below the diaphragm (Fig. 19).

6.5 Oesophagitis

Inflammation of the oesophagus is not an indication for CT. Oesophagitis may be noted incidentally during the course of a CT staging examination or follow-up (Berkovich et al. 2000). High-grade oesophagitis manifests in 33–41% of patients with malignancies, who are treated with concurrent chemoradiotherapy. Painful oesophagitis decreases the nutritional status of patients and can lead to treatment interruptions, which in turn adversely affects survival.

6.5.1 CT Findings

The inflamed oesophageal mucosa shows uniform, circumferential wall thickening that usually involves a relatively long oesophageal segment. Inflammatory and neoplastic wall changes cannot be reliably distinguished based on CT morphology. Short segments of ulcerative wall thickening are more suggestive of a malignant lesion, while longer segments are more consistent with an inflammatory process. The most common CT findings are a thickened oesophageal wall and a target sign. Although endoscopy is a more sensitive modality for detecting this condition, the CT finding of a relatively long segment of circumferential oesophageal wall thickening, with or without a target sign, should suggest the diagnosis of oesophagitis in the proper clinical setting (Fig. 20).

6.6 Oesophageal Varices

Varices of the oesophagus are mainly caused by portal hypertension. In this case gastric varices communicate with the oesophageal and perioesophageal veins, which are drained via the azygos/hemiazygos venous system to the superior vena cava (Balthazar et al. 1987).

6.6.1 CT Findings

Oesophageal varices are best visualised in the portal venous phase or in the delayed phase after administration of contrast material.

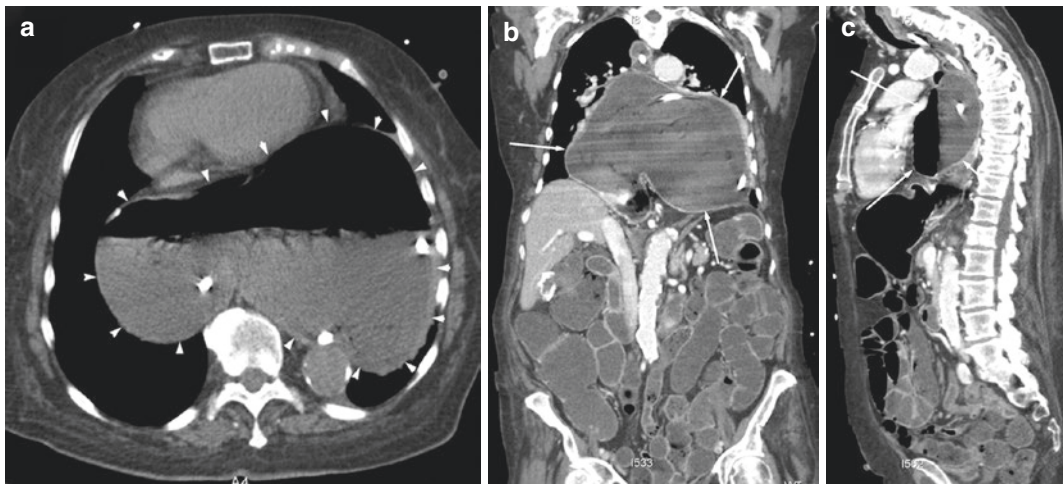

Fig. 19 Hydro-MDCT of the oesophagus in axial (**a**), coronal (**b**), and sagittal (**c**) reformations shows a large paraesophageal hernia with the so-called upside-down stomach, which is an extreme form in which all of the stomach has herniated into the thoracic cavity and no portions of the stomach can be detected below the diaphragm (*arrows* and *arrowheads*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

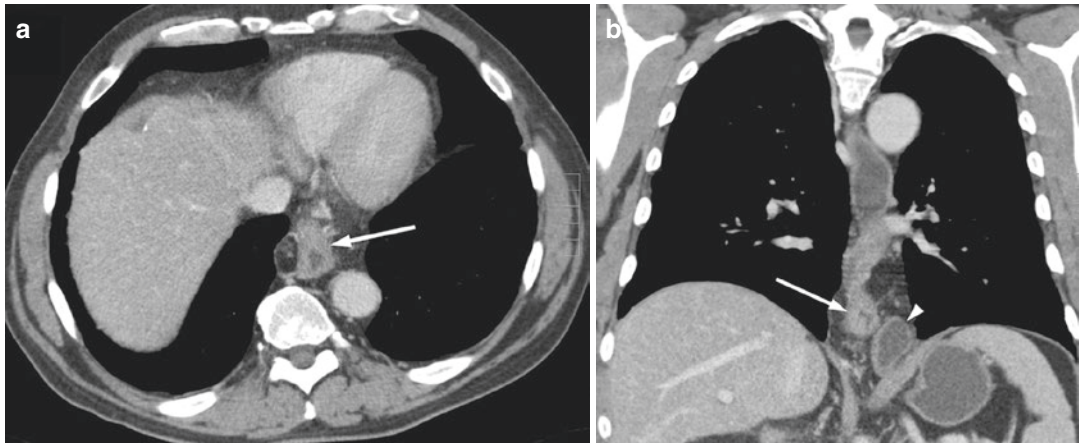

Fig. 20 Hydro-MDCT of the oesophagus in coronal reformation shows a small axial herniation of the stomach that results in a small retrocardiac mass, and the cardia is displaced into the thoracic cavity (*arrowheads*). The gastroesophageal junction and distal oesophagus show marked wall thickening due to reflux oesophagitis (*arrow*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

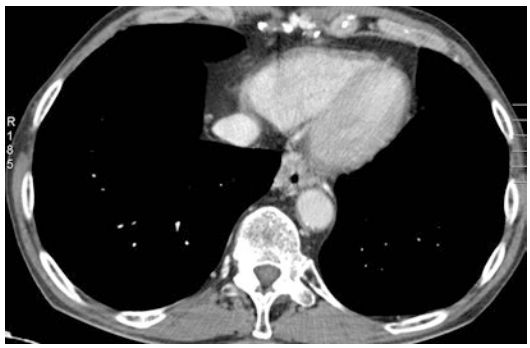

Fig. 21 Hydro-MDCT of the oesophagus in the axial reformation (venous phase) views in a patient with oesophageal varices, which appear as brightly enhancing dot-like structures within the oesophageal wall (*arrows*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

Oesophageal varices present as intraluminal (intramural, submucous) tubular, often dot-like structures that show marked pooling of intravenous contrast medium (Fig. 21). Paraoesophageal varices are often larger and have a more serpiginous structure. CT criteria for oesophageal varices are defined more specifically as nodular or tubular enhancing lesions within the oesophageal wall that contact the intraluminal surface, thus distinguishes oesophageal from paraoesophageal varices. While oesophageal varices can be appreciated easily by endoscopy, paraoesophageal varices are only seen on CT or endoscopic sonography (Fig. 22).

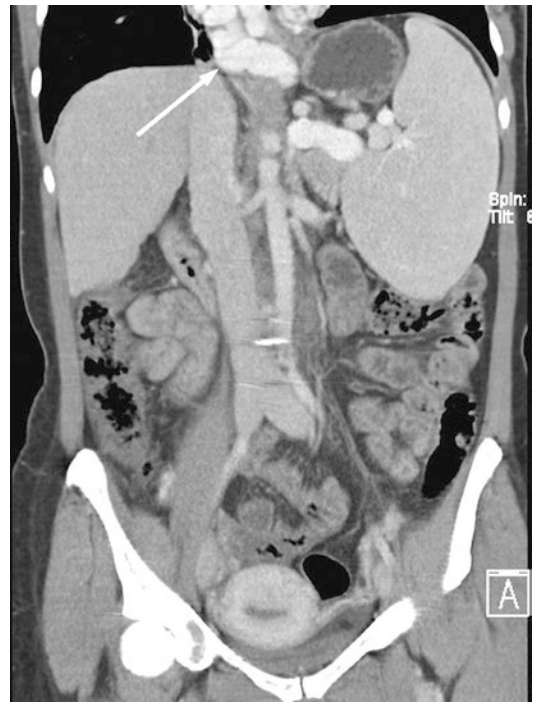

Fig. 22 Hydro-MDCT of the oesophagus in the coronal view in a patient with paraoesophageal varices, which appear as brightly enhancing tortuous veins adjacent to the oesophageal wall (*arrow*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

6.7 Dysphagia Lusoria and Aortic Disease

Aberrations in the course of the aortic arch or supraaortic branches can displace or compress the proximal oesophagus, leading to dysphagia. The most frequent cause is an anomalous right subclavian artery that arises from the descending aorta as a fourth supra-aortic branch and passes behind the oesophagus that rarely causes dysphagia (dysphagia lusoria) (Fig. 23). Other causes are a duplicated aortic arch or an aortic aneurysm. In cases of an anomalous right subclavian artery its aortic origin may be wide due to a congenital aortic diverticulum (Kommerell's diverticulum) (Fig. 24). In this case dysphagia is more likely due to compression of the oesophagus (Keum et al. 2006). CT angiography has

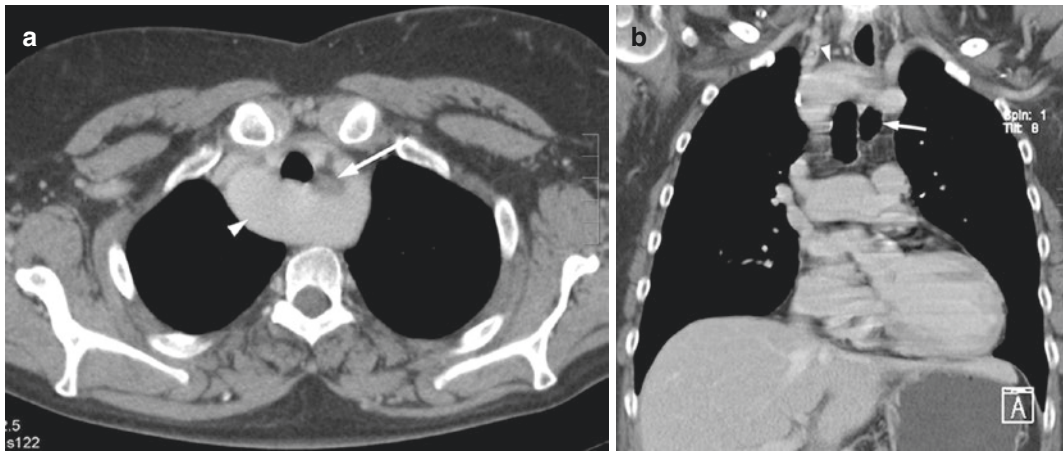

Fig. 23 Hydro-MDCT of the oesophagus in axial (**a**) and coronal (**b**) reformations shows an abberrant right subclavian artery (*arrowhead*) that courses more posteriorly to the compressed oesophagus (*arrow in* **a**), indicative of dysphagia lusoria. Note the non-compressed oesophagus distally (*arrow* **b**). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

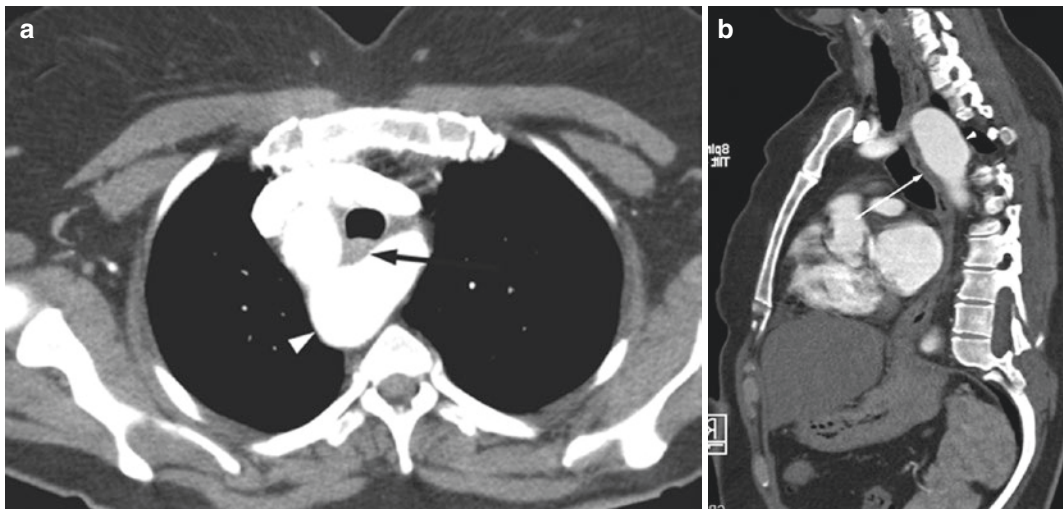

Fig. 24 Hydro-MDCT of the oesophagus in axial (**a**) and sagittal (**b**) reformations shows a right-sided aortic arch with retro-oesopahgeal left subclavian artery (lusoria type) arising from an aortic diverticulum of Kommerell (*arrowhead*), which must not be confused with an aneurysm of the origin of the subclavian artery. The oesophagus is compressed (*arrow*). Published with kind permission of Medical University of Vienna 2017. All Rights Reserved

already replaced invasive DSA in the evaluation of thoracic vascular anomalies and has become the diagnostic procedure of first choice.

6.7.1 CT Findings

Contrast-enhanced MDCT allows the diagnosis of the variants of the aortic arch very easily. The aberrant right subclavian artery, or dysphagia lusoria, demonstrates a typical pattern on contrast-enhanced MDCT and is more easily diagnosed using multiplanar reconstructions. It arises more posteriorly than normal, and runs behind the oesophagus (Fig. 23). An aortic diverticulum appears as a circumscribed asymmetric aneurysm like protrusion from wide funnel-shaped origin of the subclavian artery in the distal aortic arch (Fig. 24).

7 Clinical Value of Multi-Detector CT

Hydro-MDCT especially in combination with FDG-PET is particularly useful in the evaluation and initial staging of patients with oesophageal carcinoma as well as for treatment planning and assessing tumour response to therapy. At present, CT or FDG-PET/CT plays a major role as a triage tool to aid in choosing the appropriate treatment for patients with oesophageal cancer. FDG-PET/CT may help distinguish between surgical candidates with limited disease and possible curative surgery or patients who need preoperative chemoradiation for downstaging, and patients who need only palliative therapy in advanced cases with distant metastases. Thus, the pre-surgical assessment of patients with oesophageal cancer with surgical exploration prior to the decision about further therapeutic procedures can be avoided. If CT or PET/CT depending on availability shows definitive advanced disease with extended tumour spread, pre-surgical chemotherapy is used to downstage the tumour. After completion of chemotherapy, restaging of the tumour will be performed. If there is a positive response to chemotherapy, curative surgical therapy will be attempted. Therefore, preoperative staging of oesophageal cancer appears to be, by far, the most important indication for FDG-PET/CT of the oesophagus. In addition, multi-detector CT plays an important role in the evaluation of postoperative complications and detection of tumour recurrence following oesophagectomy. MDCT can determine the presence, location, and severity of oesophageal perforations. Furthermore, hydro-MDCT is an evolving method for the assessment of other intra- and extraluminal processes of the oesophageal wall.

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Endoscopy of the Pharynx and Oesophagus

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1 Introduction

The pharynx and oesophagus belong to the upper digestive tract; their morphology and function enable normal swallowing. Dysphagia is one of the main symptoms in patients with laryngeal, pharyngeal and oesophageal diseases. Diagnostics need to consider the entire swallowing chain from the oral cavity to the stomach. However, there is a close relationship between diseases of the pharynx, larynx and oesophagus: gastrointestinal disorders, e.g. reflux disease, may show extraoesophageal manifestations in the pharynx and larynx, and in case of tumours in the upper aerodigestive tract or oesophagus, there may occur additional simultaneous tumours urging for early diagnosis.

For diagnostic evaluation, endoscopy has emerged as the "first-line" examination. Technical progress has improved the quality of endoscopic imaging and enabled video documentation in clinical routine. In addition to the endoscopic visualization of the aerodigestive tract, biopsies allow histological diagnosis, recently assisted by molecular diagnostics like PCR. A huge variety of therapeutic manipulations can be performed. Together with radiology, endoscopy has become indispensable in the management of diseases of the pharynx and oesophagus. A main focus of diagnostic interest is the differential diagnosis between structural diseases and functional disorders. For therapeutic decision-making, it is of utmost importance to prove or exclude malignancy and aspiration.

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Patients with pharyngeal and oesophageal diseases will often cross specialty lines. About 80% of patients with oesophageal disorders present first to an otolaryngologist because they suffer from head and neck symptoms, like dysphagia, cough or globus sensation. Whereas otolaryngology deals with laryngopharyngeal disorders, the management of oesophageal diseases falls more appropriately within the realm of gastroenterology, which is competent for the whole intestine, as well as thoracic surgery. This interdisciplinary approach is reflected by the two authors of this chapter.

Endoscopy and radiology are not the only instrumental methods in the diagnostic armamentarium. In addition, depending on the patient's symptoms and endoscopic or radiologic findings, further examinations may be needed for conclusive analysis of the pharynx and oesophagus. For example, manometry, manofluorography, (impedance/)pH-metry, scintigraphy for quantification of the pharyngooesophageal transport or electromyography provides valuable information.

It is the goal of this chapter to describe the endoscopic examination of the upper aerodigestive tract and examples of typical findings. Advantages and limitations of endoscopy are demonstrated. Moreover, the role of endoscopy within the diagnostic workup of dysphagic patients and future aspects will be discussed.

2 Endoscopy of the Pharynx and Larynx

A critical area for deglutition without aspiration is crossing of the airway and digestive tract, which is localized in the hypopharynx. Apart from deglutition, pharyngeal structures belong to the vocal tract, which is responsible for articulation and resonance. Therefore, the pharynx and larynx as part of the upper aerodigestive tract have to be evaluated in context by the otolaryngologist. With the mirror examination, the ability to adequately visualize the pharynx and larynx may be limited. Therefore, endoscopy has become a standard examination in clinical routine.

Indications for endoscopy of the pharynx and larynx are patients presenting with symptoms of respiratory and swallowing diseases. Symptoms are dysphagia, aspiration, regurgitation, odynophagia and dysphonia (hoarseness). Before endoscopy is carried out, a history has to be taken and a mirror examination of ears, nose, mouth, pharynx and larynx is performed.

The indirect endoscopy of the pharynx and larynx views their inner surface via optical instruments. It can be performed transorally with rigid endoscopes (telescopes) and transnasally with flexible endoscopes. Video documentation should be obtained whenever possible.

2.1 Indirect Rigid Endoscopy of the Hypopharynx and Larynx

Rigid 70° and 90° telescopes (Fig. 1) are used to evaluate the hypopharynx and larynx indirectly. They provide a magnified view in high resolution, allow videotaping for documentation and can be used in association with stroboscopy to evaluate vocal fold vibrations. In addition, indirect rigid endoscopy enables the performance of office-based laryngeal surgical procedures under topical anaesthesia (biopsies, indirect phonosurgery for voice improvement in selected cases).

For endoscopy, the patient sits in an upright position, with his tongue protruded, and the examiner gently inserts the objective end of the telescope posteriorly over the base of the tongue until the hypopharynx and larynx are seen. The unphysiological patient condition allows only the examination of "hi"-phonation, but not the direct observation of articulation and swallowing. In cases of gag reflex, local anaesthesia can facilitate the examination. The observer examines morphology (e.g. signs of inflammation, tumour) and function (respiratory and phonatory vocal fold mobility, pooling/aspiration of saliva).

2.2 Flexible (Video-)Endoscopy of the Pharynx and Larynx

Transnasal flexible nasopharyngolaryngoscopy is a common procedure among otorhinolaryngologists for assessing nasal, velopharyngeal and laryngeal pathology. Moreover, it is used for the evaluation of the pharyngeal phase of swallowing

Fig. 1 Rigid telescope and flexible rhinolaryngoscope

and as a treatment tool in biofeedback therapy of voice and swallowing disorders.

There are two types of flexible rhinolaryngoscopes: fibrescopes and videoendoscopes. The flexible rhinolaryngoscope consists of an objective lens at the distal end of the insertion portion of the endoscope. The diameter of the insertion tube of the scope is kept as small as possible (2.2–4 mm). A xenon or halogen light source is used. The videoendoscopic technique is the clinical standard for oesophagogastroscopes. Recently, technical progress has made video-rhinolaryngoscopes with a small diameter (about 3.2 mm outer diameter) possible for transnasal insertion (Kawaida et al. 2002). The image transfer is not performed via the fibres, but with a chip camera at the tip of the endoscope. This technique provides better optical resolution and digital signal modulation. A digital recording is strictly recommended.

The flexible nasopharyngolaryngoscope is inserted through the nasal passage, and a topical anaesthesia (e.g. anaesthetic and decongestant spray) can be applied before. The examination starts with the visualization of the nasal fossa, the epipharynx and velum. The velopharyngeal competence and closure are tested. Then, the endoscope is passed down to just above the epiglottis where the larynx and oro-/hypopharynx can be seen (panoramic view). Tongue base, position and morphology of the epiglottis, configuration of the posterior pharyngeal wall, vallecular spaces, piriform sinuses, arytenoids and vocal folds are investigated. After that, the scope is moved further down just above the vocal folds for detailed inspection (larynx view). Signs of inflammation, mucosal abnormalities, mass lesions and vocal fold mobility can easily be observed. If local anaesthesia was administered to reduce the cough reflex, the glottic level can possibly be passed for inspection of the subglottic region and trachea.

Flexible endoscopy is also appropriate for patients who cannot be examined by mirror or rigid endoscopy because of a strong gag reflex and for patients who are not able to cooperate, e.g. paediatric or emergency patients. The main advantage is that the flexible endoscope can be left in position during phonation, articulation and swallowing; therefore it is used for evaluation of functions. As a limitation, it has to be pointed out that the image quality of flexible fibre-optic endoscopy does not reach that of rigid endoscopy. Whenever videostroboscopy is performed, the method of choice is rigid endoscopy.

Our experience with more than 5000 endoscopies shows that flexible endoscopy is a procedure without major complications. However, vasovagal reaction, laryngospasm or epistaxis is described in the literature. Therefore, all measurements for managing such complications must be available.

2.3 Examples of Typical Findings

Normal Hypopharynx and Larynx. The base of the tongue, posterior pharyngeal wall, piriform sinus and supraglottis are covered by intact epithelium, the vocal folds present in white colour due to the non-keratinizing squamous epithelium. Both vocal folds move symmetrically between the respiration and phonation position. No pooling of saliva or food is seen.

Hypopharynx Carcinoma. Foreign tissue and perhaps ulceration are seen in the hypopharynx (posterior pharyngeal wall, piriform sinus or postcricoid region). Due to tumour infiltration, vocal fold motility may be disturbed. Figure 2 shows an exophytic tumour mass in the left piriform sinus, reaching the postcricoid wall. Due to tumour infiltration the left vocal fold is paralysed. The patient's symptoms included dysphonia, dyspnea and long-lasting slowly progressive dysphagia.

Reflux Laryngitis. Gastrooesophageal/pharyngeal reflux disease can lead to a laryngitis which is not always limited to the posterior larynx. Possible morphological findings are reddening of the arytenoids, hypertrophy in the posterior commissure,

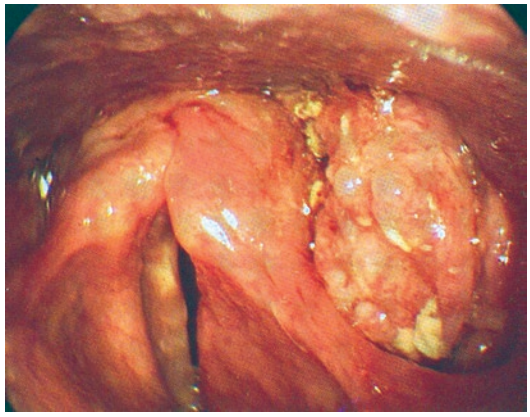

Fig. 2 Hypopharynx carcinoma tumour mass in the left piriform sinus (indirect rigid hypopharyngolaryngoscopy [From Becker et al. (1983)]

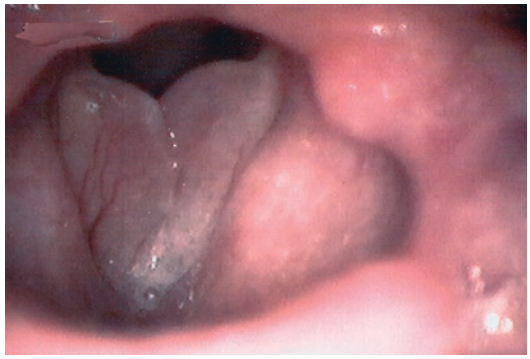

Fig. 3 Reinke's oedema (rigid hypopharyngolaryngoscopy)

contact granuloma of the vocal process or glottic/subglottic stenosis.

Reinke's Oedema. This type of chronic laryngitis frequently occurs in smokers, in patients with vocal abuse and in endocrinological dysfunctions (e.g. menopause, hypothyroidism). It presents with oedematous, thickened vocal folds and vasectasias (Fig. 3). The voice typically sounds low and frequently hoarse.

Leukoplakia of the Vocal Folds (Fig. 4, left vocal fold). The epithelium is covered by a white coat, and distinction from malignancy can only be made histologically. Stroboscopy helps to judge whether the process is infiltrating or not, but cannot replace histology. If the vocal fold does not vibrate in stroboscopy, an infiltrating process is present, and urgent microlaryngoscopy with biopsy for histological examination is indicated.

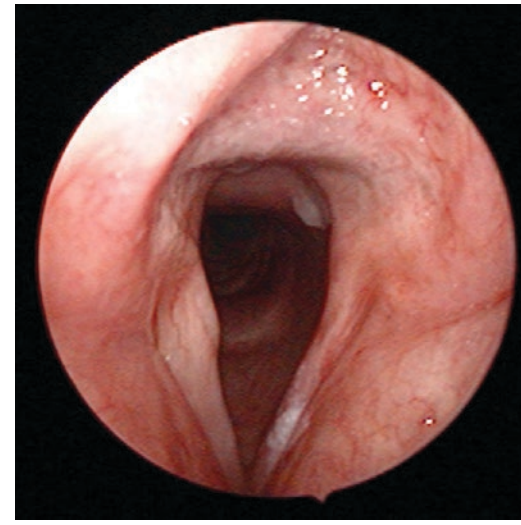

Fig. 4 Leukoplakia of the left vocal fold (flexible hypopharyngolaryngoscopy)

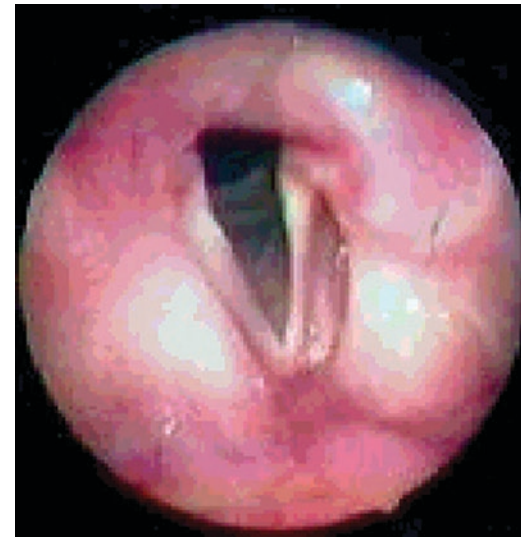

Fig. 5 Vocal fold paresis, left side (flexible hypopharyngolaryngoscopy)

Unilateral Vocal Fold Paralysis. The paralysed vocal fold is in fixed position (median, paramedian, intermediate or lateral), and the arytenoid may be dislocated anteriorly. During phonation, depending on the position of the vocal fold, glottic closure is incomplete. Stroboscopy may be of some prognostic value: the presence of the mucosal wave is a good prognostic sign. Figure 5 shows a left-sided vocal fold paresis in paramedian position.

2.4 Fibre-Optic (Flexible) Endoscopic Evaluation of Swallowing (with Sensory Testing): FEES (ST)

The fibre-optic endoscopic evaluation of swallowing (FEES) was introduced by Langmore et al. (1988). Bastian (1991) combined the flexible endoscopic examination of swallowing function with videodocumentation and described the procedure as videoendoscopic swallowing study (VESS). Due to the recent technical development of videoendoscopes the term flexible instead of fibre-optic endoscopic evaluation of swallowing is more appropriate. FEES allows an evaluation of the pharyngeal swallow and has become a routine procedure (Langmore 2017). It aims at defining the individual swallowing profile of the patient examined, which enables an adequate treatment planning and recommendation for feeding. FEES is regarded to be more than a screening procedure and does not only identify dysphagia and aspiration, but also reveals the pathophysiology of the swallowing disorder. The complication rate of FEES is minimal, but awareness and equipment must be appropriate to manage possible adverse reactions (Naccia et al. 2016).

Flexible endoscopic evaluation of swallowing with sensory testing (FEESST) is the combination of FEES with laryngopharyngeal sensory testing and was first described by Aviv et al. (1998, 2002). The quantitative testing of sensory thresholds is performed by endoscopically delivered standardized air puffs to the mucosa innervated by the superior laryngeal nerve to elicit the laryngeal adductor reflex.

Similar to the modified barium swallow, FEES(ST) is performed as a tailored examination (Bigenzahn and Denk 1999; Denk and Bigenzahn 2005; Schröter-Morasch 1999; Schröter-Morasch et al. 1999; Langmore 2001): coloured food in different consistencies is used depending on the history and clinical findings. Suction must be available in case of aspiration. Before endoscopy, the patient has to be observed in the clinical examination, and neurological symptoms or disorders of speech, language or voice have to be noted.

The patient is in an upright position with the head slightly down to facilitate swallowing function. Generally, no local anaesthetic spray is used in order not to impair pharyngolaryngeal sensibility. If needed, only cotton balls with local anaesthetic and decongestant are positioned into the nose before endoscopy. The flexible rhinopharyngolaryngoscope is introduced transnasally into the oro- and hypopharynx and is left in place during deglutition. Digital recording allows an analysis in slow motion and discussion of the findings in the interdisciplinary management team.

The endoscopic examination consists of two parts: non-swallowing and swallowing assessment. In the "non-swallowing assessment", anatomy and function are investigated. The mobility of the vocal folds, glottic closure, epiglottic tilting, the occurrence of hyperkinetic movements, pooling/aspiration of saliva, cough reflex (elicited by gently touching the glottis with the tip of the endoscope) and the possibility of intentional (voluntary) throat clearing are tested. Velum, pharynx and larynx are observed not only during respiration, but also during phonation, breathhold manoeuvres, throat clearing and coughing to test the intentional and reflexive mobility. The second part of the procedure comprises the swallowing assessment, i.e. "dry swallow" with saliva and "food swallows" with measured quantities of food and liquid of different consistencies, dyed with blue food colouring according to a standardized protocol. The endoscope is positioned in the panoramic view above the tip of the epiglottis. In tracheostomized patients, endoscopy via the tracheostoma is performed in addition (Fig. 6).

Swallowing function is evaluated with regard to saliva pooling, triggering of the swallowing reflex, leaking, penetration, retention, aspiration, cough reflex and regurgitation. Hypopharyngeal regurgitation leads to suspicion of a hypopharyngeal/oesophageal stenosis or Zenker's diverticulum. Aspiration before and after the swallow can be viewed, whereas aspiration during the swallow cannot be seen directly. Also, the amount of aspiration cannot be judged securely (only in patients without cough reflex or tracheostomy). The ability to effectively clear the throat of retention and aspirated material is tested. Finally, compensatory postures, swallowing techniques and different food consistencies are evaluated for establishing an individually tailored treatment programme. Various severity scales try to classify the dysphagia/aspiration.

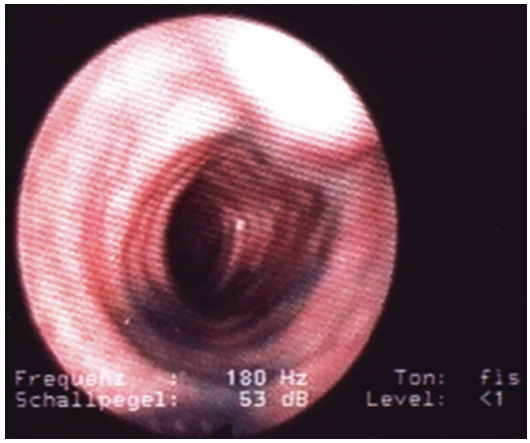

Fig. 6 Aspirate in the trachea—flexible endoscopy via tracheostoma.

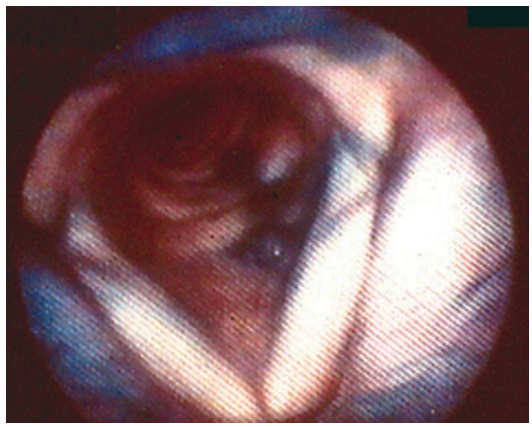

Fig. 7 Aspiration (flexible hypopharyngolaryngoscopy) [From Bigenzahn and Denk (1999)]

A clinically widely used 8-point scale to describe penetration and aspiration events was developed by Rosenbek et al. (1996, Penetration-Aspiration Scale). Moreover, flexible endoscopy has proved to be a treatment tool for visual biofeedback training in functional swallowing therapy (Denk and Kaider 1997). The combination with other diagnostic procedures may be useful. Commercially available "workstations" eventually comprise sonography, electromyography or other diagnostic methods in addition. Figure 7 shows a static image of aspiration. Coloured liquid is pouring down the subglottic region into the trachea.

2.4.1 Advantages and Limitations

The following *limitations* of FEES have to be taken into account:

- There is no direct visualization of the bolus on its entire way from mouth to stomach as offered by videofluoroscopy.
- Laryngeal closure (because of epiglottic tilting) and aspiration during the swallow cannot be examined directly. The view during the swallow is obscured because pharyngeal mucosa and the bolus touch the tip of the endoscope.
- Larynx/hyoid elevation and upper oesophageal sphincter function are not shown. Diseases of the pharyngooesophageal segment and oesophagus can only be indirectly supposed in the case of pharyngeal residue and/or pharyngeal regurgitation.
- Routinely, oesophagoscopy is not part of the examination. Some authors propose to use a longer flexible endoscope to routinely evaluate the oesophagus during FEES (Herrmann 1998), especially when transnasal oesophagoscopy is performed (Tong et al. 2012).

The influence of the endoscope as a foreign body during swallowing has not yet been evaluated exactly.

On the contrary, there are many *advantages* of FEES*:*

- The direct visualization of the upper aerodigestive tract reveals even subtle morphological or functional findings.
- It is a non-invasive procedure without any radiation exposure, repeatable as often as necessary and available also as a bedside examination, e.g. at the intensive care unit (ICU).
- Regular food, not barium, is used.

2.4.2 Comparison of FEES(ST) and Videofluoroscopy

The only methods for visualization of aspiration are videofluoroscopy (VFS) and FEES(ST). VFS visualizes the bolus on its entire way from the oral cavity to the stomach and was the first instrumental procedure for the assessment of dysphagia (Logemann 1993, 1998; Jones and Donner 1991; Ekberg and Olsson 1997). FEES(ST) directly shows the upper aerodigestive tract. Especially with regard to cost-effectiveness, the question arises which method is

best for the evaluation of dysphagia. Literature and own studies show that these dynamic methods are not alternative, but complementary procedures (Schima and Denk 1998). Both are valuable; each procedure has its place in the clinical setting. A study by Aviv (2000) could show that the outcome of dysphagia management with regard to pneumonia incidence was the same using videofluoroscopy and FEESST. Comparing the findings of FEES(ST) and VFS, there is excellent agreement with regard to aspiration and retention. Due to the limitations of FEES(ST) mentioned above, VFS remains indispensable ("gold standard") for the evaluation of the complete upper digestive tract in one examination. FEES(ST) is the method of choice for the first-line examination, for follow-up examinations, for unfit patients in the intensive care unit and for the evaluation of compensatory manoeuvres.

2.5 Direct Endoscopy of the Pharynx and Larynx

Direct rigid endoscopy of the pharynx and larynx, which was developed by Kleinsasser (1968) ("laryngeal suspension microlaryngoscopy"), does not only allow microscopic evaluation of the pharynx and larynx, but also surgical interventions (biopsies, cold steel and laser surgery, phonosurgery with the primary aim of voice improvement). The procedure is carried out under general anaesthesia. Various laryngoscopes are available in different sizes and types, e.g. according to Kleinsasser (1968) (Fig. 8). The patient is lying in supine position. After protecting the teeth, the laryngoscope is inserted down to the level of the vocal folds under inspection of the hypopharynx and supraglottis. Then, the laryngoscope is held by a laryngoscope holder that rests on a table over or directly on the patient's chest. The microscope is then positioned.

Fig. 8 Laryngoscope according to Kleinsasser for direct microlaryngoscopy

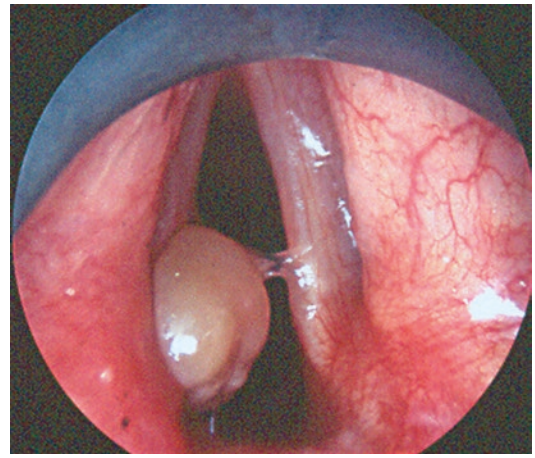

Fig. 9 Granuloma of the left vocal process (direct microlaryngoscopic view, tubeless jet ventilation)

Recently developed ventilation techniques have led to the possibility of tubeless jet ventilation to avoid intubation (Aloy et al. 1991). This method improves the operative conditions for the surgeon by providing more space for manipulation and better visibility (Fig. 9). Moreover, it is also suited for laryngeal laser surgery, thus avoiding flammable tubes, and for endoscopic surgery of stenoses.

2.5.1 Examples of Typical Findings

Vocal Fold Granuloma. Figure 9 shows the microlaryngoscopical view of a typical vocal fold granuloma, which is located on the vocal process. It may occur after intubation (intubation granuloma) or is often associated with reflux disease (contact granuloma). Additional risk factors for development of a contact granuloma are functional voice disorders and psychogenic factors. For therapy, conservative treatment with proton pump inhibitors and logopaedic voice therapy can be tried. If the pathology persists or if a histological diagnosis is necessary, microlaryngoscopic surgery is performed.

Zenker's Diverticulum. As an alternative to the external approach with resection of a Zenker's diverticulum, endoscopic laser surgery may be performed. In Fig. 10, the party wall between the oesophagus and Zenker's diverticulum is seen when endoscopically exposed before laser surgery.

Laryngeal Carcinoma. An irregular mucosal surface or a tumour mass may be observed in the supraglottic (Fig. 11), glottic or subglottic area. Vocal fold motility may be impaired. Depending on the tumour size, the airway may be compromised.

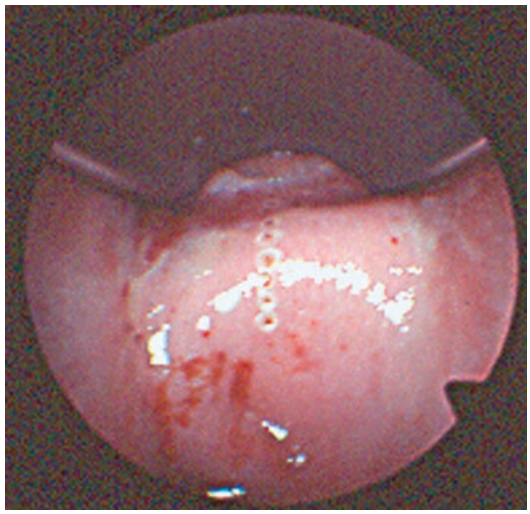

Fig. 10 Zenker's diverticulum (direct hypopharyngoscopic view), intraoperative view on a party wall between the oesophagus and Zenker's diverticulum. The laser marking for the planned laser resection can be seen

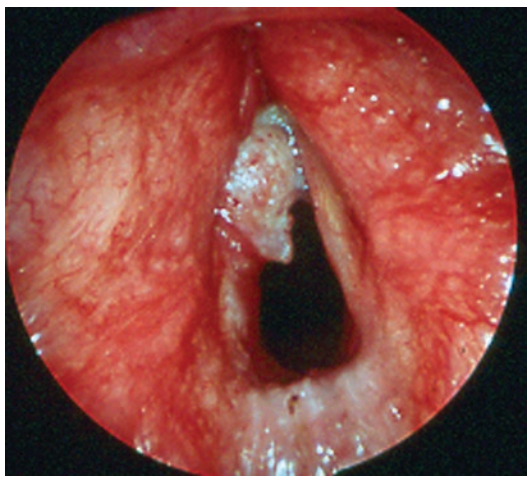

Fig. 11 Carcinoma of the larynx (direct microlaryngoscopy). The tumour mass is seen on the vocal folds

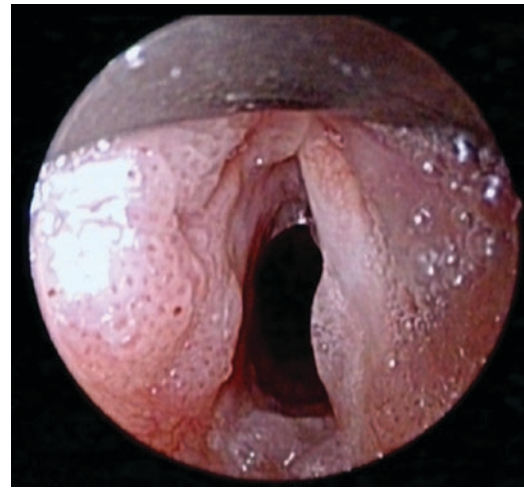

Fig. 12 Recurrent Respiratory papillomatosis of the larynx (direct microlaryngoscopy). Papillomas are seen at the glottis level bilaterally and the left supraglottic region (ventricular fold)

Recurrent Respiratory Papillomatosis (Fig. 12). Papillomas are present at the glottic level (bilaterally), the left supraglottis region and the posterior commissure.

2.5.2 Recent Developments and Future Aspects

New technologies, such as HD- (High-Definition) technology or 4K (Ultra HD) resolution, try to enhance the endoscopic information during microlaryngoscopy.

Narrow Band Imaging (NBI). NBI is an optical image enhancement technology that uses a specially filtered light (2 spectral regions: 415 nm, 540 nm) and improves the visibility of vessels and other tissues on the mucosal surface. This is especially helpful in the diagnostics of laryngeal dysplasia and early laryngeal carcinoma (Davaris et al. 2017).

Autofluorescence Endoscopy. The aim of this development is to enhance the endoscopic information during microlaryngoscopy. Autofluorescence is induced by filtered blue light of a xenon short arc lamp and processed by a CCD camera system. During microlaryngoscopy, the use of

autofluorescence can improve the early detection and preoperative assessment of laryngeal cancer and its precursor lesions (Malzahn et al. 2002).

Contact Endoscopy. Contact endoscopy tries to improve the assessment of benign, premalignant and malignant pathologies of the larynx during microlaryngoscopy. The aim is to make epithelial cells visible, as in gynaecology. After staining the tissue with methylene blue, the magnifications obtained with contact endoscopy (60× and 150×) enable observation of the epithelium cells and their characteristics (Andrea et al. 1995). However, it does not replace biopsy sampling (Warnecke et al. 2010).

3D Endoscopy. For scientific purposes, 3D endoscopic techniques were used in microlaryngeal surgery using tubeless jet ventilation (Schragl et al. 1995). This technique has not yet become clinical routine.

3 Endoscopy of the Oesophagus

Endoscopy of the oesophagus as part of the endoscopic evaluation of the upper gastrointestinal tract is one of the most frequent procedures performed in Western health care systems (Owings and Kozak 1998). The aim of oesophagoscopy is diagnosis, differential diagnosis and follow-up of oesophageal diseases. Moreover, endoscopy supports further diagnostic procedures, such as endosonography, and enables therapeutic interventions. Two forms of oesophagoscopy are in use: rigid and flexible endoscopy. Gastroenterologists and surgeons are used to flexible gastroscopes to perform total oesophagogastroduodenoscopy, whereas otorhinolaryngologists prefer rigid instruments.

3.1 Symptoms of Oesophageal Diseases

As the oesophagus provides the bolus transport in the oesophageal phase of swallowing, diseases of the oesophagus bring about symptoms related to swallowing function. No single symptom is typical of a specific disorder. The localization of symptoms by the patient is unreliable. Patients who suffer from oesophageal diseases (Table 1) may report the following symptoms (see also Chap. 2):

- *Dysphagia*: In the case of oesophageal stenosis (e.g. oesophageal carcinoma) or functional motility disorders (e.g. achalasia of the lower oesophageal sphincter), the bolus transport is disturbed and causes the feeling of a stop of the bolus passage especially for solid food. The symptom dysphagia needs the analysis of all the four phases of deglutition (oral preparatory, oral, pharyngeal and oesophageal phase), since oropharyngeal and oesophageal dysphagia

Table 1 Oesophageal diseases (modified from Seiden in Parparella et al. 1991)

Motility disorders
Primary disorders
Achalasia
Diffuse oesophageal spasm
Nutcracker oesophagus
Non-specific dysfunction (hypertensive lower oesophageal sphincter, diminished amplitude of oesophageal peristalsis)
Secondary disorders
Scleroderma and other connective tissue disorders
Diabetes mellitus
Alcoholism
Central nervous system disorders
Presbyesophagus
Chagas'disease
Structural disorders
Extrinsic compression
Webs, rings
Diverticula
Reflux oesophagitis and stricture
Ingestion of caustic substances
Hiatal hernia
Varices
Foreign bodies
Neoplasms (benign, malign tumours
Congenital disorders
Atresias
Tracheoesophageal fistulas
Duplications
Dysphagia lusoria
Achalasia

Table 2 Grading of dysphagia

0 = able to eat normal diet/no diet dysphagia
1 = able to swallow semi solid foods
2 = able to swallow only semisolid foods
3 = able to swallow liquids only
4 = unable to swallow anything/total dysphagia

(Knyrim et al. N Engl J Med 1993)

may influence each other or occur in combination. Malignity correlates with rather fast progression of dysphagia, benign strictures with slowly progressive dysphagia, whereas functional disorders like achalasia like to vary severity of symptoms over time. Grading of dysphagia can assist indication and quality measurement of treatment, see Table 2.

- *Regurgitation:* Reflux of swallowed bolus material from the oesophagus to the pharynx/mouth due to retrograde oesophageal motility, stenosing oesophageal diseases or retained material (e.g. in Zenker's diverticulum). *Odynophagia:* painful swallow.
- *Globus sensation* (globus pharyngeus): Globus sensation often derives from gastro-oesophageal reflux disease. Other possible underlying causes that have to be considered for differential diagnosis are diverticula, webs, and rings, but also thyroid gland diseases, cervical spine syndrome or functional voice disorders.
- *Heartburn*, *retrocardiac chest pain*: These symptoms occur in gastro-oesophageal reflux disease, but also in oesophageal carcinoma, oesophageal spasms or oesophagitis of other aetiologies. In approximately 40% of patients suffering from reflux disease, the typical symptom of heartburn is lacking. Exclusion of ischemic heart disease, pericarditis, aortic dilatation and pleuritis is mandatory.
- *Cough* of unknown aetiology: Cough may be due to aspiration or occur in oesophageal reflux disease.
- *Gastrointestinal bleeding*: Bleeding from the mouth without source in the nose, mouth, pharynx or larynx or overt/occult blood in the stool necessitates urgent oesophagogastroduodenoscopy.

If one of these symptoms is present, endoscopy of the oesophagus is indicated.

Oesophagoscopy is further appropriate in (suspected) foreign body ingestion or as part of gastroduodenoscopy.

3.2 Rigid Oesophagoscopy (Rigid Hypopharyngooesophagoscopy)

Traditionally, rigid (open tube) oesophagoscopy is the method of choice for otorhinolaryngologists to remove foreign bodies located in the pharyngooesophageal segment or cervical oesophagus and to perform tumour staging (panendoscopy) in patients with primary malignancies in the head and neck to exclude/diagnose simultaneous additional malignancies (Dhooge et al. 1996). The incidence of simultaneous oesophageal malignancies is about 8.4% (Dammer et al. 1999).

Usually rigid oesophagoscopy is performed under general anaesthesia after informed consent. The patient is lying on his back, with the neck flexed and the head extended. The open-tube oesophagoscope (Fig. 13a) is inserted after protection of the teeth. Behind the arytenoids, the oesophageal entrance is passed. The oesophagoscope has to be advanced gently to avoid perforation. It is not possible to visualize the gastric mucosa safely with an open oesophagoscope in all cases. If evaluation of the distal oesophagus is needed, an oesophagoscope with air insufflation can be used.

Risks include tooth damage, luxation of the arytenoids, bleeding and perforation of the hypopharynx or oesophagus with consecutive mediastinitis or peritonitis. The complication rate lies under 1% (Schmidt et al. 1998).

3.3 Flexible Oesophagoscopy

Oesophagoscopy is performed for diagnosis of oesophageal diseases, follow-up purposes, additional diagnostic procedures and for therapeutic measurements (haemostasis, dilatation, stenting, argon plasma coagulation, endoscopic mucosal resection, endoscopic submucosal dissection).

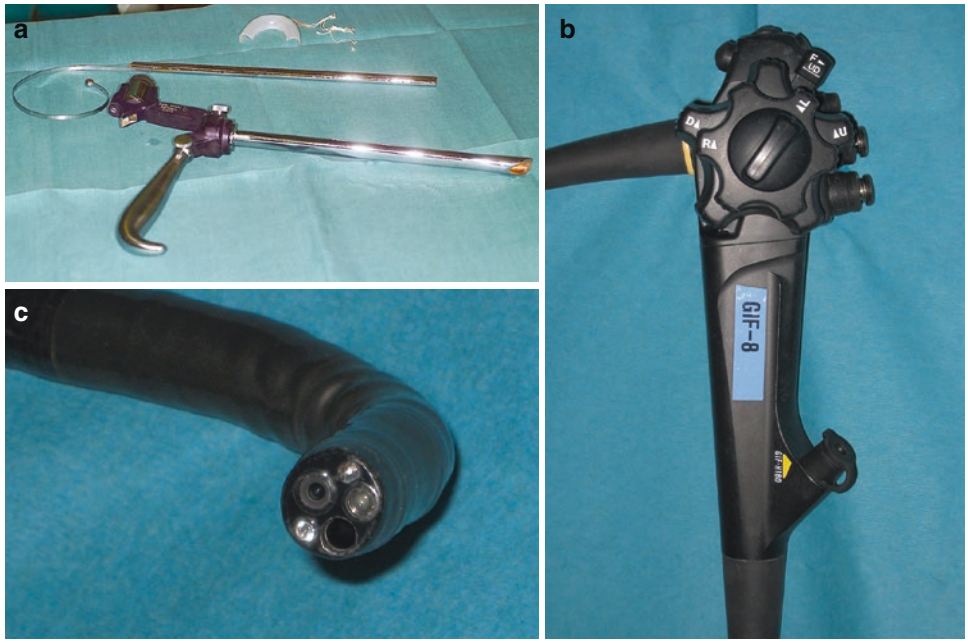

Fig. 13 (**a**) Rigid oesophagoscope. (**b, c**) Flexible gastroscope; control part (**b**), tip (**c**)

Today fibre endoscopes have been replaced completely by video endoscopes with a CCD camera (charge-coupled device) at the tip. This facilitates additional techniques like zooming, enhancement of contrast and improvement of resolution (e.g. high definition technology, endomicroscopy). A channel in these endoscopes allows other instruments (forceps, brush, snare, injection needle, dilatation balloon) to be passed through in order to take tissue samples, remove polyps, inject varices, dilate strictures or others. The length of the oesophagogastroscope (Fig. 13b, c) is about 100–120 cm, with a diameter of about 5–1 mm, depending on its purpose (ultra-thin stricture endoscope, therapeutic instruments with extra-thick channels). It has become standard to record the examination on a video/DVD recorder or file images in an electronic processing system for documentation. Flexible endoscopy of the oesophagus is usually performed on an outpatient basis in local anaesthesia using a spray containing benzocaine or tetracaine hydrochloride. The patient, who is kept without oral intake for 6–8 h prior to endoscopy, is offered intravenous sedation (e.g. with midazolam or propofol). He is placed in the left lateral decubitus position. After a hollow mouth piece is introduced, the lubricated endoscope is inserted under visual control. In the case of pathological or unclear findings in hypopharynx or larynx the patient has to be referred to the otorhinolaryngologist. The instrument is advanced until the tip of the endoscope reaches the gastro-oesophageal junction (approximately 40 cm from the incisors). For examination of the stomach and duodenum (flexible oesophagoduodenoscopy), the tip is further advanced through the cardia, and the different portions of the stomach (cardia, fundus, corpus with greater and lesser curvature, antrum) are inspected. Afterwards, the tip is passed through the pylorus, into the duodenal bulb and the descending part of the duodenum.

The examination evaluates the lumen, wall, contents, peristalsis, and appearance of the mucosal surface and visualizes/excludes flat, protruded or excavated lesions. If indicated, biopsies and brushing for histological, cytological and bacteriological examinations are performed.

Large clinical series report an incidence of moderate or severe complications in 0.1–0.2%, and mortality lies between 1 in 100,000 and 1 in 5000, depending on the severity and urgency of

underlying diseases and the proportion of therapeutic procedures. The following complications may occur: perforation, bleeding, cardiopulmonary complications, aspiration, side effects of premedication and infection.

3.3.1 Examples of Typical Findings

Normal oesophagus. The oesophageal mucosa (non-keratinizing stratified squamous epithelium) appears pale, whereas the gastric mucosa is reddish (columnar epithelium). The transition between these two types of epithelium (oesophagogastric junction) should be well visible. Because of its saw-toothed pattern, it is called Z-line (Fig. 14).

Reflux oesophagitis. Among the numerous patients with reflux symptoms, endoscopy can define the subgroup of those with reflux oesophagitis characterized by reddening, erosions, ulceration or stricture at and above the z-line. A grading of reflux oesophagitis can be given with the Savary and Miller (1977), the MUSE (metaplasia, ulcer, stricture, erosions) or the Los Angeles Classification. According to the grading by Savary and Miller (1977), four or five subgroups are described:

Grade 1, singular erosions; grade 2, confluent erosions; grade 3, oesophagus is covered by circular erosions; grade 4, complications with peptic stricture, with or without signs of inflammation, or ulceration; grade 5, Barrett's oesophagus. Figure 15 shows a reflux oesophagitis Grade 2, and Fig. 16 a severe reflux oesophagitis with stricture.

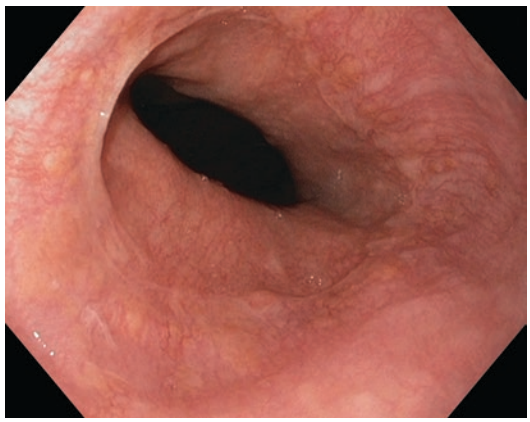

Fig. 14 Oesophagogastric junction without pathology

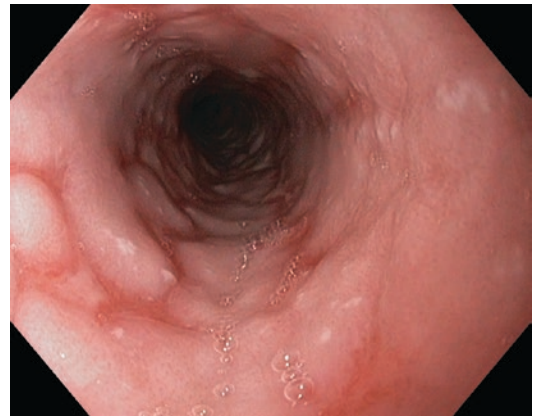

Fig. 15 Reflux oesophagitis (grade 2 according to Savary and Miller)

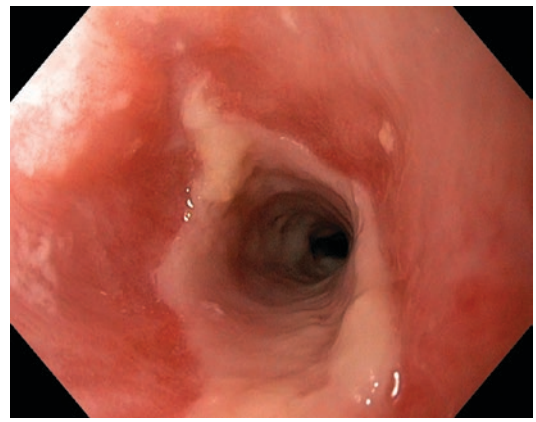

Fig. 16 Peptic stenosis in the distal oesophagus

Barrett's Oesophagus. Due to long-lasting peptic reflux, the squamocolumnar junction in the distal oesophagus moves upwards and the squamous epithelium is replaced by a specialized columnar epithelium with intestinal metaplasia. Its extent is described by the Prague classification, C standing for circumferential extent and M for the maximal longitudinal extent of Barrett's oesophagus in cm. Barrett's metaplasia (Fig. 17) is a well-known risk factor for the development of dysplasia and adenocarcinoma (Fig. 18, early adenocarcinoma in Barrett's oesophagus). Endoscopically, metaplastic gastric mucosa is recognized in the oesophagus because of its

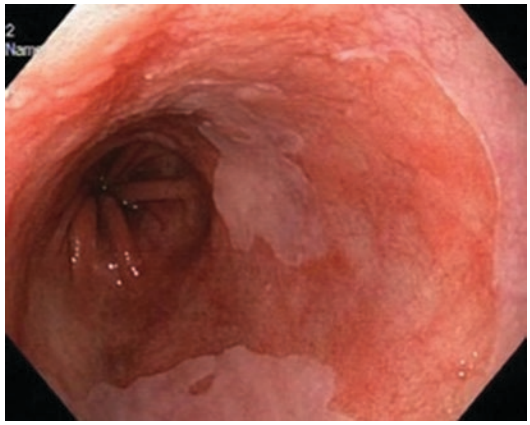

Fig. 17 Metaplasia due to chronic reflux (Barrett's oesophagus)

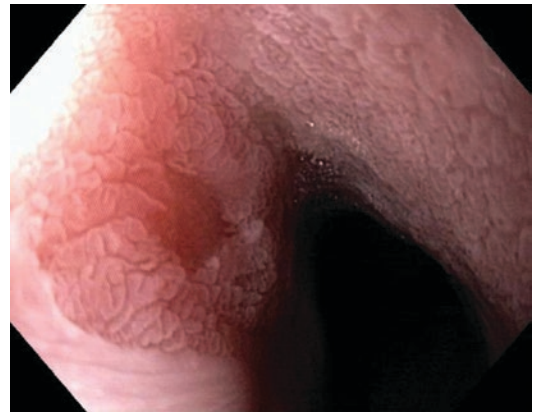

Fig. 19 Barrett's oesophagus with high grade dysplasia, chromoendoscopy with acetic acid

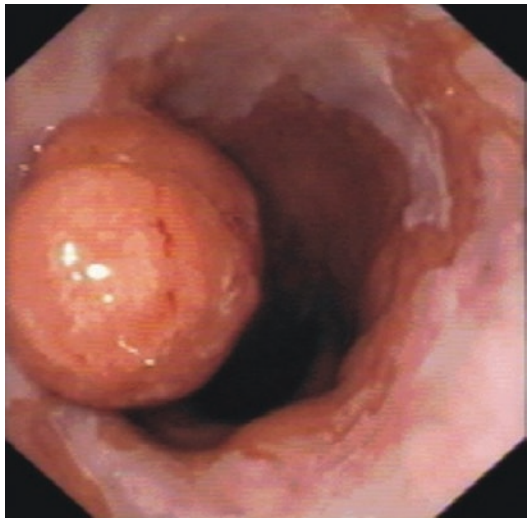

Fig. 18 Early adenocarcinoma in Barrett's oesophagus

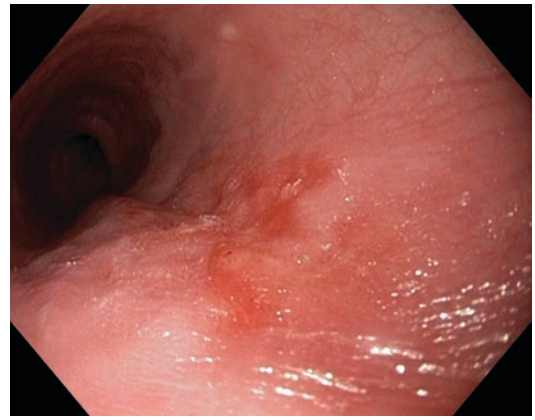

Fig. 20 Early squamous cell carcinoma of the mid-oesophagus

salmon red appearance. Therefore, follow-up examinations with biopsies are necessary. For improving the diagnostic yield, chromoendoscopy with acetic acid (Fig. 19) or indigocarmine, optical filter technology (NBI) or digital image reprocessing should be added to the routine procedure.

Oesophageal carcinoma. Endoscopy shows early cancer (Fig. 20) or a polypoid or ulcerated mass or infiltration that can obstruct the oesophageal lumen (Fig. 21). Multiple biopsies are taken for histological diagnosis. The incidence of adenocarcinomas derived from Barrett's oesophagus increases in the USA and Europe dramatically, whereas the alcohol and tobacco-associated squamous cell carcinoma becomes less frequent. High grade dysplasia and early cancer limited to the mucosa or superficial submucosa can now be removed endoscopically by Endoscopic Mucosal Resection (EMR—Fig. 22) or Endoscopic Submucosal Dissection (ESD). Photodynamic therapy and Radiofrequency ablation can assist in curative treatment of these premalignant and early malignant states. In the case of a symptomatic tumour stricture, a balloon dilatation or bougienage can be performed

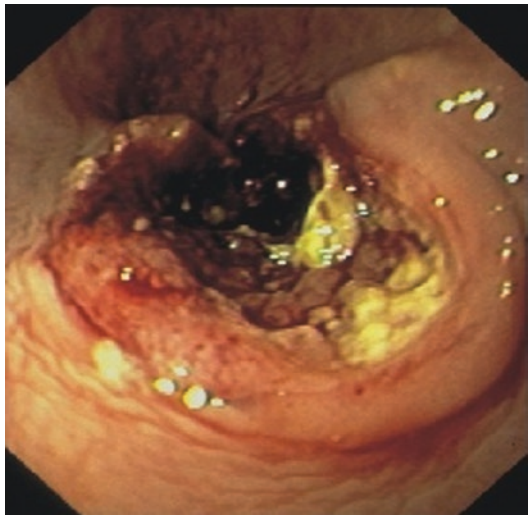

Fig. 21 Advanced ulcerated squamous cell carcinoma of the distal oesophagus

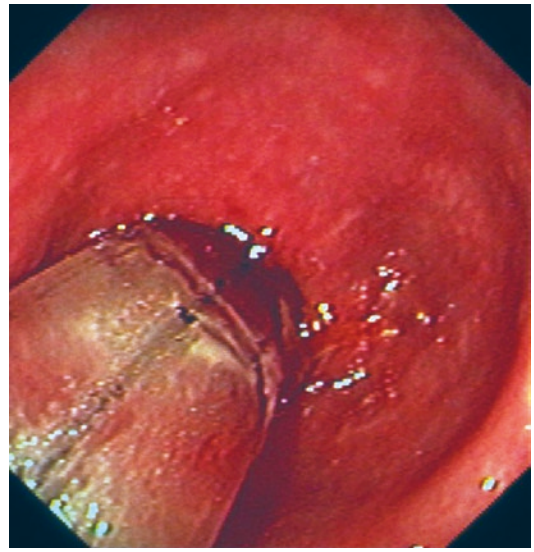

Fig. 23 Balloon dilatation of an oesophageal stricture

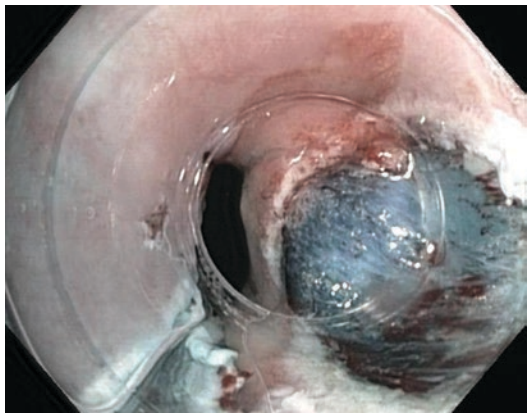

Fig. 22 Endoscopic mucosal resection (EMR)

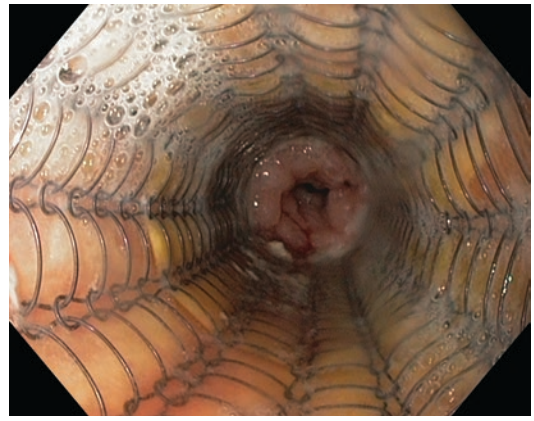

Fig. 24 Metallic stent for palliation of obstructing tumour

(Fig. 23) and a metal stent positioned as part of a multimodal therapy or a palliative approach (Fig. 24).

Varices: In portal hypertension collaterals are found preferably in the distal oesophagus. The blue, more or less prominent strings can be ligated endoscopically with rubber bands or injected with glue to treat or prevent bleeding (Fig. 25).

Schatzki Ring. Endoscopy reveals a stricturing membrane in the distal oesophagus. It may cause dysphagia, especially concerning solid food, and give rise to an impacted foreign body. For therapy, dilatation or thermal ablation during endoscopy is performed.

Soor oesophagitis. A white coverage or single white spots (Fig. 26) are seen on the oesophageal wall that can be removed with a forceps, but not with rinsing. Brush cytology easily depicts *Candida* during microscopic examination.

Viral oesophagitis: In immunocompromised patients viral infections (e.g. herpes simplex, cytomegaly virus) can lead to inflammation of the oesophagus with scatterd ulcers. Biopsies prove the diagnosis by histologic, immunochemical or molecular evidence (Fig. 27).

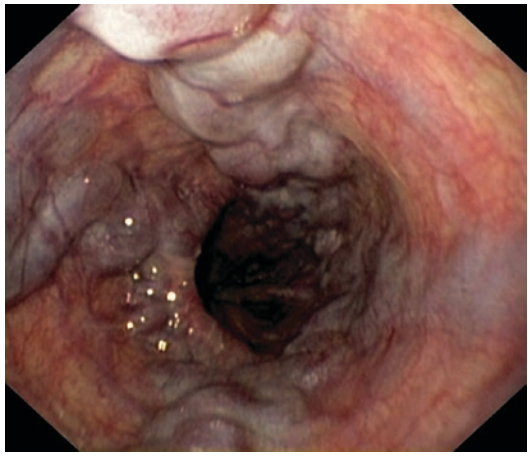

Fig. 25 Oesophageal Varices

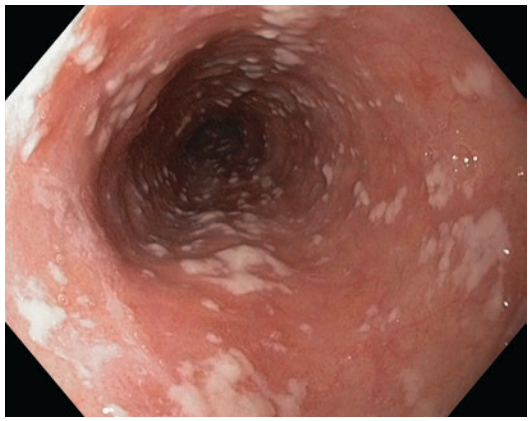

Fig. 26 Soor oesophagitis

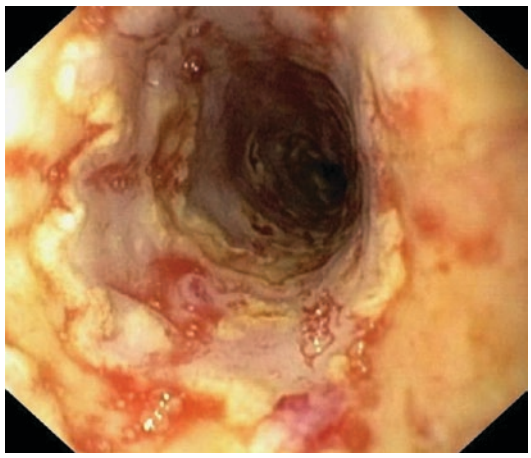

Fig. 27 Herpetic oesophagitis with severe ulcerations in an immunocompromised patient

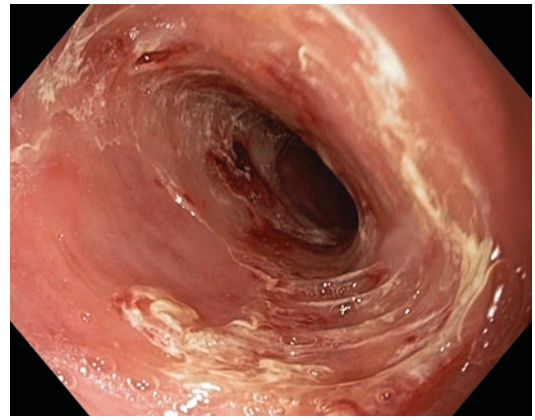

Fig. 28 Eosinophilic oesophagitis

Eosinophilic oesophagitis: It is an allergic inflammation of the oesophageal wall, histologically characterized by infiltrating eosinophilic granulocytes. Ridges, furrows, or rings as well as white exudates may be seen in the oesophagus. Topical steroids are a preferred treatment (Fig. 28).

Oesophageal web. Oesophageal webs may be due to reflux disease, iron-deficiency anaemia (Plummer Vinson syndrome) or idiopathic. They are either destroyed when passing the endoscope or removed with dilatation or bougienage.

Achalasia. Achalasia is a neuromuscular disorder of the oesophagus that is characterized by a delayed oesophageal emptying due to inadequate oesophageal peristalsis and a non-relaxing, hypertensive lower oesophageal sphincter. Diagnostic method of choice is videofluoroscopy and manometry, but endoscopy is necessary to rule out other causes of dysphagia. It shows a dilated oesophagus, weak non-propulsive oesophageal peristalsis and retention of secretion and food. Endoscopic ultrasound reveals a thickened hypertrophic muscle layer of the oesophagogastric sphincter. Endoscopy can also be used for therapeutic purposes, as pneumatic dilatation or botulinum toxin injection. POEM (peroral endoscopic myotomy), a newly emerging endoscopic technique, becomes an alternative to the classical surgical Heller' myotomy.

3.3.2 Endoscopic Ultrasound

The combined endoscopic and sonographic evaluation of the oesophagus (endoscopic ultrasound, EUS) allows the identification of the different layers of the oesophageal wall and contributes to the staging of oesophageal tumours and locoregional nodal involvement (Tio 1998; Bergman and Fockens 1999; Richards et al. 2000; Wakelin et al. 2002). EUS proved to have a better accuracy in staging, especially in T1 and T2 tumours, than computed tomography (Ziegler et al. 1988; Tio 1998). High-frequency EUS has been performed in early oesophageal cancer to select patients for local endoscopic treatment.

EUS is a valuable tool to differentiate and further define submucosal tumours and extrinsic compression. Adding fine needle aspiration to EUS improves the detection of malignancy in mediastinal processes or wall tumours of the oesophagus substantially.

3.4 Rigid Versus Flexible Oesophagoscopy

Both methods are less competing than substituting each other (Hörmann and Schmidt 1998): flexible equipment provides better imaging and allows air insufflation for distension, whereas rigid endoscopes facilitate instrumentation. Traditionally, otorhinolaryngology focuses on rigid hypopharyngo-oesophagoscopy for removing foreign bodies and for panendoscopy in patients with malignant tumours in the upper aerodigestive tract to reveal additional simultaneous malignancies. Gastroenterology uses the flexible endoscope not only for the endoscopic evaluation of the oesophagus, but also of the stomach and duodenum (oesophagogastroduodenoscopy, EGD). The indication for rigid or flexible endoscopy depends on the necessities of individual case and the experience of the surgeon (Schmidt et al. 2010).

Rigid oesophagoscopy is superior to flexible endoscopy in the evaluation of the hypopharynx and cervical oesophagus. The skill and experience of the examiner remain of utmost importance (Monnier and Lang 1997). Flexible oesophagoscopy does not allow a distinct examination of the upper oesophageal sphincter region. In case of suspected malignancy in this region, rigid endoscopy should be performed. As foreign bodies mostly occur in the proximal oesophagus, rigid endoscopy is an adequate procedure for the management of (suspected) foreign body ingestion (Alberty et al. 2001). Due to a higher perforation risk in the distal portion of the oesophagus with rigid oesophagoscopy, foreign bodies in that part are often removed by flexible endoscopy.

3.5 Recent Developments and Future Aspects

The development of ultra-thin oesophagogastroscopes with an outer diameter of 5–6 mm allows the transnasal insertion of the endoscope, which may give rise to a greater acceptability and less discomfort of the patient (transnasal oesophagogastroscopy). *Chromoendoscopy* has become a valuable adjunct to flexible endoscopy in oncological indications. It remains uncertain if new technologies, like *zoom endoscopy*, *spectroscopy*, *optical coherence tomography, endocytoscopy* or *confocal laser microscopy*, will become established. For sure, molecular pathological analysis of specimens will be of great clinical importance in the future.

4 Role of Endoscopy in the Diagnostic Workup of Dysphagic Patients

Differential diagnosis of dysphagia is based upon endoscopy and histopathological findings of biopsies, radiography, manometry and (impedance/)pH-metry. Radiology and endoscopy are both standard procedures which complement each other. Oesophagoscopy is routinely performed to search for malignancy or to extract a foreign body. It is a method of first choice and capable of performing the differential diagnosis between structural and functional disorders. For motility disorders, videofluoroscopy, endoscopic ultrasound, manometry or (impedance/)pH-metry should be performed.

The advantage of radiographic studies is the identification of oesophagotracheal fistulas, diverticula, atresia and hiatal/paraoesophageal hernia. For radiological evaluation of dysphagia, the dynamic method of videofluoroscopy is regarded as the gold standard. However, subtle morphological changes are not visible radiographically.

The diagnostic indications for oesophagoscopy are a matter of discussion: should endoscopy be performed primarily or not? Because of direct visualization, endoscopy is best for assessing mucosal integrity, inflammation and malignancies. Furthermore, it enables biopsies to be taken for histological examination. Therefore, endoscopic follow-up is indicated in many diseases, e.g. Barrett's epithelium or achalasia.

In recent years, gastrointestinal endoscopy has gradually supplanted gastrointestinal radiography as the initial diagnostic study for the majority of patients with suspected gastrointestinal pathology. Technical developments (advances in lighting, imaging and flexibility) have improved the sensitivity and specificity and have made it a widely spread examination technique.

Conclusion

Endoscopy of the hypopharynx and oesophagus contributes to the diagnostic workup of the dysphagic patient. In many cases, it is the method of choice. However, radiography, especially videofluoroscopy, remains indispensable. For the future, the technical progress will stimulate and enable new endoscopic and radiographic developments. It aims at the highest possible quality of diagnosis and optimal patient acceptability.

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In Vitro Models for Simulating Swallowing

Waqas Muhammad Qazi and Mats Stading

Contents

Abstract

This chapter gives an overview of the in vitro models that are currently used for studying swallowing. The focus is on the construction, geometry, and performance of mechanical models. Swallowing simulations and mathematical modeling are also considered. The in vitro models that are concerned with the oral, pharyngeal, and esophageal phases of swallowing linked to bolus properties are discussed. The pharyngeal phase is given special consideration, as it is involved in both food transport to the stomach and air transport to the lungs, and therefore constitutes the most critical phase of swallowing.

1 Introduction

Clinical examination is the usual practice to study swallowing function in humans. In clinical trials, individuals are examined using videofluoroscopy or endoscopy. Endoscopy entails fiber-optic endoscopic evaluation of swallowing (FEES), traditional manometry (Butler et al. 2009), or the recently developed high-resolution manometry (HRM) (Lin et al. 2014). Videofluoroscopy is an X-ray-based technique that exposes the patient to radiation. Moreover, contrast media (iodine or barium based) are needed to make the bolus opaque to the X-rays during videofluoroscopy, which may alter the bolus rheology (Popa Nita

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et al. 2013; Steele et al. 2013, 2015). The main advantage of videofluoroscopy is that it allows one to follow the sequence of events taking place during swallowing. However with videofluoroscopy, it is not possible to measure the propulsive forces applied on the bolus by muscles involved in swallowing (Chang 1998). In order to understand the complete picture it is more beneficial not only to follow the sequence of events taking place during bolus swallow but also to perform manometry.

Videofluoroscopy is often complemented with FEES (Butler et al. 2009) and more recently with HRM (Ferris et al. 2016). Both FEES and manometry are invasive methods, as they involve intraluminal insertion of some kind of catheter. Thus, bolus flow can be impeded and the actual physiology can be changed while performing clinical trials (Mowlavi et al. 2016). This creates a challenge for clinical trials with foods that have different rheological properties. A further complication is the intersubject variation, given that the human body is not the ideal system for a general evaluation of the influences of food properties on swallowing. As a consequence, in vitro studies of the swallowing process are gaining in popularity as a means to address some of the food-related issues before performing clinical studies, potentially reducing the number of cumbersome and expensive clinical trials.

Research groups have looked at in vitro swallowing systems from different perspectives, such as the biomechanics of swallowing, mathematical modeling/simulations, and different stages of swallowing.

2 In Vitro Models of the Oral Phase of Swallowing

Food processing in the oral compartment is highly complex, involving the teeth, tongue, gums, and saliva, the latter of which contains amylase that actively changes the bolus properties (Leonard et al. 2014). The activities of all of these components are aimed at reducing food particle size and creating a bolus that is easy to swallow (Wang and Chen 2017). In the literature, in vitro models for studying the oral stage of food processing have been described. Morrel et al. (2014) have discussed these models in much detail in a review article.

Most of the models reported in literature for oral processing concentrated on the dental aspects, such as the application of a compressive force to a given food, chewing simulation (Daumas et al. 2005; Salles et al. 2007), and influence of mastication on flavor release (Arvisenet et al. 2008; Harrison et al. 2014). Other aspects, such as bolus particle size distribution, in vitro deformation of the tongue and bolus using an artificial tongue (Ishihara et al. 2013), and oral processing of food using image analysis, have been considered (Matsuo and Palmer 2016; Hoebler et al. 2000; Chen et al. 2013). Nicosia and Robbins (2001) have studied Newtonian bolus ejection from the oral cavity by modifying the bolus density and viscosity. Bolus flow was initiated using two approaching parallel plates. The plates used in the model mimic the tongue and the palate, with the tongue being modeled as a rigid structure. Peristalsis-induced flow was investigated in the study of De-Loubens et al. (2010, 2011), in which they looked at the coating left after swallowing and the flavor release mechanism.

To the best of our knowledge, the most advanced oral simulator is the Artificial Masticator 2 (AM2), which was developed at the University of Auvergne. This device covers most aspects of oral processing of food up to the point where the bolus is ready to be swallowed (Fig. 1). These aspects include the number of chewing cycles, chewing cycle duration, temperature control of the chamber, variation in force applied to the bolus, and saliva addition. The results obtained from the model were validated through d_{50} particle size comparison in a study performed with 30 subjects (15 male, 15 female) and good agreement was observed (Woda et al. 2010).

3 In Vitro Models of the Pharyngeal Phase of Swallowing

The pharyngeal phase plays a critical role in safe swallowing. It is also the most challenging phase of swallowing, since the pharynx is common to

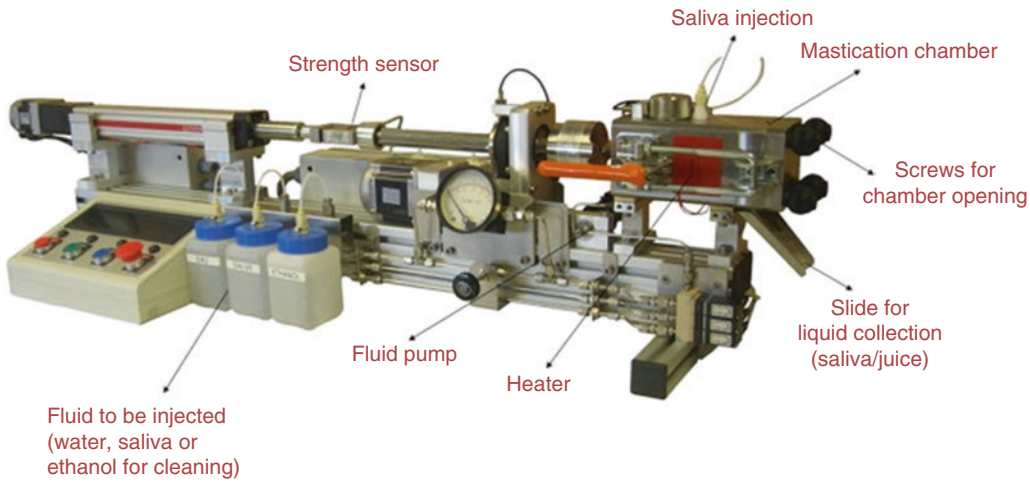

Fig. 1 General view of the Artificial Masticator (AM2). Reprinted with permission from the publisher (Morrel et al. 2014)

the airways and food tract (McFarland et al. 2016). Misdirection of the bolus in this phase could direct the bolus towards the airways (Noh et al. 2011).

The biomechanics of pharyngeal phase have been modeled in vitro by Mackley (Mackley et al. 2013) and Noh (Noh et al. 2011), and more recently by Stading and colleagues (Stading and Qazi 2017). Much of the pioneering research on swallowing simulations has been conducted by Japanese research groups. For example, researchers in the Kobalab (Chen et al. 2012), University of Tokyo, have developed an in vitro model of swallowing that encompasses both the oral and pharyngeal phases of swallowing. The device, which was patented in 2004, has been scaled to 240% of the actual size of the swallowing tract; muscular movement in the device is supported by actuators, while movement to the muscles is executed via wire assembles (Fig. 2). The device has been subsequently refined to include epiglottis and hyoid bone movements (Kikuchi 2009).

Noh et al. (2011) developed an in vitro simulator that uses videofluoroscopy to study bolus flow. The device reproduces the actual motion of swallowing process using data collected from the literature and MRI imaging. The organs involved in swallowing, such as the tongue and mandibles, are redesigned based on computer tomography images. The reproduced organs are actuated by polytetrafluoroethylene-coated wires, motors, and pulleys.

The device uses videofluoroscopy to analyze bolus flow, as in clinical studies. According to the author, the wire system loses speed with time, making accurate position measurements of the tongue and mandibles difficult. The device does not simulate epiglottis function, thus limiting its ability to mimic severe dysphagia (Chen et al. 2012). Experiments performed with the device have confirmed the reduction in speed of the bolus upon increased bolus viscosity, coupled with an increased number of residues, as also observed in clinical studies (Steele et al. 2014). Use of the device by Noh et al. further revealed that a liquid-consistency bolus travels much faster in the oropharynx, leaves fewer residues, and increases the risk of aspiration during swallowing. The videofluoroscopy unit captured images both from the front and lateral views. The study concluded that both front and lateral images should be considered when assessing food residues in the oropharyngeal cavity.

The swallowing model described by Mackley (Mackley et al. 2013), called the "Cambridge Throat," is based on an idealized, static, rectangular geometry (Fig. 3). This means all the involved parts (organs) remain stationary, including an open epiglottis, which represents a case of severe dysphagia (i.e., the patient cannot close the airways at all during swallowing). The

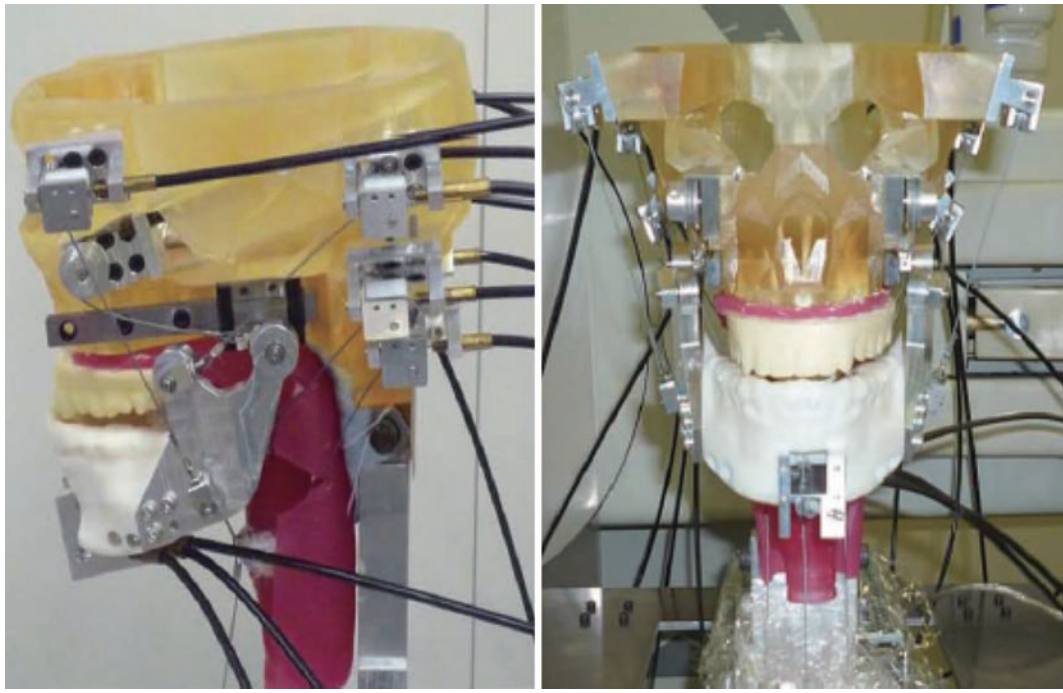

Fig. 2 Swallowing device (Noh et al. 2011) IEEE. The *left image* shows the lateral view and the *right image* shows the frontal view. Reprinted with permission from the publisher

Cambridge Throat model however represents a good starting point for studying in detail the flow during the swallowing process, especially with respect to texture-altered foods. A special feature of the Cambridge Throat model is the rotating roller that pushes the bolus towards the pharynx, which represents the peristaltic action of the tongue against the palate during the oral phase. The Cambridge Throat model was used in a second study conducted by Hayoun and coworkers (Hayoun et al. 2015) to introduce a mathematical theory of bolus rheology with respect to bolus transit time. The theory is based on the geometry and dynamics of the Cambridge Throat model taking into account the applied force, viscous dissipation, and angular acceleration of the system. When the developed mathematical theory was compared for transit times with the data from the swallowing model and images acquired from in vivo experiments using ultrasonics, good agreement was observed between the theoretical and experimental observations. This study further presents the benefits of increasing bolus viscosity and the potential advantage of having increased time for slower airway response in dysphagia, with the consequent disadvantage of post-swallow residues, as noted in clinical studies (Steele et al. 2014). The present study is limited to Newtonian fluids, ignores the role of shear thinning, and is restricted to the oral phase (rather than the pharyngeal phase where the actual aspiration takes place).

The limitation of a Newtonian bolus is however addressed in a later study (Mowlavi et al. 2016) using the same Cambridge Throat model of swallowing. That study concludes that shear-thinning liquids are better than Newtonian liquids at controlling pre-swallow leakage of the bolus. According to the study, leakage is avoided in the case of a shear-thinning liquid, since at low shear rates prior to swallowing, the bolus is more viscous and, consequently, its flow is better controlled. Another conclusion from the study performed with the improved Cambridge Throat model is that the density of the bolus is irrelevant when studying the bolus flow properties. This means that the use of high-density contrast media, as applied in the clinical studies, will not

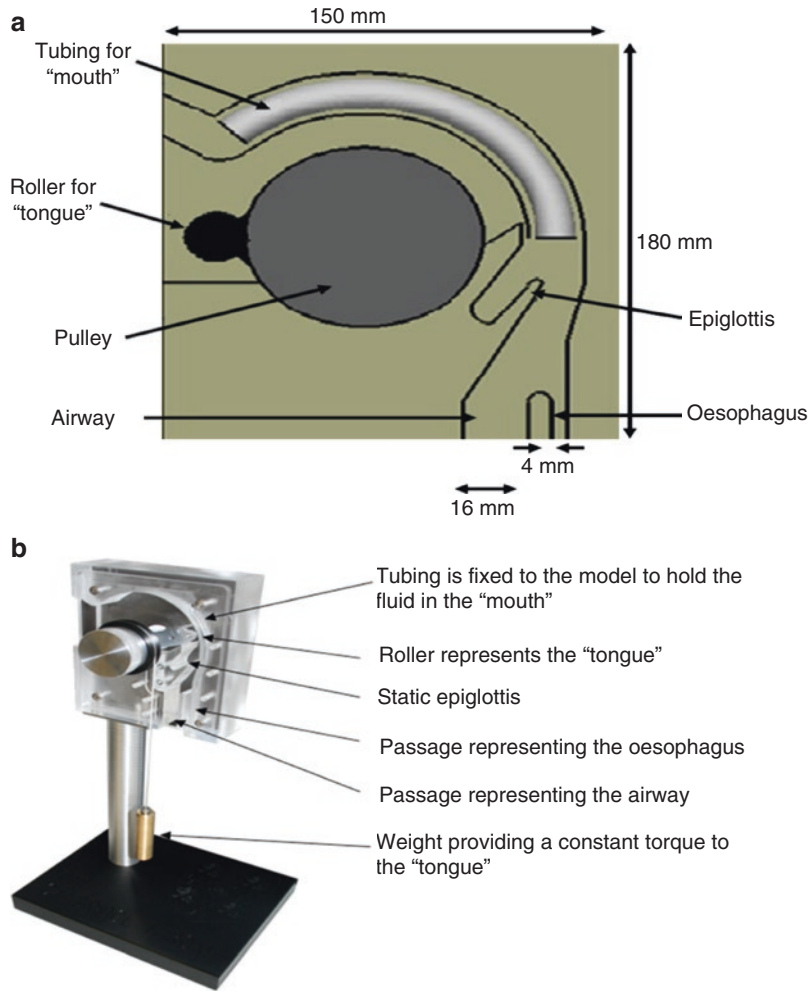

Fig. 3 The Cambridge Throat model. (**a**) Schematic diagram of the Cambridge throat with main dimensions. (**b**) Image of the whole apparatus showing torque control mechanism. Reproduced from (Mackley et al. 2013), with the permission of The Society of Rheology

influence the flow properties provided that the viscosity of the bolus matches that of the thickener solution.

The authors of this chapter have designed a new swallowing device, termed "The Gothenburg Throat," which simulates the pharyngeal swallowing process while allowing monitoring of the bolus velocity profile and shape, as well as the pressure levels at three locations in the pharynx and one location in the nasopharynx. The oral phase is modeled using a syringe that delivers a bolus of fixed volume and speed into the pharynx, thereby mimicking the tongue thrust movement. The device (Fig. 4) is based on the human pharyngeal geometry with specifications taken from the literature. The elliptical flow channel is rigid, mimicking the geometry at the instance when the bolus passes through the pharynx. The elliptical geometry was chosen to replicate as closely as possible an average human throat having a realistic area, even if the real pharynx has a shape that is more irregular than elliptical. The device can simulate closing of the larynx by employing a valve and a moving epiglottis. The upper esophageal sphincter (UES) is modeled using a clamping valve, and a separate valve opens and closes the channel to the nasopharynx. Thus, the device is designed for studies of the breathing-swallowing relationship.

The velocity profile, movement, and location of the bolus are monitored with a moving ultrasonic transducer (Wiklund et al. 2007; Wiklund and Stading 2008). The technique is based on ultrasonic pulses transmitted through the wall of

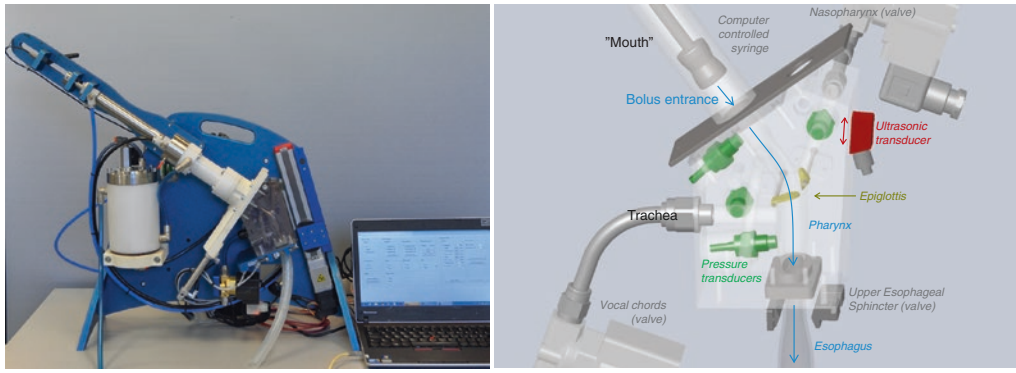

Fig. 4 The Gothenburg Throat model. *Left panel*: Photograph of the complete model. *Right panel*: Schematic of the essential features, including the syringe pump, pressure sensors (in *green*), ultrasound sensor (in *red*), and moving epiglottis and opening to the nasopharynx (in *yellow*)

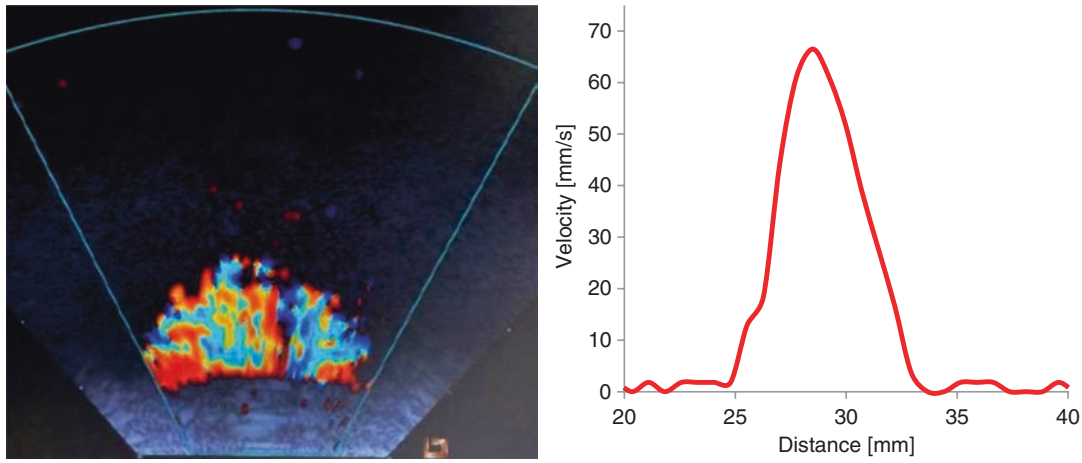

Fig. 5 Velocity profile in the "Gothenburg Throat" model during continuous flow of a thickened solution. *Left panel*: Medical scanner showing velocity and flow direction in colors. *Right panel*: Absolute velocity profile

the pharynx model and reflected by the fluid elements of the flowing bolus, giving their location and speed in real time. The transducer records a flow profile in less than 100 ms. The position and movement of the ultrasonic transducer and the opening of the valves and the epiglottis are controlled from a connected PC, which also collects the pressure and velocity data. This means that the relative timing of the separate events can be controlled, thus mimicking the various states of dysphagia.

Early results obtained with the Gothenburg Throat show good agreement with the manometric results from clinical studies (Stading and Qazi 2017). Figure 5 shows an example of the velocity profile of a shear-thinning bolus, which clearly demonstrates that a wide range of shear rates are present in the bolus during its passage through the pharynx.

Since the geometry of the model pharynx was designed to prioritize the determination of bolus flow properties, the device cannot simulate the laryngeal movement during swallowing. Laryngeal elevation and epiglottis closure act together to seal the airways, ensuring safe passage of the bolus towards the esophagus (Chang et al. 1998). Thus, the airways closure lacks the peristalsis-assisted flow that supports pharyn-

geal bolus transport, as reported in the literature (Salinas-Vázquez et al. 2014; de Loubens et al. 2010, 2011).

4 In Vitro Models of the Esophageal Phase of Swallowing

Mimicking the esophageal phase of swallowing is comparatively easy, as the esophagus has a geometry that is simpler than that of the pharynx and the flow driven by peristaltic contraction is well understood (Chen et al. 2012, 2014). The esophagus typically has a tubelike, nonrigid structure of length 20–26 cm and internal diameter of 1.1 cm, together with an inner mucosal layer (Daniel et al. 2007; Chen et al. 2014). Bolus flow in the esophagus is driven by a peristaltic wavelike motion, with a transit time of 6–10 s for liquids (Jørgensen et al. 1992). Esophageal motility is assessed by manometry based on the intraluminal placement in the esophagus of a catheter with pressure sensors and following the evolution of pressure changes in response to the peristaltic wave down along the esophagus (William and Paterson 2006).

Chen and coworkers (2014) studied the esophageal phase of swallowing by replicating as closely as possible the peristaltic behavior, pressure measurement, and material use to make the surface of esophagus resemble the actual biological setup. In the device, the peristaltic wave is generated by pumping compressed air so as to drive the bolus through the passage. The nonrigid structure in the simulator is composed of silicon rubber, so as to resemble the physiological tissue. Manometry in the device is performed by magnetic sensors, which are distributed equidistantly along the conduit.

The device was further modified to improve sinusoidal peristaltic wave generation (Dirven et al. 2015b). In another study, the improved device has been used to study the bolus flow of solutions thickened with starch, to determine whether the peristaltic transport is influenced by the bolus rheology (Dirven et al. 2015a). It was noted that the peristaltic wave pressure gradient increased with increasing bolus viscosity and with increasing wave velocity.

The model does not consider the transition of the bolus transport from the pharyngeal phase to the esophageal phase through the UES narrowing. Therefore, the link between the studied esophageal phase and the oral/pharyngeal phase of swallowing is missing.

Our overview (presented in Table 1) is based on the following keywords: in vitro swallowing; pharyngeal swallowing; in vitro manometry; mechanics of human swallowing; modeling of human swallowing; and dysphagia. Surprisingly, not a single study was found that has considered in vitro manometry during the pharyngeal phase of swallowing. However, manometric measurements have been considered in the oral and esophageal phases in some studies (Table 1). The in vitro manometric data could be combined with either the results of videofluoroscopy carried out using a high-speed camera or the results obtained using visualization techniques similar to videofluoroscopy in combination with manometry.

5 Examination of Swallowing Using the Simulation

Simulation studies enable a virtual examination of the swallowing process, taking into account the motion of the organs as well as the properties of the bolus, and have the advantage of being noninvasive (Kikuchi et al. 2017). Typically, radiographic images are used to create a 3D model, which is used to demonstrate the coordination of different muscles and to measure structural changes during swallowing (Kikuchi et al. 2015; Lin et al. 1996). Preliminary computer-based studies have been performed using barium-based swallowing and assuming a Newtonian bolus (Meng et al. 2005; Lin et al. 1996; Chang et al. 1998). Kikuchy and coworkers have considered non-Newtonian fluid properties and have concluded that a starch-thickened shear-thinning consistency decreases bolus speed and thereby helps to reduce aspiration (Kikuchi et al. 2017). The 2D geometry used by Meng and colleagues (Meng et al. 2005) was updated to 3D geometry by Salinas and

Table 1 Summary of the various systems for in vitro mechanical modeling of the swallowing process in humans

Author and year	Title	Focus of the study	Limitation	Main conclusion	Temperature/manometry consideration
Nicosia and Robbins (2001)	The fluid mechanics of bolus ejection from the oral cavity	Fluid mechanics of bolus ejection from the oral cavity towards the pharynx	Only considers bolus ejection from the oral cavity assuming Newtonian fluids	Fluid density and viscosity play governing roles in transferring the bolus from the oral cavity to the pharynx	No/yes
(Koga et al. 2008)	Signatures by a peristaltic swallowing robot	Oral rehabilitation through massage therapy	Limited application to swallowing	An oral rehabilitation robot was developed (with some limitations) that can provide massage to the oral muscles	Yes/no
Noh (2009)	Development of tension/compression detection sensor system designed to acquire quantitative force information while training the airway management task	To develop a training robot for studying the airways force information	Limited/indirect application to swallowing	A sensor system was developed that measures the force applied to organs during abnormal airways training	No/no
Woda et al. (2010)	Development and validation of a mastication simulator	Development of a mastication simulator to form a bolus	Limited to the oral phase	Mastication simulator (AM2) was developed that can perform in vitro bolus formation, mimicking human mastication behavior	Yes/yes
De Loubens et al. (2010, 2011)	A biomechanical model of swallowing for understanding the influence of saliva and bolus viscosity on flavor release	Mechanism and quantification of pharyngeal mucosa coating using forward-roll coating	Primary focus is on the oral phase; moreover saliva is assumed to be Newtonian in the model	Mechanical model presented is claimed to clarify saliva and food bolus coating with respect to swallowing: Literature values were used for comparison	No/no
(Spence et al. 2011)	Stereoscopic PIV measurements of flow in the nasal cavity with high-flow therapy	Mapping of in vitro flow velocity in nasal cavity using stereoscopic particle image velocimetry to understand the unassisted breathing	Limited/indirect application to swallow	Physiologically similar flow rates were recorded from the constructed in vitro model and during in vivo experiments. The three-component SPIV technique used here provided valuable information regarding velocity profile in lateral direction in addition to the velocity profile in axial direction	Yes/yes

Noh (2011)	Development of a robot which can simulate swallowing of food boluses with various properties for the study of rehabilitation of swallowing disorders	In vitro videofluoroscopic analysis of boluses with different textures	No epiglottis, tongue, soft palate, or larynx functionalities	Thickened boluses leave a post-swallow residue	Yes/no
Chen et al. (2012)	Review of the swallowing system and process for a biologically mimicking swallowing robot	Oral and pharyngeal swallowing	Scaled to 240% size; bolus rheology is not considered	Published in the review paper mentioned here Chen et al. (2012); direct access to the study is not available	No/no
(Bonawitz and Duvvuri 2013)	Robotic assisted oropharyngeal reconstruction with local flaps	Treatment of soft tissue defects of the oropharynx	Appropriate for surgical uses	The surgical robot developed can be applied to study head and neck pathologies, with some exceptions	No/no
Chen et al. (2013)	Soft activator mimicking human esophageal peristaltic for swallowing robot	Study of human esophageal peristaltic movement in a biologically inspired device having a nonrigid structure	Applies only to the esophageal phase	Uncontrolled deformation of the structure of the soft material makes it difficult to design the actual peristalsis in the esophagus; restricted to the pharyngeal phase, and no bolus simulation	No/yes
Mackley et al. (2013)	The rheology and processing behavior of starch and gum-based thickeners	Tongue pressure	No epiglottis function; 2D device in which all the boundaries are static, except those of the tongue	Thick bolus delays transport of the bolus to the back of the throat	Yes/no
Hayoun et al. (2015)	A model experiment to understand the oral phase of swallowing of Newtonian liquids	Effects of bolus rheology with respect to bolus transit times and oral residues	Only a Newtonian fluid is studied, while the residues in the pharyngeal phase, where the actual aspiration takes place, are ignored	A lower force applied during swallowing decreases the velocity and increases the oral transit time	No/no

(continued)

Table 1 (continued)

Author and year	Title	Focus of the study	Limitation	Main conclusion	Temperature/manometry consideration
Dirven et al. (2015b)	Biomimetic investigation of intrabolus pressure	Influence of bolus rheology on a peristaltic wave generated in the esophagus	Applies only to the esophageal phase	Peristaltic wave generated in the esophagus is influenced by the bolus rheology	No/yes
Mowlavi et al. (2016)	In vivo observations and in vitro experiments on the oral phase of swallowing of Newtonian and shear-thinning liquids	The Mackley throat is used to study the oral phase of swallowing with respect to Newtonian and shear-thinning liquids	The primary focus of the study is the oral phase; it is not clear whether the subjects used are patients with dysphagia or healthy individuals	Lower tongue force delays oral transit and, therefore, the individuals may be subjected to an over-thickened bolus. With shear thinning liquids, pre-swallow slippage is avoided	No/no
Stading and Qazi (2017) (manometry)	An in vitro model of the pharynx for evaluation of bolus flow	Construction and validation of the Gothenburg throat model, which has a realistic pharyngeal geometry. Determination of bolus velocity and breathing-swallowing relationships	Static pharynx geometry; no laryngeal movement	Pressures during swallowing and pharyngeal transit times comparable to in vivo studies. Bolus velocity profile determined	Yes/yes

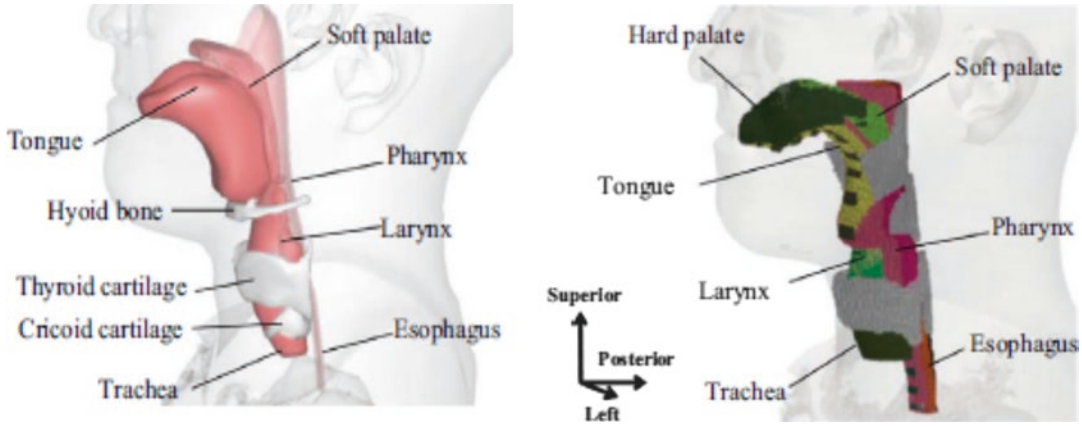

Fig. 6 Simulation model showing the left-front view (*left panel*) and the particle model left-front view (*right panel*). The control regions are shown in *gray* and *black*. Reprinted with permission from (Kikuchi et al. 2017)

coworkers (Salinas-Vázquez et al. 2014) to allow studies of abnormal swallowing of non-Newtonian fluids, and they concluded that the bolus is subject to extensional stresses, in addition to shear stresses. Based on this, the author suggested that extensional deformation should also be considered as part of the bolus modification strategy.

More recently, a Japanese group (Kikuchi et al. 2017) presented a comprehensive swallowing simulator using moving particle simulations. The simulation shows the interactions between the food bolus and the physiological organs during swallowing (Fig. 6). The organs considered are the tongue, larynx, pharynx, palate, and esophagus. This simulation can reproduce both normal bolus flows during swallowing and penetration aspiration encountered during abnormal swallowing. Moving particle simulations ably mimic the flow of Newtonian fluids, such as water, although they are not used for non-Newtonian fluids.

5.1 General Observations

An important parameter that has not been considered to date in studies that model pharyngeal swallowing is the temperature to which the bolus is exposed to in the pharynx, and how it influences the actual bolus rheology from the oral to pharyngeal stage and onwards to the esophageal stages. Temperature is important, especially in cases of dysphagia, as the oropharyngeal response of the patient with dysphagia is slower than that of normal individuals, which increases the risk of bolus modification during swallowing (Ekberg et al. 2010).

According to our knowledge, there is currently no in vitro model of swallowing that covers simultaneously all the three main stages: oral, pharyngeal, and esophageal. A comprehensive in vitro model should cover all the stages of swallowing and the transitions between these stages. The model should preferably be based on the actual geometry that changes during swallowing, respecting the actual timing of events as in humans.

Some difficulties arise in the mimicking of swallowing in humans, in particular:

- The construction of a dynamic geometry that executes the same functions as the actual bio-phenomena
- The reproduction of airway-protective measures, such as those that involve closure of the vocal cords and tilting of the epiglottis at the rates seen in the actual human body
- The identification of a material with surface properties that allow it to be insalivated as in the real-life situation, thereby enabling the study of the actual bolus flow

From the materials perspective, an obvious limitation to the numerical simulations of bolus flow is the complexity of bolus rheology (encompassing shear thinning, yield stress, elasticity,

and particle content) and the complex, changing geometry of the pharynx during swallowing. Bolus elasticity promotes safe swallowing (Nystrom et al. 2015), while a recent study by the current authors shows that gum-based thickeners have a minor yield stress due to the stranded network structure visualized in electron microscopy (Waqas et al. 2017). Finally, rheology considers the bulk properties only, whereas the mechanical interactions of the tissues during the oral phase and during peristalsis would in addition require the study of tribology.

Conclusion

In vitro modeling of human swallowing allows accurate mimicking of several of the complex phenomena that occur during swallowing, and permits the researcher to focus on the effect of bolus rheology. In contrast to clinical studies, it is possible to perform a large number of experiments in a well-defined geometry, thereby eliminating inter- and intra-subject variabilities.

A definitive swallowing device that covers all aspects of the swallowing process, from the oral to pharyngeal and esophageal stages, is still lacking. Nevertheless, there are several promising models, which combined with numerical simulations and validated in clinical trials could give valuable insights into the mechanisms of swallowing, as well as the influences of specific bolus properties.

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The Therapeutic Swallowing Study

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Contents

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1 Introduction

When selecting an instrumental procedure to assess oral and pharyngeal swallowing dysfunction videoradiography is the only technique where the entire swallowing sequence could be analyzed (Donner 1988; Jones and Donner 1989; Ekberg 1990, 1992; Dodds et al. 1990a, b; Bingjie et al. 2010; Pisegna and Langmore 2016; Nordin et al. 2017). Accordingly this is an excellent tool for the dysphagia therapist in the management of dysphagic patients.

The videofluoroscopic swallowing study (VFSS) is also referred to as the modified barium swallow study (MBSS) and has been shown to have high clinical yield (Martin-Harris et al. 2000; Gates et al. 2006; Martin-Harris and Jones 2008). Because of the therapeutic implications of the swallowing study, as well as the therapeutic approaches that can be applied and tested during the examination, the study will be described as "the therapeutic swallowing study—TVSS" in this chapter. The therapeutic swallowing study permits observation of upper aerodigestive tract function as the patient swallows varied volumes and textures of different radiopaque materials (Logemann 1986). It has been showed that VFSS protocols using foods with different consistencies would be valuable before recommending normal diet for patients suffering from stroke or other brain injuries (Kang et al. 2011). For accurate and reliable implementation and

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interpretation of test results specialized training is required (Logemann et al. 2000).

During the TVSS digital technique is most often used and the entire examination could be recorded on a dynamic medium such as videotape or computer disk making it possible to analyze structural movements in relation to contrast flow in slow motion and frame by frame. However, nowadays digital radiography, i.e., different high-resolution videofluoroscopic recording devices, is used in most radiological departments. The examination could then be transmitted digitally to an electronic picture archiving and communication system (PACS) to provide rapid retrieval and analyses of the entire swallowing sequence. The availability is excellent and easy to handle and any pathophysiology could be analyzed in detail related to the flow of different given textures. For example disordered timing and coordination of structural movement, and the presence, degree, timing, and cause of aspiration, can be documented.

The therapeutic swallowing study is a dynamic procedure that examines the mechanical passage of food and liquid from the mouth to the stomach. However, in most studies the focus lies on oral and pharyngeal phases of deglutition. Comprehensive examination includes the observation of oral bolus manipulation, lingual motility efficiency of mastication, timing of pharyngeal swallow initiation, soft palate elevation and retraction, tongue base retraction, pharyngeal contraction, superior and anterior hyolaryngeal movement, epiglottic inversion, and extent and duration of pharyngoesophageal segment opening (Martin-Harris et al. 2000).

Martin Harris et al. have developed a new modified barium swallow study tool, the Modified Barium Swallow Impairment Profile, or MBSImP, that has "demonstrated clinical practicality, favourable inter- and intrarater reliability following standardized training, content, and external validity" (Martin Harris et al. 2008). "The MBS ImP technique is described as an evidence-based, standardization of the MBS study in adults. The MBSImP assesses 17 critical components of swallowing and provides an objective profile of the physiologic impairment affecting adult swallowing function. For the first time, the MBSImP provides the means for clinicians to communicate MBS study results in a standardized, evidence based manner that is consistent, specific, and accurate" (Shaw Bonilha et al. 2013).

Various therapeutic strategies, such as postural techniques, maneuvers, and techniques improving oral sensory awareness, can be systematically applied and tested and their effect on function can be observed (Ekberg 1986; Logemann et al. 1989; Martin et al. 1993; Martin 1994; Bülow et al. 2001). Different materials are given to the patient to identify optimal food and liquid textures that facilitate a safe and efficient oral intake.

Clinical experience and research findings provide evidence that aspiration, and more importantly the cause of aspiration, can be missed during observations made from test swallows included in a clinical or bedside examination. Studies have shown that clinicians do not consistently identify the presence of aspiration during clinical examinations. The sensitivity and specificity of the bedside examination in detecting aspiration and in predicting patient outcome warrant further study. Furthermore, it has been reported that 50–60% of patients who aspirate do not cough (Linden and Sibens 1983; Splaingard et al. 1988; De Pippo et al. 1992; Nathadwarawala et al. 1992, 1994; Zenner et al. 1995; Miller et al. 2014; Jaffer et al. 2015).

Despite its limitations, the bedside or noninstrumental examination provides important information regarding signs and symptoms of potential swallowing disorders and need for further instrumental examination, impressions regarding the patient's language and cognitive status, propensity for fatigue during eating and drinking, and a realistic picture of the patient's eating and drinking patterns.

2 How to Perform the Study

At the radiological department of Skåne University Hospital, SUS, Malmö, Sweden, we started our examinations in 1993, and have now almost 25 years of experience. Our swallowing assessment team includes collaboration between speech/language pathologists and radiologists in the performance and analysis of the therapeutic swallowing study. We perform our studies twice a week, and have the opportunity to schedule at least 10–12 patients every week. The teamwork of the two specialists provides rapid and adequate information about current swallowing dysfunction and management recommendations to the referring clinician, patient, and caregivers.

The swallowing recording equipment includes:

- **Digital technique** (Philips multidiagnost ELEVA)
- Sectra (RIS, PACS)
- PACS (picture archiving and communication system)
- **Microphone**
  Another equipment mostly used in swallowing research is the KAY Pentax 72 45 C, swallowing work station.

The patient is administered controlled food and liquid textures that are mixed with contrast resulting in a simulated diet but dense enough to allow X-ray visualization. Typically, barium sulfate is used and allows for optimal visualization of bolus passage through the alimentary tract (Murray 1999). However, the sensory properties of food may be affected by adding barium sulfate (Ekberg et al. 2009; Stokely et al. 2014). In another study the importance of rheologically matched test materials is discussed (Groher et al. 2006).

The procedure is most often performed with the patient seated in an upright position (Fig. 1). If the individual is unable to assume and maintain a seating position, adaptive seating devices can be employed. If such devices are not available, the patient may be placed on the fluoroscopic table and the examination is performed with the patient lying down. The head and trunk can then be raised to a semi-upright position. The individual can also be positioned seated in his/her own wheelchair if there is adequate distance between the floor and fluoroscopic tube to permit oropharyngeal and cervical esophageal viewing.

Fig. 1 The laboratory with a patient in an upright position

The study typically begins with the subject in lateral view, the optimal position for visualizing penetration or aspiration of material into the laryngeal vestibule before, during, and after swallowing. In lateral view the profile contours of the soft palate, base of the tongue, posterior pharyngeal wall, epiglottis, aryepiglottic folds, anterior hypopharyngeal wall, and the region of the cricopharyngeal muscle or pharyngoesophageal segment can be assessed. The patient is then positioned in a frontal view permitting assessment regarding asymmetric contours, surface of the base of the tongue, median and lateral glossoepiglottic folds, tonsillar fossa, valleculae, and hypopharynx (Fig. 2).

In our experience the amount of radiation during the study is low, 2–5 mSv (absorbed dose), which is about one-eighth of the amount when performing a colon examination. The average radiation exposure time is 2–3 min. Radiation dose in videofluoroscopic swallow studies was studied in the UK by Zammit-Maempel et al. (2007). They concluded that videofluoroscopy could be performed using minimal radiation dose. Their data is based on the largest number of videofluoroscopic swallowing studies published to date. In another study from 2013 it was found that a standardized protocol for MBSS did not cause unnecessary radiation exposure time during the MBSS (Bonilha et al. 2013).

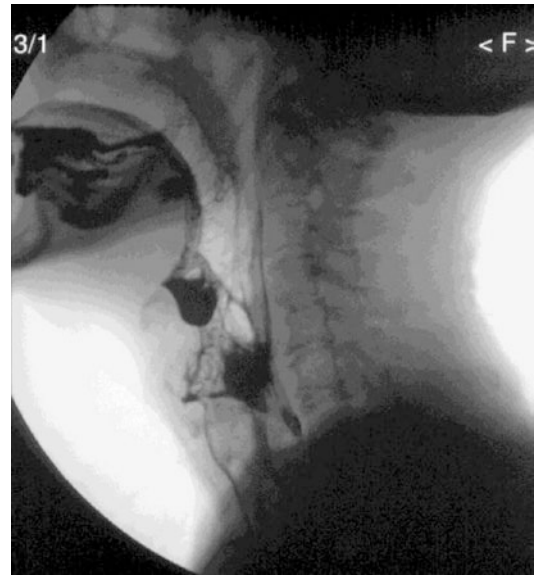

Fig. 2 The lateral radiograph illustrates a tracheal penetration and residue in valleculae and pyriform sinus secondary to a brain-stem stroke

It is critical and of importance that caregivers, nurses (e.g., depending on the medical status of the patient), and/or family members could be present and observe the study either at the time of the examination or at a later viewing of the recorded examination. This provides the opportunity to educate the caregivers in the nature of the patient's swallowing problem, and the necessary precautions and management strategies that must be applied to ensure airway protection and efficient oral intake.

3 Routines During the Study

If possible the patient has to fill in a self-report instrument before the examination. At our clinic we use a validated version in Swedish of Sidney Swallowing Questionnaire (SSQ) (Arenaz Búa and Bülow 2014). During the examnation we complete one of our swallowing protocols. Which one depends on the specific examination (Tables 2 and 3).

The Swallowing Pathologist

- Decides how the procedure will be performed based on actual referral or from observations of the patient during a bedside examination. The volumes and textures of contrast materials used in the study should be tailored to meet the particular needs of the patient based on his/her clinical swallowing presentation.
- Selects contrast materials (mixing, measured volumes, order).
- Talks to the patient before the examination, and if possible asks for actual symptoms, and gives information about the examination.
- Systematically applies trial therapeutic strategies based on the observed nature of the swallowing disorder.
- Completes the swallowing protocol during the procedure.
- Documents a collaborative report. If necessary together with the radiologist. The report includes recommendations for nonoral intake, appropriate food/liquid textures and bolus volumes, and necessary therapeutic strategies such as compensatory postures, maneuvers, and exercises.

The Radiologist

- Operates the fluoroscopic equipment and observes anatomic abnormalities.
- Documents a collaborative report with the swallowing therapist.

The Assistant Nurse

- Prepares the fluoroscopy suite for the study.
- Prepares the appropriate test material, and administers the material to the patient.
- Completes the registration and operates the videotape recorder.
- Assists the patient before and after the study.

4 Test Material

Every procedure is individually adapted to the patient, even if the same routines are used. If there is a suspicion of aspiration and/or we do not know for sure whether the patient will initiate a pharyngeal swallow, the procedure starts with 2 or 3 mL of water-soluble contrast either as thin or thickened liquid. The patient may not be exposed to any risk of severe aspiration.

The normal procedure consists of the following consistencies (Fig. 3a and b):

- **Pudding** (made from berries)
- **Timbale** (smooth consistency, fish, meat, or vegetables)
- **Sorbet** (sour and cold)
- **Paté** (corny consistency)
- **Chopped solid material** (normal food chopped into small pieces; either meat, fish, or vegetables in sauce.)
- **Thickened liquid**

  Thickened liquid is made fruit puré.

- **Carbonated liquid**

  The carbonated liquid is prepared with tap water and a soda stream machine.

- **Thin liquid**

  See Table 1 for the test material recipe.

From many years of clinical experience we have learned that the amount of contrast mixed with the different materials, solids or liquids, should be 60% test material and 40% contrast.

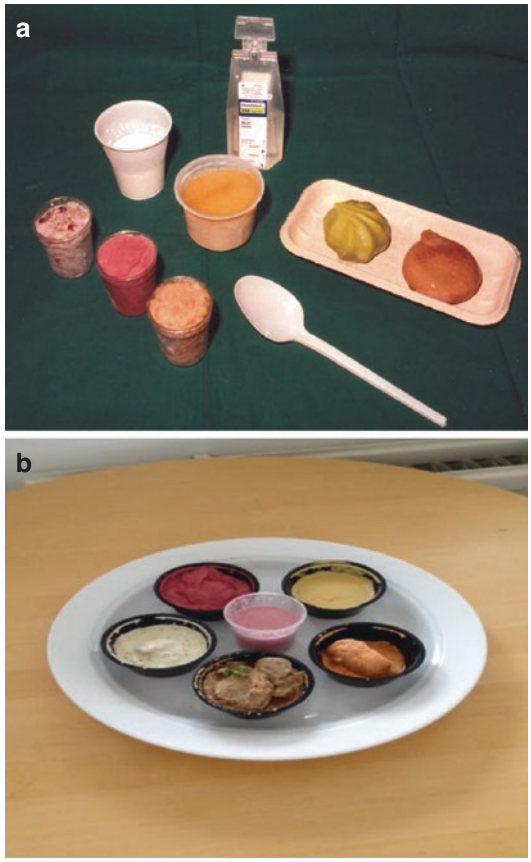

Fig. 3 Test material

Table 1 Recipe of material for the therapeutic swallowing study

• 1 Portion solid bolus consists of 45 g product and 15 g of E- Z-HD barium sulfate for suspension and gives 60 g ready-mixed material (0.5 dL)
• 1 Portion thickened liquid consists of 100 g product and 30 g of E- Z-HD barium sulfate for suspension and gives 130 g ready-mixed material (1 dL). Each dose on 5 mL has a weight of 5 g.
• 1 Portion of thin liquid consists of E- Z-HD barium sulfate for suspension 40% w/w
• 1 Portion carbonated liquid consists of tap water mixed in a soda stream machine. 400 mL of carbonated water is mixed with 100 mL (2 × 50 mL) Omnipaque 350 (350 = mg iodine per mL liquid) just before it has to be used, and should be served cold

Another important observation after analyzing thousands of patients with swallowing dysfunction is that most patients do not need to be recommended several grades of thickened liquids. Our protocol consists of one thick liquid and carbonated liquid. Several different thickened liquids may be confusing for the patient, and may not be easy to handle and use.

When testing mastication some sort of crisp bread covered with barium paste could be used.

Most test material is, if possible, given two times in various amounts from 3 mL, 5 mL, to 10 mL or more. However, depending on the severity of the swallowing impairment and degree of aspiration water-soluble contrast may be used. The patients are fed by the assistant nurse but may if possible also feed themselves, giving important information about their habitual eating and drinking behaviors. However, if nursing staff or significant others are present at the examination they could feed the patient.

Patients suffering from right hemispheric damage often take excessive amounts of solids and liquids during mealtime. This is an important behavior to identify and modify. Studies showing typical bolus volume during thin-liquid swallows indicate that the average volume habitually ingested by males is 21.3–29.3 mL and 13.6–20.4 mL in females (Adnerhill et al. 1989). If the patient wishes, or if he/she reports symptoms with only very specific food or liquid items, he/she may bring material to the examination where it will be mixed with barium contrast and tested.

The test material used in our clinic is prepared by a master chef working at a nursing home, and thereby experienced in cooking for elderly persons with special need of modified textures. In our opinion individuals coming for a TVSS examination, in most cases elderly persons, should get the same food as they are used to. So therefore, food well known for most persons, and therefore easy to recognize, are given to our patients. The only difference is that the test material is food mixed with contrast, either barium sulfate or iodine contrast, in small amounts. However, even if today it is possible to buy readymade test meals from the food industry we have learned that it is of importance for our patients to feel comfortable, and be familiar with the food they get during the examination.

When the test material comes to the radiological department in small cans, 0.5 dL for a solid bolus and 1 dL for thickened liquids, it is placed in a freezer. Before every assessment the assistant nurse takes it from the freezer in time for the study. Every patient gets his/her individual combination of test material depending on the nature of the swallowing problem (Tables 2, 3 and 4).

Table 2 Protocol for therapeutic videoradiographic swallowing examination

Therapeutic Videoradiographic Swallowing Study (TVSS) Date:_____ Radiologist SLP Name:_____Person number: Actual status:_____ Referral _____									
Lateral view	2	10	Independent	Oral dysfunction	Delayed	Absent	Pharyngeal	Penetration	Rosenbek Penetration/ aspiration scale
	3	15	Has to be fed		Pharyngeal swallow	Pharyngeal swallow	Retention	Subepiglottic	
	5 mL	20 mL	Syringe				Mild	Supraglottic tracheal	
							Moderate		
							Severe		
Solids (smooth consistency)									
Sorbet									
Timbale (smooth consistency)									
Paté (corny consistency)									
Hackad kost									
Regular food									
Thin liquid									
Thickened liquid									
Carbonated liquid (soda stream)									
Water-soluble contrast									
Bread									
Other									

Therapeutic strategies
Sensory stimulation:
TTS
Push down with a spoon against the tongue
Sour bolus (lemon)
Larger bolus volume
Cold bolus—sorbet
Chewing
Postural techniques:
Chin tuck
Head back
Head rotated to damaged side
Head rotated
Head tilt to stronger side
Swallowing techniques:
Supraglottic swallow
Super-supraglottic swallow
Effortful swallow
Mendelsohn maneuver
Recommended treatment: Diet modification:

Table 3 Protocol for therapeutic videoradiographic swallowing examination, Radiological Department, University Hospital MAS, Malmö

Consistencies		Thin liquid	Thick liquid	Carbonated	Pudding	Puree	Solid bolus
Lateral view:							
Oral preparation:	Normal	0	0	0	0	0	0
	Incomplete lip closure	1	1	1	1	1	1
	Delayed bolus preparation	2	2	2	2	2	2
	Diffuse spreading of bolus in oral cavity	2	2	2	2	2	2
Oral phase:	Normal	0	0	0	0	0	0
– Leakage	Anterior:	1	1	1	1	1	1
		2	2	2	2	2	2
	Posterior:	1	1	1	1	1	1
		2	2	2	2	2	2
– Tongue movements	Normal coordination	0	0	0	0	0	0
	Inefficient	1	1	1	1	1	1
– Mastication	Normal	0	0	0	0	0	0
	Inefficient	1	1	1	1	1	1
– Delayed bolus transport	Mild	1	1	1	1	1	1
	Moderate	2	2	2	2	2	2
Regurgitation into nasal cavity		1	1	1	1	1	1
Dissociation	<0.5 s	0	0	0	0	0	0
	0.5–2 s	1	1	1	1	1	1
	3–5 s	2	2	2	2	2	2
	>5 s	3	3	3	3	3	3
Pharyngeal phase:							
– Laryngeal elevation, Movements of os hyoid	Normal	0	0	0	0	0	0
	Reduced	1	1	1	1	1	1
	Anterior movement incomplete	2	2	2	2	2	2
	Elevation absent	3	3	3	3	3	3
– Epiglottic movement	Normal	0	0	0	0	0	0
	Incomplete	1	1	1	1	1	1
Vestibulum penetration—aspiration	No	0	0	0	0	0	0
	Subepiglottic penetration	1	1	1	1	1	1
	Supraglottic penetration	2	2	2	2	2	2
	Tracheal penetration	3	3	3	3	3	3
Constrictor muscles/ retention	No	0	0	0	0	0	0
	Weak muscles, +/− mild retention	1	1	1	1	1	1
	Paresis one segment, +/− moderate retention	2	2	2	2	2	2
	Severe paresis, +/− severe retention	3	3	3	3	3	3
PES	Normal opening	0	0	0	0	0	0
	<25% impaired	1	1	1	1	1	1
	25–50% impaired	2	2	2	2	2	2
	>50% impaired	3	3	3	3	3	3
Frontal view:							
Unilateral paresis							
Bilateral paresis							
Vocal fold closure							
Comments: Total points:							

Table 4 Disorders documented on videofluoroscopy and management (modified from Martin (1994))

Radiographic presentation	Cognitive and sensory stimulation, oral motor exercises, diet modification, alternative nutrition	Head positioning	Maneuvers
Oral phase: Anterior leakage due to incomplete lip closure Oral residue Posterior leakage due to spill over tongue base Delayed bolus preparation Diffuse spreading of bolus in oral cavity Inefficient tongue movements and mastication Delayed bolus transport Aspiration before pharyngeal swallow Regurgitation into nasal cavity	Optimise liquid/ food texture Sufficient bolus volumes Intraoral placement to unimpaired side Labial resistive exercises Buccal range of motion exercises and resistive exercises Lingual range of motion exercises and resistive exercises Bolus control exercises Thickened liquids, cold liquids, semisolids, soft solids Controlled bolus volume Thickened liquids and semisolids Bolus hold exercises	Head tilt to unimpaired side	Lip pursing Double swallow Supraglottic swallow
Dissociation: Delayed initiation of pharyngeal swallow	Thermal Tactile Stimulation. Thickened liquids. Cold stimulus. Controlled bolus volume Bolus hold exercises	Chin tuck	Supraglottic swallow
Pharyngeal phase: Laryngeal elevation reduced Movements of os hyoid: Elevation incomplete, anterior movement incomplete Epiglottis – Incomplete closure Misdirected swallows: Vestibulum laryngis – Subepiglottic penetration – Supraglottic penetration Tracheal penetration -aspiration Weakness of constrictor muscles: Mild, moderate or severe Retention Unilateral, pocketing in valleculae or/and pyriform sinus Bilateral, pocketing in valleculae or/and pyriform sinuses	Controlled bolus volume Slightly thickened liquids Thinned semi-solids Cold stimulus Thickened liquids Thermal tactile stimulation Bolus hold exercises Controlled bolus volume Liquids, semisolids and soft solids Hard swallow Controlled bolus volume Liquids and thinned semi-solids	Chin tuck Head rotation toward impaired side Head tilt toward unimpaired side Head rotation	Mendelsohn manoeuver Mendelsohn manoeuver Supraglottic swallow Supraglottic swallow Double swallow Modified supraglottic swallow Double swallow Modified supraglottic swallow
PES: – Impaired opening Regurgitation from esophagus to pyriform sinuses	Liquids, semisolids and soft solids Controlled bolus volumes		Mendelsohn maneuver Double swallow Modified supraglottic swallow
Absent pharyngeal swallow	Thermal tactile stimulation Tube feeding		

5 Protocol I: Therapeutic Videoradiographic Swallowing Examination

The protocol normally used during the TVSS examination is given in Table 2.

6 Protocol II: Therapeutic Videoradiographic Swallowing Examination

When performing research project different protocol could be used. One example is given in Table 3.

7 Swallowing Management

Upon completion of the therapeutic swallowing study, the swallowing therapist has identified the nature and severity of the swallowing disorder, makes recommendations for oral versus nonoral intake, and designs an individual treatment plan directed toward specific swallowing functional outcome goals. Every applied treatment strategy must be based on a sound rationale according to the nature of the swallowing problem and the physical and cognitive status of the patient (Table 4). In a systematic review from 2010, Speyer et al. have found that there still are many questions remaining regarding the effect of different therapeutic strategies in oropharyngeal dysphagia performed by speech–language therapists (Speyer et al. 2010). Also other studies have concluded that further research is necessary to evaluate the effectiveness of dysphagia treatment (Ashford et al. 2009; McCabe et al. 2009).

Actual research has stated that dysphagia treatment may change from using compensatory strategies to promote brain plasticity to be able to recover the swallowing function and thereby improve brain-related swallowing dysfunction (Cabib et al. 2016).

At Rose Center, University of Canterbury, New Zeeland, Professor Maggie Lee Huckabee has developed a training protocol named Biofeedback in Strength and Skill Training (BiSSkiT). This is an interesting new option for rehabilitation and outcome measurement of swallowing impairment that seems to be very promising: http://www.rose-centre.canterbury.ac.nz/bisskit/

However, often used strategies may still be used and include postural techniques, sensory improvement techniques, swallowing maneuvers, isometric exercises applied to the muscle groups of the tongue and suprahyoid musculature, and bolus volume and texture modification. Combinations of different management strategies are often used (Bülow et al. 1999; Bodén et al. 2006; Carnaby et al. 2006; Logemann 2008; Pauloski 2008).

In the managements of the dysphagic patient a team approach is often necessary and one of the most important partnerships is between speech–language pathologists and dieticians (Heiss et al. 2010). Another interdisciplinary way of management is described in a study from 2005 (Denk and Bigenzahn 2005).

A critical component in the management of dysphagic patients is providing accurate *information*. *To inform and explain current problems in an understandable way* is essential for the patient, family members, and nursing staff in terms of heightening awareness and understanding of the dysfunction, and highlighting the necessity for swallowing precautions and treatment. The successful rehabilitation of a dysphagic patient will to a large extent depend on the implementation of a team approach, with the patient and family as key components of the team.

Education of the medical and nursing staff regarding how to observe potential swallowing problems, and hosting routine patient care rounds, facilitates appropriate patient referrals and expedites the care of dysphagic patients

7.1 The Postural Techniques

To change head or body posture in dysphagic patients is for most individuals relatively easy to perform and can successfully eliminate misdirected swallows (penetration/aspiration) on liquids 75–80% of the time and is widely known and used among several speech–language pathologists (Logemann 1998; Okada et al. 2007; McCulloch

et al. 2010). *Head down (chin tuck)* widens the valleculae, pushes the tongue base backward toward the pharyngeal wall, places the epiglottis in a more posterior position, and narrows the entrance to the larynx. This position is used in cases where there is a reduction in posterior tongue base motion, unilateral laryngeal dysfunction, delayed initiation of pharyngeal swallow, and reduced laryngeal closure. For patients with weak pharyngeal constrictor muscles, a chin tuck position makes the difficulties worse, especially when swallowing a masticated bolus, which could lead to increased retention in the pharyngeal recess and post-swallow aspiration (Shanahan et al. 1993; Elmståhl et al. 1999; Welch et al. 1993; Bülow et al. 1999; Baylow et al. 2009). But chin tuck could reduce the depth of misdirected swallows (penetration/aspiration) (Bülow et al. 2001).

By using the *head back* posture, gravity can facilitate more efficient clearance of the oral cavity when oral transit is disturbed; however, good airway protection and pharyngeal swallowing mechanics must be present for safe implementation of this posture. When the *head is rotated to the damaged side* the passage through the damaged or weakened side is reduced permitting primary bolus passage through the stronger side. The *head rotation posture also pulls* the cricoid cartilage away from the posterior pharyngeal wall and facilitates passage into the cervical esophagus as in the case of decreased pharyngoesophageal segment opening (Logemann et al. 1989). *Head tilt to the stronger side results in* bolus passage down on the stronger side in *the case of* unilateral oral and pharyngeal weakness. *Lying down on one side* will take advantage of the gravity effect on pharyngeal retention, and reduce the likelihood of aspiration of residue after the swallow in cases of reduced pharyngeal contraction.

7.2 Sensory Improvement Techniques

Techniques such as thermal tactile stimulation and bolus manipulation are designed to improve oral sensory awareness and improve the timing of swallow initiation (Lazzara et al. 1986; Rosenbek et al. 1996; Lim et al. 2009; Teismann et al. 2009). Furthermore, bolus could be manipulated in different ways such as giving a sour bolus, a cold bolus, a larger volume bolus, and a bolus that requires chewing. Pressure applied to the tongue during spoon administrations of food may also facilitate productive tongue movement toward a functional swallow.

7.3 Swallowing Maneuvers

The four different techniques that are designed to change a selected aspect of the physiology of pharyngeal swallow include supraglottic swallow, super-supraglottic swallow, effortful swallow, and the Mendelsohn maneuver (Logemann 1998; Logemann and Kahrilas 1990; Kahrilas et al. 1992). Swallowing maneuvers showed during videofluoroscopy a greater range of hyoid bone displacement (van der Kruis et al. 2010). Despite their proven effectiveness in some patients, the complexity of the maneuver often precludes their usage with patient experiencing language-cognitive impairment, pulmonary disease, deconditioning, and fatigue.

7.4 Supraglottic Swallow and Super-Supraglottic Swallow

The primary purpose of these techniques is to ensure airway protection prior to and throughout the swallow.

- The techniques include instructing the patient to (1) take a breath, hold it, and, in the super-supraglottic swallow, bear down; (2) swallow; (3) clear their throat without inhaling; and (4) dry swallow. It has been shown that instructing the patient to hold their breath" hard" and" bear-down" results in optimal glottic and supraglottic closure (Martin et al. 1993; Logemann 1998).

The purpose by bearing down in the super-supraglottic swallow technique is to assist the closure of the posterior glottis and the false vocal folds.

7.5 Effortful Swallow

The purpose of this technique is to increase posterior motion of the tongue base during pharyngeal swallow. The increase in tongue base retraction associated with the maneuver should facilitate improved bolus clearance from the valleculae (Logemann 1998). This technique could also reduce the depth and severity of misdirected swallows (penetration/aspiration) (Bülow et al. 2001). In later studies effortful swallow has been studied from different perspective by using electromyography and pharyngeal manometry (Huckabee and Steele 2006; Witte et al. 2008).

Instructions

- Squeeze hard with all of your tongue muscles when you swallow.

7.6 Mendelsohn Maneuver

The purpose of this maneuver is to increase the duration and extent of laryngeal elevation and thereby increase the width and duration of (pharyngoesophageal) cricopharyngeal opening (Logemann 1998). Following early relaxation of the cricopharyngeus muscle, the pharyngoesophageal segment is pulled open as the cricoid cartilage is moved away from the posterior pharyngeal wall during upward and forward movement of the hyoid bone and larynx. The functional result of this technique is to facilitate bolus passage through the pharyngoesophageal segment and decrease the degree of pyriform residue (Lazarus et al. 1993; Wheeler-Hegland et al. 2008).

Instructions

- Pay attention to your neck by swallowing your saliva several times.
- Try to feel how your Adam's apple lifts and lowers as you swallow.
- Swallow again, and when you feel the Adam's apple lift, keep it in its highest position by squeezing the muscles of your tongue and neck for several seconds.

7.7 Oral Motor Exercises

By performing specialized exercises to the striated musculature of the tongue, pharynx, and cervical esophagus region, there is some evidence to suggest that it is possible to improve muscle strength and range of motion (Logemann 1983, 1995; Sonies 1993). The exercise program must be individually adapted depending on the specific type(s) of "swallowing impairment", and clearly documented and explained to ensure independent patient implementation whenever possible. Some exercises have prescribed intensities and frequencies, such as the Shaker exercise (Shaker et al. 1997). Other isometric strengthening exercises are usually introduced in a hierarchy of difficulty, with a gradual increase in intensity and frequency. Based on what is known about skeletal muscle physiology in other parts of the body, it is likely that the patient will need to continue an exercise maintenance program even after functional swallowing skills are acquired.

7.8 Diet Modification

Food and liquid texture modifications are in most cases found to be necessary based on the results of the therapeutic swallowing study, and to enable that the patient could maintain adequate oral nutrition. Several of our patients may suffer from language disabilities that makes it difficult to understand instructions and thereby perform different swallowing techniques. Therefore diet modifications are often the most important way to help the patient to establish a safe swallow. We have learned that sour sorbet could be very effective in the management of patients with oral swallowing dysfunction. Also carbonated liquids are a very good option for many patients, and may often be better tolerated than thickened liquids (Bülow et al. 2003; Sdravoue et al. 2011; Michou et al. 2012).

We have also found that it often may be a problem to communicate the different textures between health care professionals. The

terminology and the different textures may be very different from one health care setting to another. Wendin et al. have tried to develop a system of objective, quantitative, and well-defined food texture categories by using a combination of sensory and rheological measurements (Wendin et al. 2010).

7.9 Oral Versus Nonoral Feeding

Tube feeding methods, such as nasogastric tube, percutaneous endoscopic gastrostomy (PEG), or jejunostomy, are sometimes the only safe and efficient avenues for feeding in severely dysphagic patients. It is a common occurrence for a patient to have tube feedings as the primary source of nutrition and hydration, with safe supplementation of small amounts of modified food and liquid textures for pleasure and optimizing of quality of life. It has been found that dysphagic stroke patients who were recommended thickened-fluid dysphagia diet failed to meet their fluid requirements which was not the case in patients on enteral feeding and intravenous fluid regime (Finestone et al. 2001). Dziewas et al. analyzed however a nasogastric tube-worsened dysphagia in patients with an acute stroke. Their results showed that a correct placed nasogastric tube did not cause a worsening of stroke-related dysphagia (Dziewas et al. 2008).

In their study Logemann et al. have analyzed what information clinicians use when recommending oral versus nonoral feeding in oropharyngeal dysphagic patients (Logemann et al. 2008).

8 Therapeutic Strategies (Table 4)

Several different therapeutic strategies may be applied according to actual swallowing dysfunction. In Table 4 disorders documented on TVSS, and suggestions regarding appropriate therapeutic techniques are presented.

Conclusion

In the therapeutic swallowing study a trained speech–language pathologist and a radiologist collaborate in performing the examination.

The competence of the two specialists provides an opportunity for a complete visualization and analysis of the entire swallowing sequence. Testing swallowing function with varied bolus volumes and textures and the implementation of trial therapeutic strategies are integral components of the examination. The technique is an important tool for the SLP in the management of swallowing dysfunction.

Despite the strengths and clinical utility of the therapeutic swallowing study, there are several limitations with interpretation of test results across swallowing centers. However, new methods as the MBSS ImP allow to perform the examinations in a standardized way and thereby make the analyses of the study more efficient and the result and therapeutic intervention easier to communicate between different swallowing centers.

Evaluation of oropharyngeal swallowing function is however in its infancy. We expect that evidence-based studies will increase across centers in Europe and the United States to assist us in further determining the optimal test protocols, item analysis, and treatment strategies for improved swallowing function in our dysphagic patients, and thereby improve their quality of life.

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Surgical Aspects of Pharyngeal Dysfunction, Dysphagia, and Aspiration

Hans F. Mahieu and Martijn P. Kos

Contents

Abstract

Surgical treatment of oropharyngeal dysphagia and aspiration resulting from different disorders is a difficult issue. Sometimes the aim of the surgery is complete correction of the disorder (e.g., extraluminal obstruction), but more often no more than a reduction of the symptoms can be achieved (e.g., laryngeal suspension). The most frequent disorders eligible for surgical treatment are described and some others are described as examples of possible surgical approaches. The surgical techniques described are aimed at preservation or restoration of the function of the larynx and pharynx.

1 Introduction

Surgical treatment is presently only feasible for some disorders in the pharyngeal or esophageal phase of swallowing and is hardly an option in the oral phase. This is because the oral phase primarily consists of transportation of the bolus into the pharynx by shaping, lifting, and compression of the tongue. Surgical reconstruction of the tongue as a reconstructive part of extensive head and neck surgery can at best create a mass in the mouth to facilitate compensatory techniques of rehabilitation of swallowing. It is an illusion to try to restore the versatile and complex movements of the mobile tongue by surgical means.

Even in disorders in the pharyngeal or esophageal phase, where surgical therapy can theoretically

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or technically be applied, a large proportion of patients will not be eligible for surgical treatment because either they are not fit to undergo surgery or their underlying disorder is too rapidly progressive for them to benefit from a surgical procedure with a considerable recovery period.

The options for surgical treatment of swallowing disorders are dependent on the specific localization and type of the dysfunction. In the case of anatomical disorders, such as Zenker's diverticulum (ZD), surgery can be indicated.

In severe cases of dysphagia caused by retropharyngeal masses (e.g., osteophytes of cervical spine, benign tumors, and meningoceles), surgery is also often the treatment of choice. It is important to realize that bolus obstruction because of external compression usually occurs in the area of the pharynx and upper esophageal sphincter (UES) (C4–C7) and not lower in the esophagus. This is because of the rather strict midline location of the upper alimentary tract in this area as a consequence of the attachments of the pharynx and esophageal inlet posteriorly to the relatively rigid structures of the cricoid and thyroid, located in the midline of the neck. Because of this fixation to the laryngeal cartilages, the otherwise flexible and pliable structures of the pharynx and esophagus cannot divert from the midline. Thus, even relatively small anterior bony fragments of the cervical spine at this level cannot be easily circumnavigated by the bolus, which can result in obstruction. Below the UES, the esophagus has much more flexibility and freedom to deviate laterally, so even much larger osteophytes or large tumors lower in the neck or mediastinum rarely cause an obstruction of the bolus.

If the propulsive forces of the pharynx are inadequate to propel the bolus in the esophagus because of weakness of the constrictor pharyngeal musculature or in the case of dysfunction of the UES because of late or insufficient opening of this sphincter, a myotomy of the UES can be considered. If the propulsive forces of the pharynx are insufficient and severe aspiration occurs as a consequence of concomitant insufficient laryngeal elevation, a laryngeal suspension procedure can be considered.

Cancer treatment is, understandably, directed at survival, so a dysfunctional larynx and a dysfunctional pharynx are often considered as "collateral damage." Such a problem is then often addressed by bypassing the dysfunctional larynx and pharynx with a percutaneous gastrostomy. It would, however, be beneficial for some of these dysphagic patients if more functionally oriented surgical approaches were considered, some examples of which are described in the following paragraphs. The more extensive procedures are described in another chapter.

In the case of aspiration in laryngeal paralysis, frequently seen after vagal nerve injury in surgery of the brainstem or neck, some authors also state that medialization thyroplasty should be performed as therapy in addition to, for instance, UES myotomy (Flint et al. 1997). However, medialization thyroplasty only addresses anterior glottic insufficiency, whereas aspiration in glottic insufficiency mainly occurs posteriorly. If glottic insufficiency is to be addressed in addition to UES myotomy to reduce aspiration, it seems more logical to perform an arytenoid adduction, which is mainly directed at closure in the posterior part of the glottis. Both arytenoid adduction and medialization thyroplasty are procedures mainly for voice augmentation and will not be described here.

It is impossible within the scope of this chapter to describe all the surgical procedures which have been used for treatment of dysphagia resulting from pharyngeal or laryngeal dysfunction; therefore, we will restrict our descriptions to more often used techniques and some examples of other surgical approaches.

The goal of surgery for oropharyngeal dysphagia is usually not to normalize the swallowing act, but to improve bolus passage and/or prevent or minimize aspiration with preservation of a functional larynx. It is, of course, essential to extensively counsel the patient before the surgery and give extensive information concerning the expected outcome as well as the risks of the procedure.

2 Specific Pathology and Surgical Procedures

2.1 Zenker's Diverticulum

ZD, or hypopharyngeal diverticulum, is a relatively common problem encountered by head and neck surgeons. It consists of an acquired pouch in the dorsal wall of the hypopharynx, located at the level of the transition from the relatively wide hypopharynx to the narrow esophageal inlet. It is formed by herniation of mucosa and submucosa, protruding between the fibers of the cricopharyngeal muscle (below) and the inferior constrictor muscles (above).

It is important to realize that many conditions which on their own account can cause dysphagia are often present in patients who also have ZD. Sometimes, the initial treatment should first be targeted at these other causes instead of performing a diverticulotomy. There is evidence from a postmortem study (Van Overbeek 1977) that ZD can occur without causing symptoms. If ZD is symptomatic, the prevailing complaints of ZD are dysphagia, regurgitation of undigested food, gurgling noises in the neck, a neck mass, fetor ex ore, coughing and aspiration especially in the supine position, weight loss, and, in extreme cases, an absolute food passage block. These complaints are predominantly caused by retention of food and fluid in the diverticulum, which, when sufficiently large and filled, can compress the esophagus.

Many different treatment strategies have been proposed for ZD. Traditionally, external treatment modalities were used, by some still today, most often consisting of diverticulectomy combined with cricopharyngeal myotomy.

Endoscopic surgical treatments are less extensive than the external surgical approach. All are directed toward transecting the diverticuloesophageal wall or "spur," so that an ample passage and overflow from the diverticulum into the esophagus is achieved. Since the diverticuloesophageal wall contains the cricopharyngeal and part of the upper esophageal musculature, division of this wall automatically results in a transmucosal myotomy of these muscles. The only difference in the endoscopic treatments is the technique used to divide the diverticuloesophageal wall. The endoscopic treatment was first described in 1917 by Mosher (1917), who endoscopically incised the diverticuloesophageal wall.

Dohlman and Mattson (1960) developed an endoscope with a slit in the distal end, so that the diverticuloesophageal wall could be fixed between the two lips of the endoscope. They then coagulated the wall and divided it with a diathermic knife. This method was refined by Van Overbeek et al. (1984), who modified the endoscope and started using the operating microscope coupled to a CO_2 laser, which enabled better control and more precise division of the diverticuloesophageal wall (Mahieu et al. 1996). Further development of laser techniques, with the introduction of the Acuspot in the early 1990s, facilitated precision and control of the surgical endoscopic technique. In the same period, endoscopic diverticulotomy with a stapler technique was introduced (Collard et al. 1993).

In a study (Kos et al. 2009) describing our experiences with different endoscopic treatment modalities over the years, we found that in the modern microendoscopic CO_2 laser diverticulotomy 86.7% of 61 patients were free of dysphagic complaints as evaluated 1 year after treatment and repetitive surgery was required in only 13% of the patients. Mediastinitis, the most feared complication, was not encountered in this treatment modality. The results and complication ratio of the microendoscopic CO_2 laser diverticulotomy are comparable to the reported results of the recently introduced endoscopic stapler diverticulotomy and indicate that CO_2 laser treatment is an excellent treatment modality. In approximately 10% of patients, emphysema of the neck is found and is not necessary related to the presence of mediastinitis.

The principle of endoscopic treatment is the transection of the diverticuloesophageal wall, which contains the cricopharyngeal muscle, thereby achieving an ample overflow from the diverticulum to the esophagus. It is not necessary to completely divide the wall down to the

floor of the large diverticulum; this would only increase the possibility of a perforation in the diverticulum to the mediastinum. If symptoms persist in patients with larger diverticula, repetition of the endoscopic procedure is usually possible. Our results show that a large ZD is not a contraindication for endoscopic treatment, and that there is no higher complication rate in these patients. Almost 70% of these patients experienced total relief of symptoms, and no higher recurrence rate was found.

Nowadays, endoscopic stapler diverticulotomy is used by many surgeons as the treatment of choice. This technique uses a telescope instead of a microscope to visualize the diverticulum. Besides the sharp incision of the diverticuloesophageal wall by the blade of the instrument, this procedure involves sealing the wound edges with multiple rows of staples. This sealing is said to prevent mediastinitis and perioperative bleeding and should immediately allow oral intake and thus shorter hospitalization. The outcome results are comparable to those of laser endoscopic diverticulotomy. Cook et al. (2000) reported complete relief in 71% of patients (n = 74). Saetti et al. (2006) reported complete relief or a significant reduction of symptoms in all patients (n = 106), 19.8% of them requiring repeat surgery after a median of 15 months. Although not reported by Cook et al. and Saetti et al., fatal outcome after mediastinitis has also been reported (Mirza et al. 2003).

An obvious disadvantage of the stapler technique is that smaller diverticula (less than 2 cm) cannot be easily treated because of the difficult introduction of the stapler and because exposure of the operating field can cause difficulties that can lead to a higher conversion rate to external procedures than that seen with laser endoscopic treatment. By use of the microscope in the micro-endoscopic laser technique, a superior view and superior control are obtained without the view being impaired by instruments. Our experience is that if the stapler is introduced, visualization of the tip of the instrument and visualization of the cutting of the wall are often not possible; thus, this method provides less control and accuracy in our hands. We will, therefore, describe the laser microendoscopic method in more detail.

Flexible endoscopic treatment of ZD is also performed by gastroenterologists, employing diathermy needle-knife techniques or laser techniques with fibers (Tang et al. 2008; Seaman et al. 2008; Christiaens et al. 2007). The reported series are small. Often multiple fiber-optic treatments are necessary, mainly owing to inferior visualization of the operating field, to obtain results similar to those obtained by rigid endoscopic procedures. If general anesthesia is contraindicated, this can be considered as an alternative treatment.

Although the development of malignancies in a ZD has been described, the incidence is so low that it does not justify preventive surgical treatment of an asymptomatic ZD in our opinion. Furthermore, the efficacy of such preventive surgery is very questionable in the light of reported recurrence rates of ZD.

2.1.1 Surgical Technique

To facilitate the location of the esophageal inlet, patients are requested to swallow a thread with a small metal weight attached to one end and taped to the cheek with the other end the evening before surgery. In more than 80% of cases, the metal weight had passed into the esophagus, thus facilitating identification of the esophageal inlet for introduction of the bitipped endoscope (Dohlman and Mattson 1960; Van Overbeek et al. 1984) (Fig. 1). First, careful endoscopic examination is performed to exclude malignancy in the diverticulum.

Division of the diverticuloesophageal wall is then performed under microscopic control with the CO_2 laser until an ample communication between the diverticulum and the esophagus has been established. Usually, this means dividing the diverticuloesophageal wall over three-quarters to four-fifths of its height, sometimes less in extremely large diverticula (Fig. 2).

Postoperative management consists of prophylactic antibiotics for 5 days, a feeding tube (often not used but placed at the time of surgery under direct vision, so that if necessary a way for nutritional intake can be guaranteed), and 24 h nil per os. If no fever or emphysema is present the day following treatment, feeding is started on clear liquid and 12 h later on thick liquid. The

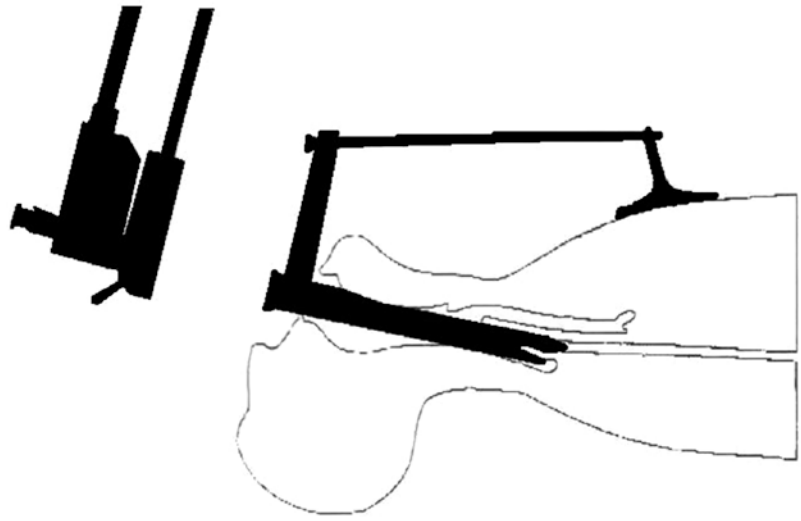

Fig. 1 Microendoscopic procedure with a CO_2 laser and a bitipped diverticulosope

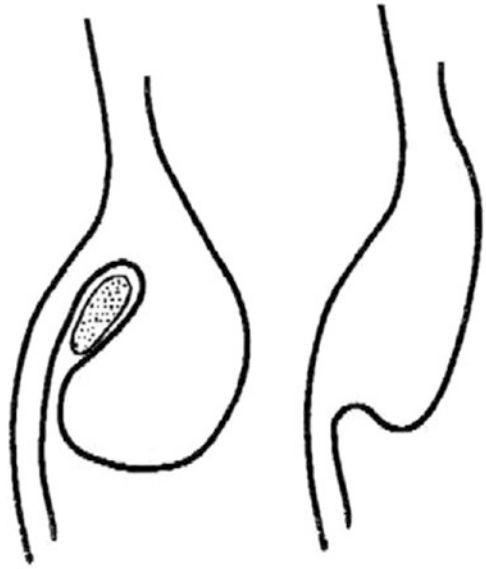

Fig. 2 Zenker's diverticulum before (*left*) and after (*right*) endoscopic treatment. The cricopharyngeal muscle (*asterisk*) located in the esophagodiverticular wall is automatically sectioned during division of this wall

feeding tube is removed if no fever or emphysema develops after 24 h oral feeding.

Contraindications for endoscopic treatment are as follows: malignancy in the diverticulum; extreme fixation of the cervical spine in an abnormal position, precluding safe endoscopy; suspicion of a large vessel in the diverticuloesophageal wall. In these cases, external diverticulectomy with cricopharyngeal myotomy can be performed.

2.2 Neuromuscular Dysfunction of Pharyngeal Constrictors and the UES

Opening of the esophageal inlet to enable passage of the bolus from the pharynx into the esophagus is achieved by a combination of (1) elevation and anterior displacement of the larynx, which assists in the esophageal inlet being pulled open, (2) relaxation of the UES, and (3) passive dilatation of the esophageal inlet as a consequence of the propulsion of the bolus being pushed downward by contraction of the pharyngeal constrictor muscles. Failure of UES relaxation or other forms of cricopharyngeal dysfunction, as well as diminished pharyngeal constrictor activity, lead to an obstruction of bolus passage (Cook 1993) and can result in aspiration of food and saliva. Usually, deglutition of the solid bolus is more affected than deglutition of liquids because a large opening of the esophageal inlet is required to enable the passage of a solid bolus, whereas a minor opening of the esophageal inlet will allow passage of liquids. Various conditions affect the complex coordinated actions of neuromuscular structures in the pharyngeal, laryngeal, and UES regions. They can be divided in neurogenic, myogenic, idiopathic, and iatrogenic causes (Guily et al. 1994; Kelly 2000). Adaptation of food bolus consistency can be the first step in treating oropharyngeal dysphagia. In severe cases, replacement of

oral alimentation by nutrition via a gastrostomy can be considered. However, this is not always a satisfactory alternative because swallowing of saliva persists and the patient is denied the quality-of-life aspects associated with the enjoyment and social aspects of eating.

The first UES myotomy was described by Kaplan (1951). The surgery was performed using an open transcervical approach in a patient following poliomyelitis. This was and continues to be the technique of choice for many head and neck surgeons, although since 1994 endoscopic laser-assisted transmucosal myotomy has been used increasingly.

The surgical intervention of UES myotomy consists of sectioning of all the muscles that constitute the functional UES unit, the last centimeters of the inferior constrictor muscles, the cricopharyngeal muscle, and the first few centimeters of the cervical esophagus, resulting in an incision of approximately 6 cm in an adult. Although myotomy is an action directed at the functional UES unit, oropharyngeal dysphagia is commonly associated with impairment of the pharyngeal musculature as the major pathophysiological factor and is less frequently caused by true cricopharyngeal dysfunction. Because correction of the weak or absent pharyngeal musculature is not possible presently, reduction of the resistance of the UES by means of a myotomy is the most logical approach to facilitate bolus propulsion. The reduced resistance of the UES will then allow opening of the esophageal inlet.

Our patients with longstanding dysphagia and/or aspiration problems of different aetiologies, who underwent UES myotomy as a single surgical treatment (Kos et al. 2010), were analysed with manometry and videofluoroscopy pre- and postoperatively to assess swallowing and aspiration. Initial and long-term results after more than 1 year demonstrated success in 75% of the patients. The best outcomes were observed in patients with dysphagia of unknown origin, non-cancer-related iatrogenic cause, and neuromuscular disease. All successful patients had full oral intake with a normal bolus consistency without clinically significant aspiration. It was concluded that in select cases of oropharyngeal dysphagia, success may be achieved by UES myotomy with restoration of oral intake of normal bolus consistency. Our long-term success rate of more than 75% is in line with that of other studies (Guily et al. 1994; Coiffier et al. 2006). Often it is said (Cook and Kahrilas 1999) that absence of pharyngeal constrictor activity is a contraindication for UES myotomy. In contrast to these statements, our results demonstrate that even in cases with absent or almost absent pharyngeal constrictor activity, UES myotomy can be successful.

Patient selection is essential and requires a complete medical history and clinical examination including functional endoscopic examination of swallowing (Leder et al. 2005), videofluoroscopy, and manometry. Esophagogastroscopy and 24-h pH-metry are usually only performed if they are indicated. We consider only severe gastroesophageal reflux to be a contraindication for UES myotomy.

We feel that it is important to perform videofluoroscopy and manometry postoperatively to evaluate the dysphagia status and determine whether myotomy has been complete. If the result of UES myotomy is not successful owing to insufficient pharyngeal propelling combined with insufficient laryngeal elevation, additional laryngeal suspension can be considered (Kos et al. 2008).

It is important to realize that in cases of slow progressive neuromuscular disease, alleviation of dysphagia by UES myotomy can be no more than temporary and can extend to many years of relief of dysphagic problems. However, in rapidly progressive neuromuscular disease, for example, amyotrophic lateral sclerosis, UES myotomy is not indicated.

Chemical UES myotomy by use of botulinum toxins can be helpful as a diagnostic treatment and can be indicated in patients with a high comorbidity. It is, however, often performed under general anesthesia, and repetitive treatments are needed (Moerman 2006). Dilatation usually gives temporary relief and is only indicated in cases where fibrosis of the UES unit is expected (Hatlebakk et al. 1998). Endoscopic myotomy, an adaptation of the endoscopic laser Zenker diverticulotomy, has increased in popularity in the last decade (Takes et al. 2005). It requires less surgical time

and a shorter postoperative hospital stay than external myotomy. Institutions that perform endoscopic Zenker diverticulotomy can easily adjust their technique and perform endoscopic UES myotomy. In the absence of the diverticular wall between the diverticulum and the UES as is present in ZD, the diverticuloscope can now be used to "catch" the cricopharyngeal muscle between both blades of the endoscope and sever the muscle fibers and overlying mucosa with the CO_2 laser. Since in this case the mucosal barrier is breached, antibiotic prophylaxis is advised.

Having extensive experience in both techniques, we prefer the external UES myotomy approach as the treatment of choice for oropharyngeal dysphagia. It is our considered opinion that the accuracy of sectioning of the muscles over the entire length of the functional UES unit is better and the risk of local stenosis is less with an external approach. We use endoscopic UES myotomy in cases of recurrent dysphagia after previous external UES myotomy and in cases with poor quality of the skin of the neck or a poor exposure of the neck. Known potential risks of external myotomy are wound infection, pharyngocutaneous fistula, and paralysis of the recurrent laryngeal nerve (Brigand et al. 2007). In our study of 28 cases, we observed none of these complications.

2.2.1 Surgical Technique

The external UES myotomy starts with an endoscopy to assess the larynx, the pharynx, and the esophagus. A tube with an inflatable balloon or cuff (e.g., Sengstaken tube no. 16; Rusch, Kernen, Germany) is then introduced into the esophageal entrance to facilitate the UES myotomy. A left-sided approach of the UES is preferred because the esophagus is usually located slightly left of the trachea and the midline and this enables a better exposure of the UES. The most important complication of an external UES myotomy is a recurrent nerve palsy. The risk of the patient developing a recurrent nerve palsy later as a consequence of other disease is much higher on the left side than on right side. If paralysis of the recurrent laryngeal nerve is already present, then the myotomy should consequently be performed on that side.

A J-shaped incision is made along the anterior border of the sternocleidomastoid muscle curving toward the midline 1–2 cm above the sternum. The omohyoid muscle and if necessary the superior thyroid artery are transected for a good exposure. The head is tilted to the contralateral side and the UES myotomy is performed extending from the lower thyropharyngeal musculature, through the cricopharyngeal muscle, and down to the longitudinal fibers of the upper esophageal musculature (usually resulting in a total myotomy length of 5–6 cm, Fig. 3). This procedure is facilitated by the inflated balloon in the UES which stretches the muscle fibers and thus allows very precise sectioning of the UES musculature (Fig. 4a). After myotomy, the balloon is deflated (Fig. 4b), and while it is being retracted from the mouth, air is blown through the tube and with saline placed in the external wound this enables an additional check of

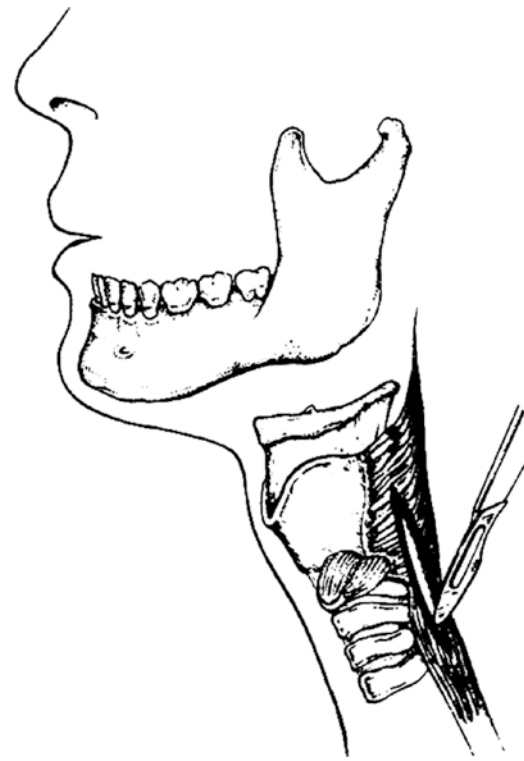

Fig. 3 Upper esophageal sphincter (UES) myotomy is performed extending from the lower constrictor pharyngeal musculature, through the cricopharyngeal muscle, and down to the longitudinal fibers of the upper esophageal musculature

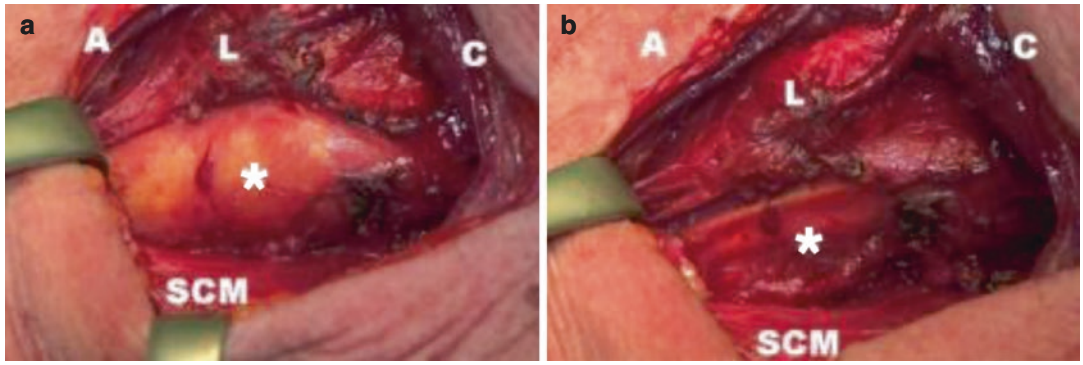

Fig. 4 (**a**) Image after the sectioning of the UES muscles with an inflated balloon (*asterisk*) endoluminally positioned in the esophageal entrance. (**b**) Image after the sectioning of the UES muscles with the balloon (*asterisk*) endoluminally positioned in the esophageal entrance but deflated. *A* anterior sternocleidomastoid muscle, *C* cranial, *L* larynx, *SCM* sternocleidomastoid muscle

the integrity of the UES mucosa. A minor perforation can be found by the escape of air bubbles. Before closure of the neck, a nasogastric feeding tube is placed, and this is carefully guided through the pharynx and UES by external palpation and gentle pressure of the surgeon's finger in the opened neck. A strict nonoral intake policy is valid for all patients in the first two postoperative days. If the integrity of the mucosa has not been breached, there is no indication for prophylactic antibiotics.

Swallowing rehabilitation starts on the third postoperative day if there have been no signs of perforation or local infection. In the first few days of the rehabilitation, edema can interfere with the swallowing act, but prolonged delay of swallow training is not considered favorable because of the possible development of local fibrosis and consequently stenosis of the UES. Patients leave the hospital after a safe and adequate oral intake has been achieved. If they fail to accomplish a sufficiently safe oral intake despite extensive postoperative swallowing rehabilitation, percutaneous endoscopic gastrostomy (PEG) feeding or adequate dietary adjustments might be necessary so that the patient can safely manage at home.

2.3 Severe Aspiration in Oropharyngeal Dysphagia

In patients with chronic aspiration and recurrent pneumonia, often a strict PEG feeding policy is applied or a total laryngectomy or some other type of permanent anatomic or functional separation of the airway and digestive tract is performed. However, in selected cases, it is possible to preserve or restore oral intake with a functional larynx by a laryngeal suspension procedure in combination with myotomy of the UES. This procedure should be considered if aspiration is caused by a combination of deficient deglutitive laryngeal elevation, lack of pharyngeal constrictor activity, and insufficient opening of the esophageal inlet.

UES myotomy is the most frequently used surgical technique for treating dysphagia and aspiration. Often, however, it proves to be insufficient to prevent aspiration. If we take into consideration the normal physiological processes of deglutition, there is evidence (Kahrilas et al. 1988) that the most important factor responsible for opening of the esophageal inlet is not relaxation of the UES, nor passive opening as a consequence of the propulsion of the bolus being pushed downward by the peristaltic contraction of the pharyngeal constrictor muscles, but deglutitive laryngeal elevation (Fig. 5). Because the UES is attached to the larynx, anterior and cranial displacement of the larynx during the pharyngeal phase of the swallowing act results in opening of the esophageal inlet. Simultaneous relaxation of the UES facilitates the opening of the esophageal inlet, and propulsive activity of the pharyngeal musculature improves the passage of the food bolus.

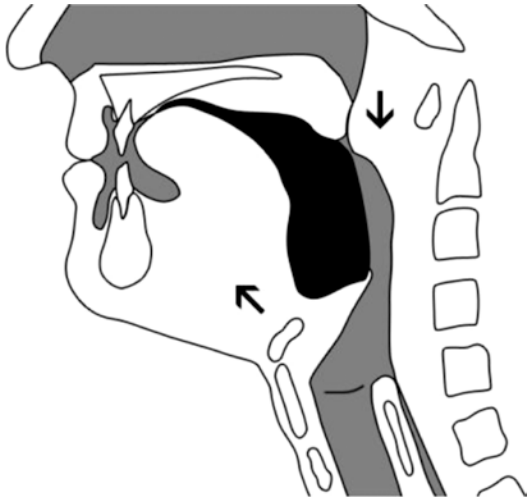

Fig. 5 Early pharyngeal phase of deglutition. Note the anterior and superior displacement of the hyoid and descending propulsive activity of constrictor pharyngeal muscles

In addition to being the most important factor in opening of the esophageal inlet, the anterior and cranial displacement of the larynx also results in other mechanisms that help to protect the airway from aspiration. The larynx is pulled out of the way of the food bolus's path, the epiglottis is lowered over the laryngeal entrance as a roof protecting the airway, and the larynx is pulled under the base of the tongue, thus providing a partial cover of the laryngeal inlet. Such a situation can be obtained surgically by means of a laryngeal suspension procedure, during which the larynx is permanently fixed in the position that it would normally acquire during the swallowing act.

Since Edgerton and Duncan (1959) and Desprez and Kiehn (1959) first described laryngeal suspension as a technique for improving function after surgical resection of the anterior floor of the mouth, this technique has been used by many surgeons (Calcatarra 1971; Goode 1976; Tiwari et al. 1993; Fujimoto et al. 2007) as an integral part of major ablative surgery entailing loss of the mandibular–hyoid integrity or extended partial laryngectomy. The intent in these cases is to restore the continuity between the laryngeal–hyoid complex and the mandible and/or floor of the mouth musculature. This is of major importance for restoration of deglutitional function and prevention of aspiration in such cases.

Most alternative surgical procedures used for treatment of severe aspiration are associated with a permanent tracheostoma and loss of normal phonation. The procedures proposed include total laryngectomy, laryngeal closure, epiglottopexy, and laryngeal diversion (Lindeman 1975; Laurian et al. 1986; Kitahara et al. 1993; Habal and Murray 1972; Mongomery 1975; Sasaki et al. 1980; Hawthorne et al. 1987). It is our considered opinion that for some of these patients with severe aspiration, surgical laryngeal suspension in combination with UES myotomy provides a less mutilating alternative, with preservation of normal phonation and respiration without permanent tracheostomy.

Our results (Kos et al. 2008) demonstrated that in nine of 17 patients (59%) long-term full oral intake without aspiration was achieved. In three patients (18%), partial improvement of deglutition was achieved, but these patients remained partly dependent on gastrostomy feeding for adequate nutrition. In two patients (12%), aspiration (of saliva) was reduced and no more aspiration pneumonias occurred, but these patients were unable to achieve even modified oral intake. In three patients (18%), a total laryngectomy could not be avoided, in two after initial success and as a result of progression of neuromuscular disease. None of the patients succumbed to aspiration pneumonia. In more than half of our patients (59%), life-threatening aspiration was successfully treated by UES myotomy and laryngeal suspension with full restoration of oral intake.

The goal of the laryngeal suspension and UES myotomy procedure is not to normalize the swallowing act, but to prevent life-threatening aspiration with preservation of a functional larynx. Even patients who were not able to achieve sufficient oral intake after the procedure had fewer problems with aspiration. The voice quality does not seem to change after elevation of the larynx. Because of potential postoperative airway compromise and anticipated difficulties with intubation as a result of the displaced larynx, elective temporary tracheotomy is routinely performed in all patients.

It seems advisable to include lower esophageal sphincter (LES) manometry in the preoperative diagnostic workup to rule out the possibility of an insufficient LES, since severe reflux is considered a contraindication to laryngeal suspension. After laryngeal suspension and UES myotomy, preexisting reflux can become worse, because this procedure abolishes the protective function of the UES against reflux. This situation can lead to severe aspiration of gastric refluxate, even in those cases in which the laryngeal suspension and UES myotomy allows relatively safe oral intake.

All patients who are eligible for this type of surgery have severe dysphagia and intractable aspiration despite intensive previous nonsurgical, and sometimes also surgical, treatment. Laryngeal suspension should be considered a procedure that can only partly compensate for the functional deglutitive deficiency and thus hopefully prevent aspiration. Patients who are unable or unwilling to accept these uncertainties in the outcome are not good candidates for the procedure. To avoid unrealistic expectations, patients should be made to understand that the goal of the surgical procedure is to prevent aspiration and not to improve the swallowing act itself. Normal deglutition will never be achieved.

In patients who, because of a loss of sensation, did not notice their aspiration (silent aspiration) before the operation, the postoperative situation can be disappointing, because propulsion of the food bolus is not normalized and these patients fail to notice the improvement with respect to the aspiration. It is, of course, essential to extensively inform the patient before the operation of the expected outcome of the procedure. For these patients with a loss of sensibility, perhaps the option of additional restoration of sensibility by neural anastomosis may be helpful (Aviv et al. 1997).

2.3.1 Surgical Procedure

The surgical procedure (Fig. 6) starts with a UES myotomy as described already. All infrahyoid prelaryngeal muscles are severed to prevent traction of the laryngeal–hyoid complex in the caudal direction after surgery. A laryngeal suspension is performed by approximating the thyroid cartilage and the hyoid bone with polytetrafluoroethylene (GORE-TEX; permanent) sutures and Vicryl 0 (Ethicon, Somerville, NJ, USA; resorbable but strong enough to overcome initial traction) tied over a polytetrafluoroethylene sheet to prevent rupturing of the thyroid cartilage and by pulling this laryngeal–hyoid complex toward the chin by two

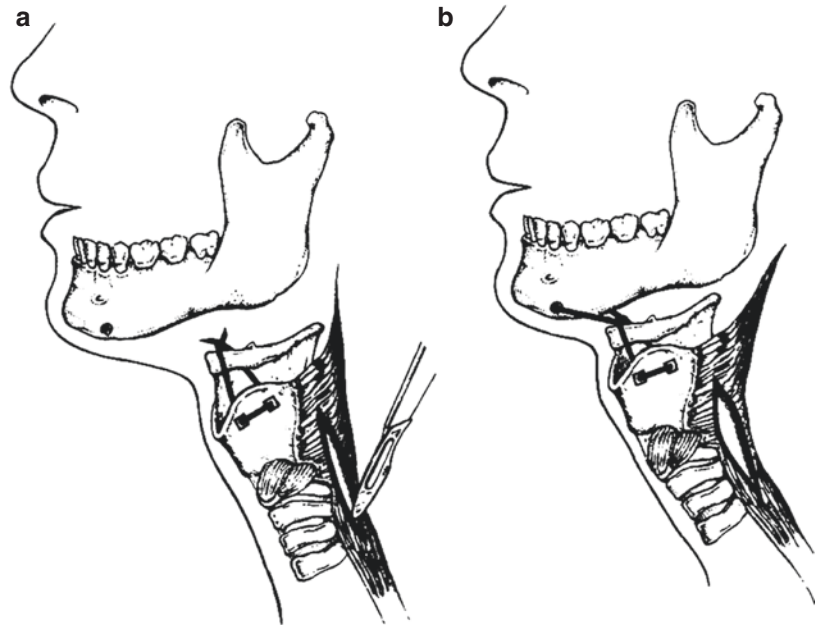

Fig. 6 The UES myotomy and laryngeal suspension procedure. (**a**) UES myotomy; thyrohyoid approximation by an Ethibond 0 (Ethicon, Somerville, NJ, USA) suture tied as a mattress suture over polytetrafluoroethylene (GORE-TEX) bolsters on the thyroid cartilage and around the body of the hyoid bone. (**b**) Thyrohyoid complex suspended from the mandible by Ethibond 0 sutures, which have been passed around body of the hyoid bone and through holes drilled in the mandible

Ethibond (Ethicon) sutures, as well as the polytetrafluoroethylene sutures, which are passed through drill holes in the mandible just posterior to the angle of the chin and anterior to the foramen of the mental nerve and are then tied. To prevent overcorrection and consequent airway compromise, laryngoscopy is performed just before tying the sutures to ensure that the epiglottis and the base of the tongue do not completely obstruct the larynx. This is not always easy to estimate, because at this moment the intratracheal tube is still in place, preventing complete obstruction of the laryngeal inlet.

If the patients did not already have a PEG tube, they are given a transnasal feeding tube for the initial postoperative period. It is advisable to perform a temporary tracheotomy to guarantee a patent airway in the postoperative period, because as a consequence of the laryngeal suspension, the laryngeal entrance is displaced anteriorly and cranially (Fig. 5), interfering with intubation in the case of airway compromise. This tracheotomy should be performed at the end of the procedure, after the actual laryngeal suspension procedure, so as not to limit the extent of the laryngeal suspension (Figs. 7 and 8).

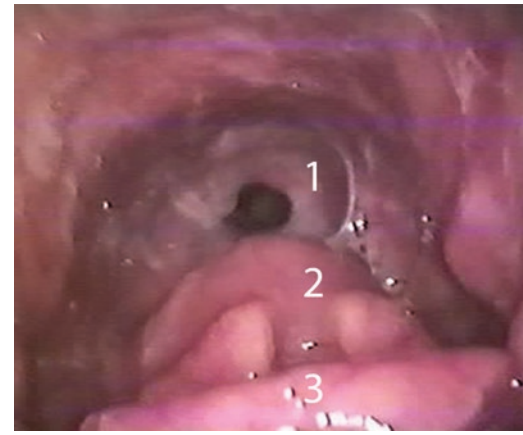

Fig. 7 View of the larynx and the esophageal inlet following laryngeal suspension, obtained with a 90° telescope during spontaneous respiration. *1* wide-open esophageal inlet, *2* posterior surface of cricoid plate, *3* epiglottis

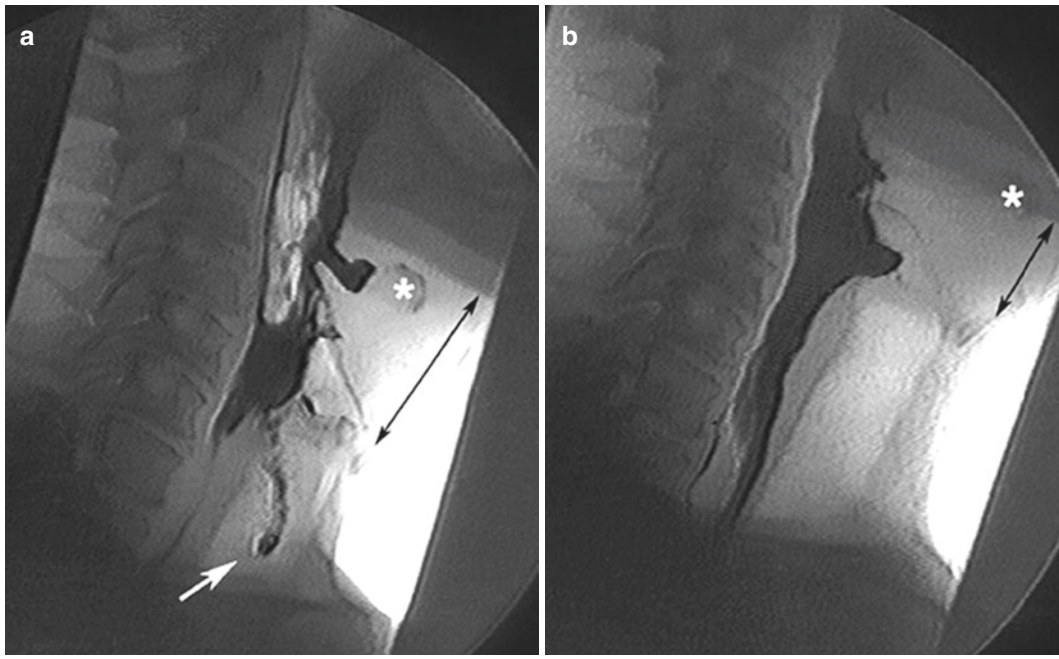

Fig. 8 Preoperative and postoperative videofluoroscopy. (**a**) Videofluoroscopic frame showing severe aspiration in the late pharyngeal phase before laryngeal suspension and UES myotomy. Note the absent pharyngeal constrictor activity and absent laryngeal elevation. (**b**) Videofluoroscopic frame in the late pharyngeal phase after laryngeal suspension and UES myotomy showing no aspiration. Note the position of the suspended larynx and epiglottis. *Asterisks* body of hyoid bone

2.4 Dysphagia Caused by Extraluminal Compression

2.4.1 Anterior Cervical Osteophytes

Anterior cervical osteophytes are a common but rarely symptomatic finding mostly seen in the geriatric population. They can occur in cases of degenerative disk disease, as part of the physiological or accelerated ageing process, but are most marked in diffuse idiopathic skeletal hyperostosis, also known as Forestier's disease (Resnick et al. 1975; Matan et al. 2002). If symptomatic, dysphagia appears to be the most common presentation, caused by mechanical obstruction of the pharyngoesophageal segment by anterior cervical hyperostosis. Exclusion of other causes of dysphagia is mandatory before blaming cervical osteophytes for dysphagic complaints. The surgical procedure is performed in collaboration with an orthopedic surgeon (Fig. 9).

Dysphagia is mostly seen in cases of cervical anterior osteophytes, mainly because C4–C7 are most often affected and compression at this level causes obstruction of the esophagus. Secondary aspiration can occur in patients with severe obstruction of the esophagus due to stasis. Primary aspiration can be caused by large osteophytes at C3–C4 directly interfering with laryngeal elevation and closure in the swallowing act. Primary aspiration can also occur as a consequence of vocal fold immobility due to damage of neural structures by the osteophytes (Giger et al. 2006). Dyspnea as a result of compression of the pharynx and larynx is extremely rare (Matan et al. 2002). More common head and neck symptoms are pain and problems with sensation (as a consequence of compression of the cervical spine or vertebral artery), Horner's syndrome (Brandenberg and Leibrock 1986), and obstructive sleep apnea (Girgis et al. 1982). Dysphagia is often more severe with extension than with flexion of the neck. Complaints are more pronounced for solid boluses than for liquid boluses.

Diagnostic investigation should include laryngoscopic ENT examination. A lateral plain radiograph can be helpful in evaluation of the cervical spine for congenital or degenerative changes. Computed tomography or magnetic resonance imaging with sagittal reconstruction is advised to enable location of anterior bony lesions in relation to the surrounding soft tissues, large vessels, and nerve sheets. Dynamic videofluoroscopy is an important diagnostic tool, in which the patient

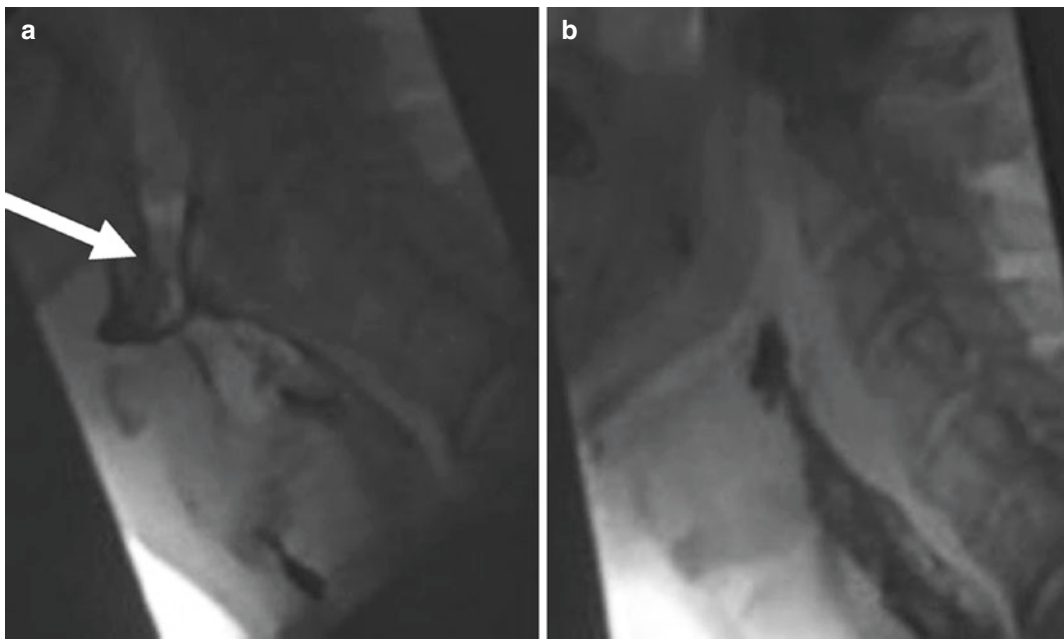

Fig. 9 Videofluoroscopic images of a 70-year-old patient with severe dysphagia and aspiration. (**a**) Preoperative image showing osteophytes at C3–C4 causing primary aspiration due to mechanical obstruction of the hypopharynx and esophageal inlet, and impairment of the epiglottis in its attempt to close the laryngeal inlet during the pharyngeal phase. (**b**) Image after removal of osteophytes showing normal bolus passage without obstruction

swallows a liquid and solid bolus so that the dynamic process of deglutition can be evaluated. The level and cause of obstruction can be determined if dynamic videofluoroscopy is combined with conventional imaging of the spine. Manometry can be helpful to exclude coordination disorders of UES function.

The treatment of patients with diffuse idiopathic skeletal hyperostosis depends on the degree of the symptoms. Initial therapy involves adaptation of food consistency. Conservative treatment with nonsteroidal anti-inflammatory drugs and antibiotics can be successful in cases with an inflammatory component (Oga et al. 1993). The symptoms will often have a more acute or subacute character in these cases.

When dysphagia is directly caused by obstruction of bony protrusions, the symptoms will be more chronic and slowly progressive. In these cases, or when there are more severe symptoms such as chronic aspiration and weight loss, surgical intervention should be considered (Richter 1995). Especially in older patients, who have a diminished cough reflex and thus an elevated risk of developing aspiration pneumonia, surgical treatment may be indicated.

Surgical approaches include anterolateral, posterolateral, and transoral approaches. Our preferred approach is anterolateral, because it provides optimal exposure of the large cervical vessels and vagal nerve and a good exposure of the prevertebral space, but it does place the recurrent laryngeal nerve at greater risk than the other approaches (Akhtar et al. 2000). The posterolateral approach offers wide exposure of the prevertebral space but requires more retraction of the carotid sheath (Carrau et al. 1990). The transoral approach has the advantage of cosmetic appeal as well as limited risk to the aforementioned structures compared with the anterolateral and posterolateral approaches. However, the disadvantages include limited exposure as well as the potential risk of fascial infection or osteomyelitis due to a contaminated surgical field.

Spondylodesis is only indicated in the case of instability after removal of cervical hyperostosis (Richter 1995; Krause and Castro 1994). If sufficient anterior ossification remains between the vertebrae, there is a low risk of postoperative cervical instability.

2.4.2 Dysphagia and Dyspnea Caused by Multiple Cervical Anterior Meningoceles

Type 1 neurofibromatosis may present with a wide spectrum of pathological anomalies. Very rarely it may present as a spinal meningocele, a protrusion of spinal meninges through a defect in the vertebral column or foramina. The pathogenesis of the lesion remains unclear, but several theories have been proposed, such as trauma (Freund and Timon 1992), dural (Bensaid et al. 1992), and/or regional bony dysplasia (Erkulurawatra et al. 1979). Magnetic resonance imaging is the preferred diagnostic tool for most spinal abnormalities. This modality accurately demonstrates the morphologic properties of a lesion, and changes in the longitudinal contour of the spinal cord can easily be detected. Computed tomography can be helpful in showing a relation of nervous structures to complex bony anatomy or in patients unable to undergo magnetic resonance imaging.

Meningoceles may be asymptomatic and do not necessarily require treatment. The probability of the gradual enlargement of the meningocele with time and the possibility that it may cause pain, dysphagia, and dyspnea should be weighed against the risks of surgical resection of the meningocele. The goal of surgical treatment of a basal meningocele is ligation of its neck at the intervertebral foramina and resection of the sac. Figures 10 and 11 demonstrate a patient with type 1 neurofibromatosis who harbored a large retropharyngeal mass, consisting of two cervical meningoceles, causing dysphagia and dyspnea, and requiring surgical removal. The procedure is performed in collaboration with a neurosurgeon.

An anterior–lateral surgical extrapharyngeal approach is used for optimal exposure of the anterior cervical spine. A transoral approach is advised against because of contamination of the surgical field and the risk of postoperative meningitis. Surgery may be difficult because of dural defects and fragility of the meningocele. A postoperative lumbar drain to diminish cerebrospinal fluid pressure is advisable.

Following excision, respiration as well as deglution normalized.

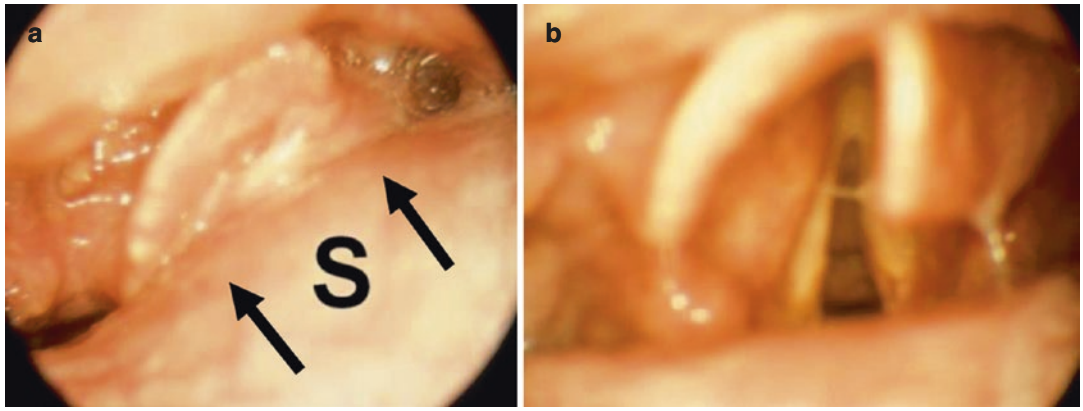

Fig. 10 Preoperative (**a**) and postoperative (**b**) endoscopic views of the larynx and pharynx. The retropharyngeal swelling (*S*) was caused by the meningoceles compressing and obstructing the laryngeal inlet as well as the esophageal inlet. Postoperatively, free laryngeal inlet and normalized pharyngeal dimensions. Remaining asymmetric fold in the epiglottis due to prior prolonged compression by the meningoceles

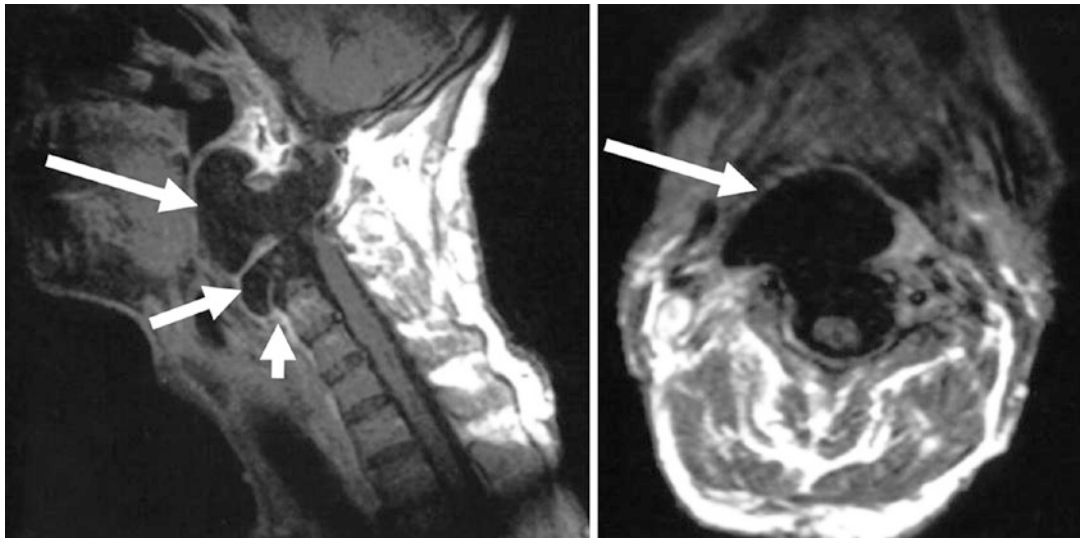

Fig. 11 Preoperative sagittal and axial T1-weighted magnetic resonance image revealing three meningoceles at the level of C3–C6. The two cranial and largest meningoceles protruding anterior to the cervical spine, the smallest remained intervertebral

2.4.3 Dysphagia and Dyspnea Caused by a Retropharyngeal Tumor Mass

Dysphagia and dyspnea can be caused by any retropharyngeal tumor of benign or malignant origin. Here, we describe an example of a 87-year-old female patient with severe dysphagia and dyspnea caused by a large retropharyngeal myxofibrosarcoma.

Myxofibrosarcoma is one of the most common sarcomas in the field of orthopedic surgery. Typically, it grows in the subcutaneous tissue of the extremities in elderly persons. Myxofibrosarcomas in the head and neck region are rare, and only a few cases of the disease in this area have been reported. Following excision, respiration as well as deglution normalized (Figs. 12 and 13).

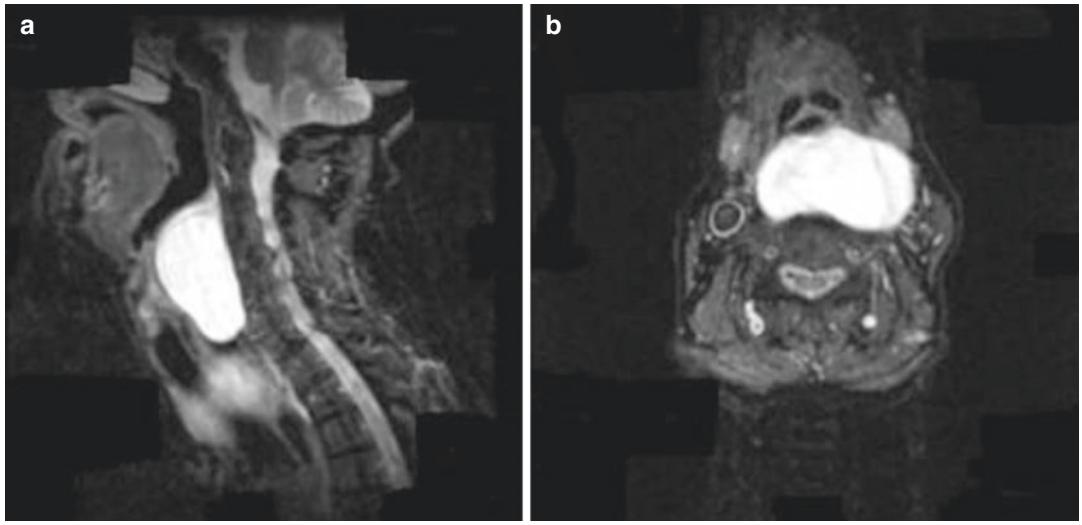

Fig. 12 T1 preoperative saggital and axial magnetic resonance images demonstrating the large retropharygeal tumor

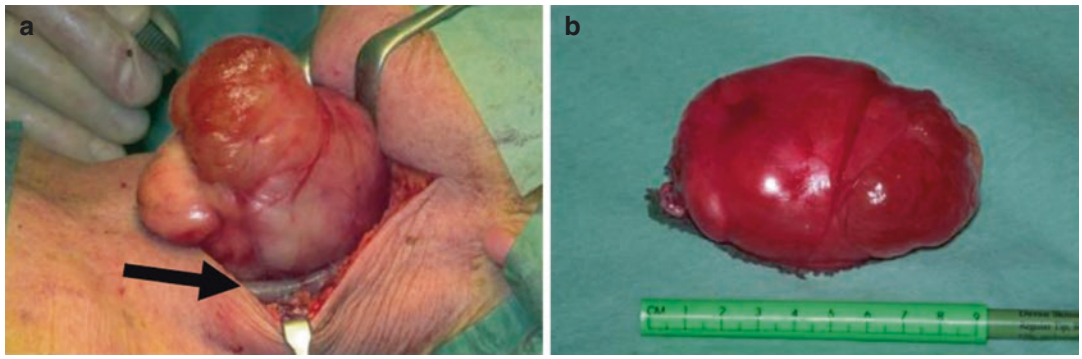

Fig. 13 (**a**) Removal of the tumor by an anterolateral approach. The longitudinal axis of the tumor was approximately 9 cm. (**b**) Tumor protruding through neck incision. *Arrow* jugular vein

2.5 Strictures and Fibrosis of Pharynx and UES

Fibrosis and strictures of the pharynx and UES are usually the result of caustic ingestion or chemoradiation and occasionally external neck trauma. Even though the nutritional status of the patient can easily be restored by tube feeding, swallowing problems generally have a considerable impact on quality of life and might also lead to social isolation (de Boer et al. 1995). Strictures are usually found in the hypopharynx or cervical esophagus, but also at more cranial levels in the pharynx. Depending on the stricture site, dyspneic complaints can be induced besides dysphagia and life-threatening aspiration. Usually (repeated) endoscopic bougienage or balloon dilations can be a successful treatment strategy (Piotet et al. 2008). Other treatment options have to be considered if stricture formation has advanced to complete stenosis or if the stricture is at a more cranial pharyngeal level.

2.5.1 Mucosal Flap Pharynxplasty with the CO_2 Laser

Strictures of the oropharynx are rare and complex problems. Severe stricture formation can occur between the lateral edges of the epiglottis

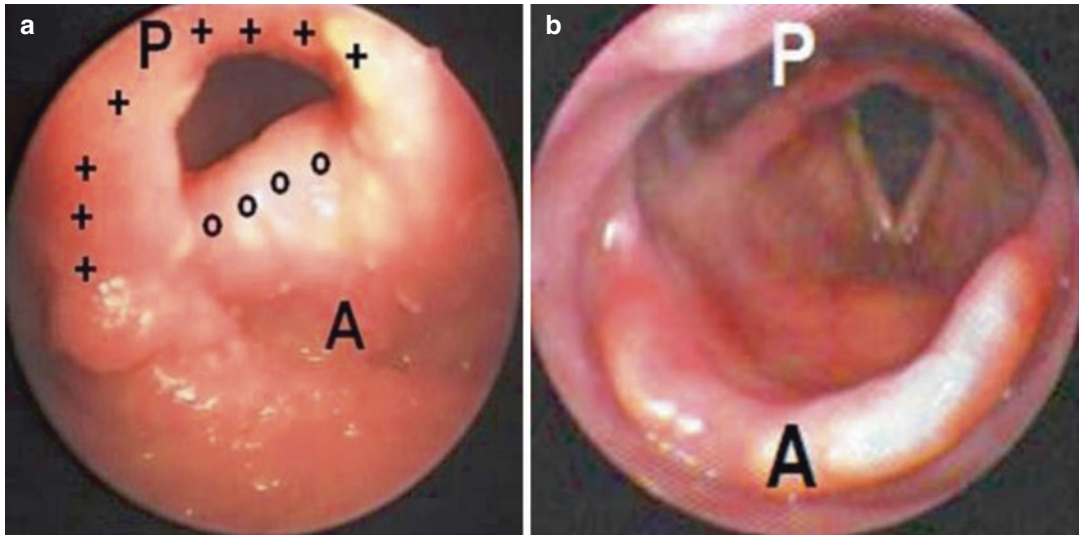

Fig. 14 (**a**) Endoscopic view of the semicircular oropharyngeal stenosis fixed to the epiglottis in a patient following radiotherapy for T1 oropharyngeal carcinoma. (**b**) Five-year postoperative endoscopic view of the larynx demonstrating only minor remains of the stenosis at the oropharyngeal level and an unobstructed view of the glottis. *Circles* the free edge of the epiglottis, *crosses* semicircular strictures attached to the epiglottis, *A* anterior, *P* posterior

and the lateral and posterior pharyngeal walls. In one patient who underwent radiotherapy for a T1 oropharyngeal carcinoma of the soft palate (Figs. 14 and 15), such a stricture left a lumen of no more than 3–4 mm. Dyspnea in exercise became apparent as well as obstruction for larger food fragments in this segment, each time also obstructing his airway. The microendoscopic use of the CO_2 laser provided an excellent approach to release these strictures from the epiglottis with excellent visualization and working space. Mucosal pharyngeal reconstruction flaps can be transpositioned to prevent recurrent contracture and stricture formation. A tracheotomy under local anesthesia was first performed to improve the working space and visualization and secure the airway. Despite the impaired pharyngeal and tongue-base muscle activity and loss of laryngeal elevation and closure, near normal oral intake was achieved in this case. However, even the possibility of restoring minimal oral intake can provide a great improvement in the quality of life and is therefore worthwhile to try to achieve (Figs. 16 and 17).

2.5.2 Anterograde–Retrograde Rendezvous Dilation for Complete Hypopharyngeal or UES Stenosis

Hypopharyngeal or UES strictures are commonly managed with bougie dilatation as long as there is still some lumen. Laurell et al. (2003) reported a 78% success rate with dilatation of hypopharyngeal strictures secondary to radiotherapy for head and neck malignancies. Patients with moderate-to-severe strictures required one to eight dilations. The reported mortality rate was 5% secondary to esophageal perforation.

In the case of complete obstruction of the hypopharynx/cervical esophagus, an anterograde–retrograde dilatation technique can be considered. In this technique, a guide wire

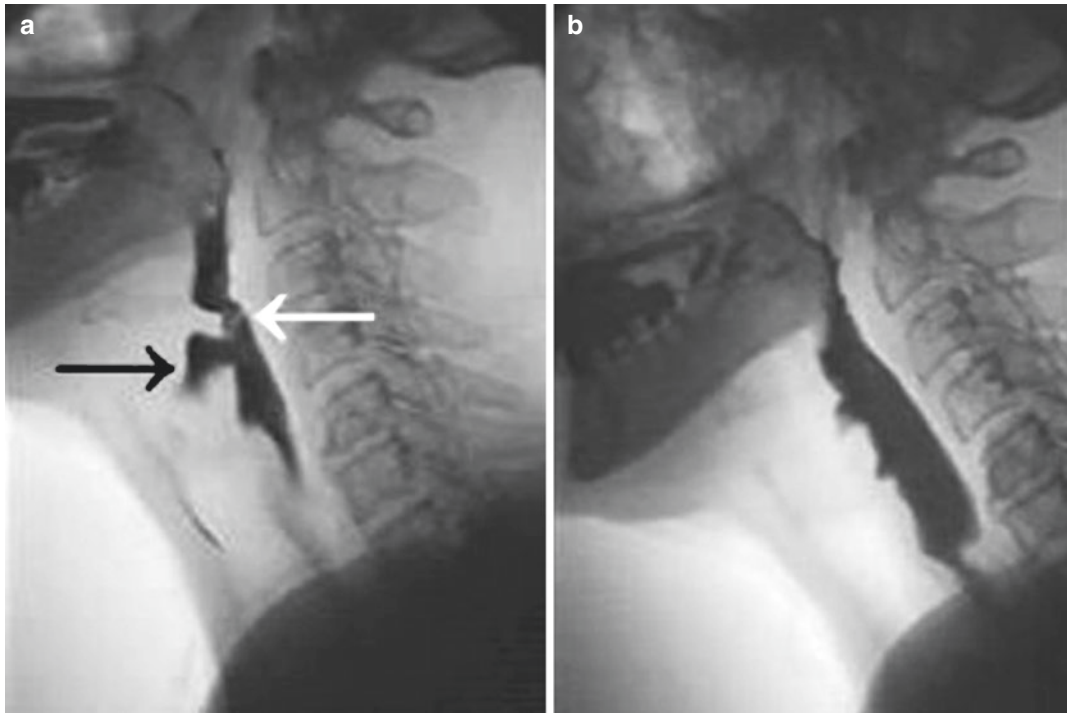

Fig. 15 Same case as in Fig. 14. (**a**) Preoperative videofluoroscopy demonstrating the oropharyngeal stenosis (*white arrow*), penetration of contrast material in the larynx (*black arrow*), primary aspiration into the trachea, and an almost absent pharyngeal constrictor muscle activity. (**b**) Postoperative videofluoroscopy in the pharyngeal phase revealing complete reduction of oropharyngeal stenosis, an increased bolus passage, and no penetration or aspiration. Of course, the pharyngeal constrictor activity is still insufficient

retrogradely introduced through a (preexistent) percutaneous gastrostomy, and the lumen of the esophagus can safely be detected from the hypopharyngeal side without creating a false route in the mediastinum, with the risk of mediastinitis. Often a rigid endoscope is required to enter the esophagus from below, because flexible endoscopes tend to curl up inside the stomach instead of passing through the LES into the esophagus. After the lumen has been resorted, intermittent anterograde bougie dilatation is often required.

The anterograde–retrograde rendezvous technique was first described by van Twisk et al. (1998), and several other small series were reported later (Petro et al. 2005; Maple et al. 2006). The advantage of this technique is that a stenosis can be punctured with a dilation guide wire away from the mediastinum, avoiding a false route in this direction and thus reducing the risk of mediastinitis. Sometimes transillumination is used from both sides to determine the direction of puncture. If the stenosis extends over a longer distance, anterograde dissection with a blunt instrument or the CO_2 laser can be performed toward an illuminated poststenotic lumen. Most patients treated this way have responded well to subsequent serial dilations and most have been able to discontinue gastrostomy tube use (van Twisk et al. 1998; Petro et al. 2005; Maple et al. 2006) (Figs. 18 and 19).

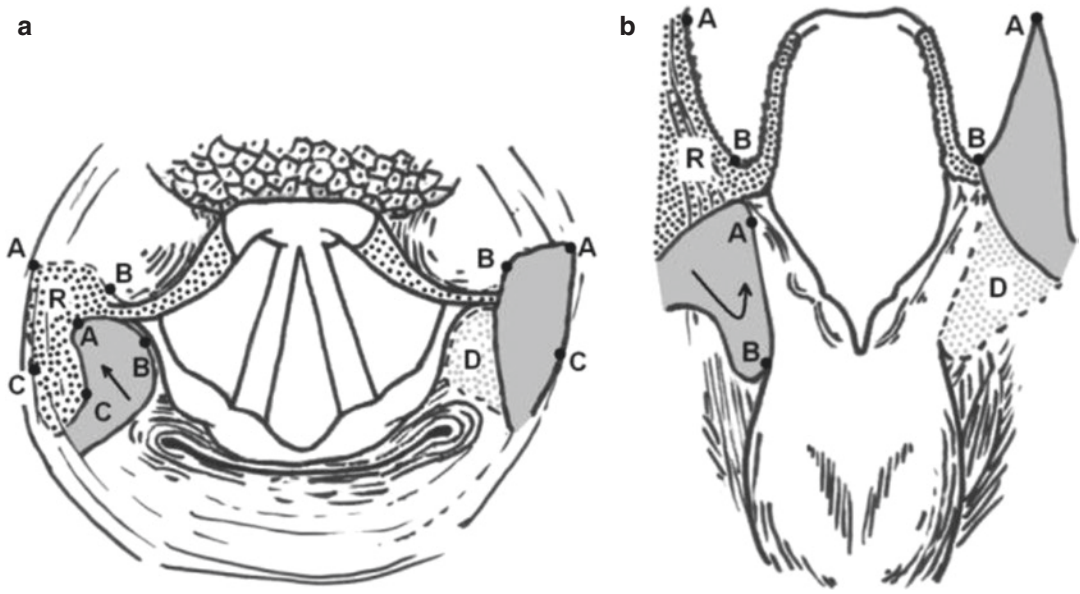

Fig. 16 (**a**) Craniocaudal and (**b**) posteroanterior views of the larynx and hypopharynx: the pharyngoplasty procedure. In each case, the *left side* shows the situation after dissection and resecting the strictures, and before transpositioning of the mucosal flap from the piriform sinus, and the *right side* shows the situation after transpositioning of the mucosal flap and suturing. The raw surface of the epiglottis edges remained uncovered. The raw surface of the lateral free edge of the epiglottis and pharyngeal wall is marked with *R*. The donor site of the transposition flap is marked with *D* and its corresponding end position points are marked with *A*, *B*, and *C*

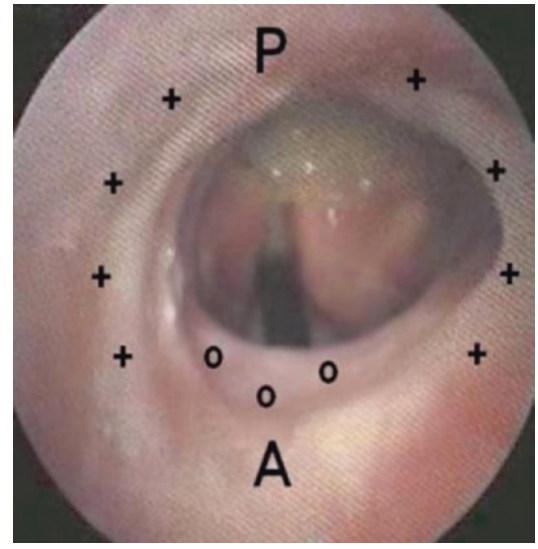

Fig. 17 Endoscopic view of the larynx of another patient demonstrating a similar, but less severe stricture (*crosses*) of the free edge of the epiglottis (*circles*) and the lateral pharyngeal walls and the arytenoids with the posterior part of the vocal folds below. In this case, the esophageal stenosis was complete in continuity with an obliteration of the piriform sinus bilaterally. *A* anterior, *P* posterior

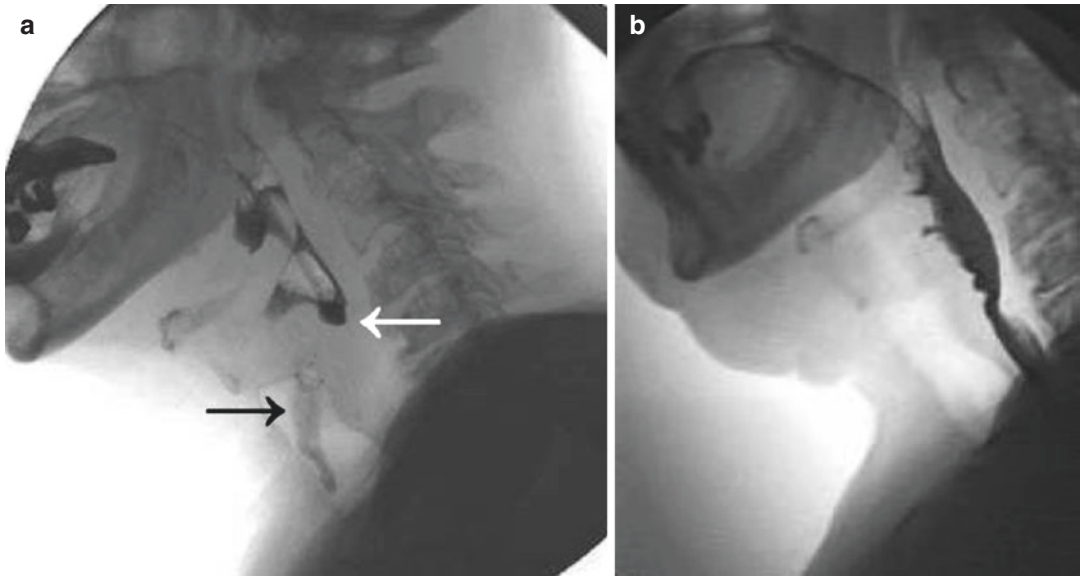

Fig. 18 (**a**) Preoperative videofluoroscopy demonstrating stenosis in the postcricoid area (*white arrow*) and severe aspiration (*black arrow*). (**b**) Postoperative videofluoroscopy demonstrating bolus passage into the esophagus with moderate residual stenosis and absence of aspiration

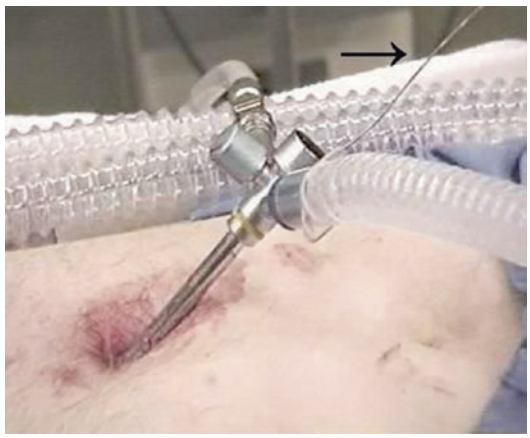

Fig. 19 Rigid endoscope introduced through the percutaneous endoscopic gastrostomy opening with a Savary dilation wire (*arrow*) introduced. The flexible tube attached to the endoscope is used for insufflation purposes

Conclusion

As in all elective surgical procedures, the dysphagic patient has to be fit enough to overcome the stress related to general anesthesia, the surgical procedure, and the recovery period. However, the patent with a severe dysphagic problem is often not in a good condition and many patients have serious comorbidity. This restricts the use of a surgical treatment option in many cases. Furthermore, not all disorders resulting in oropharyngeal dysphagia can be successfully corrected surgically. Therefore, only a minority of dysphagic patients will be able to benefit from surgical treatment. However, the results presented in this chapter show that it is worthwhile to take into consideration the several procedures which have been described, in order to optimize the quality of life of the dysphagic patient. Since the focus of this chapter was on the surgical treatment of oropharyngeal dysphasia and no mention was made of swallowing rehabilitation, it should be stated that in almost all patients following surgical treatment, with the exception of patients with extraluminal compression and patients with ZD, an extensive postoperative swallowing rehabilitation program is an integral part of the treatment.

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Surgery in Benign Oesophageal Disease

Jan Johansson

Contents

Abstract

Modern approach to benign oesophageal disease comprises endoscopic, laparoscopic and open surgical procedures. The indication for a surgical procedure is in some patients obvious, but in some patients less clear. It is important for patients and for healthcare professionals to have equal goals and expectations of a surgical procedure. The aim of this chapter is to convey to the reader a surgeon's view on the limitations of surgery for benign oesophageal disease without technical discussions of less interest to non-surgical professionals. Incidence, pathogenesis, imaging, diagnosis, differential diagnoses, treatment, side effects and complications are discussed for most of the common benign disorders such

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as gastro-oesophageal reflux disease, hernias, strictures, achalasia, eosinophilic oesophagitis, diverticula, haemorrhage, foreign bodies and perforations. Symptoms, and objective findings of failed open or minimally invasive surgical procedures, commonly known by operating surgeons only, are briefly discussed and related to normal postoperative expectations and findings.

1 Background

Traditional open surgery was for long the only option to cure patients with benign oesophageal conditions. For a long time radiological evaluations with barium oesophagram was the mainstay diagnostic tool. After the introduction of CT scans, flexible endoscopy, pH and manometry studies a better understanding of benign oesophageal disorders took place. During the late twentieth century gastro-oesophageal reflux disease was characterised, and parallel to this anti-reflux surgery was developed. More recently high-resolution manometry, new imaging techniques, therapeutic endoscopy, and laparoscopic and robotic surgery further push the envelope to better diagnosing and more tailored, less invasive surgical procedures.

2 Gastro-Oesophageal Reflux Disease

The most common oesophageal problem is gastro-oesophageal reflux. It is usually described as retrosternal symptoms with heartburn, reflux, regurgitations and chest pain and spans from occasional symptoms to severe day- and nighttime symptoms with low quality of life and sometimes with complications. Less often reflux of gastric contents spills over from the oesophagus to the airways, so-called atypical or extra-oesophageal reflux, with additional symptoms. Complications to reflux include esophagitis, strictures, metaplasia (Barrett's oesophagus), cancer and outside of the oesophagus: laryngitis, chronic cough and asthma. The transit between symptoms suggesting reflux and gastro-oesophageal reflux disease (GORD) is not exactly defined, but is best estimated by pH studies.

A dose–response relationship usually exists between the amounts of reflux into the oesophagus, symptoms and structural changes of the oesophagus. Higher exposure of gastric contents to the oesophagus gives rise to more symptoms and more structural damage. However, the relationship is not absolute, and patients with symptoms suggesting severe reflux disease may have normal findings on evaluations, and vice versa patients without reflux symptoms may have severe damage to the oesophagus due to reflux. Most symptoms and complications related to GORD are for natural reasons located in the distal oesophagus, where reflux from the stomach is most evident. Proofs suggest that nocturnal reflux is more central to the progress of severe complications than is daytime reflux. Defects in the lower oesophageal high-pressure zone and clearance mechanisms are related in part to recumbence during sleep and may explain why transient episodes of nocturnal reflux outnumber daytime episodes in patients with GORD (De Giorgi et al. 2006).

2.1 Incidence

The true incidence of GORD is difficult to assess. A population-based European study indicated that 6% reported reflux symptoms (heartburn and/or regurgitation) daily, 14% weekly and 20% less than weekly during the previous 3-month period (Ronkainen et al. 2006). Cross-sectional studies indicate that gastro-oesophageal reflux disease symptoms have a prevalence of 10–20% in Western countries and are associated with obesity, smoking, esophagitis, chest pain and respiratory disease (El-Serag et al. 2014; Dent et al. 2005). The natural course of reflux symptoms and of GORD is hard to establish due to few studies. In patients referred for reflux symptoms and objectively diagnosed with pathological reflux but conservatively treated, a considerable part of the cohort 20 years after

diagnosis still experienced symptoms of reflux and showed endoscopic progression, although no significant deteriorations were seen in manometry data and in most pH study data (Falkenback et al. 2009).

2.2 Pathogenesis

The pathogenesis of gastro-oesophageal reflux disease is multifactorial (De Giorgi et al. 2006), involving transient lower oesophageal sphincter relaxations and lower oesophageal sphincter pressure. As a result, reflux of acid, bile, pepsin and pancreatic enzymes occurs, leading to oesophageal mucosal injury. Other factors contributing to the pathophysiology of gastro-oesophageal reflux disease include hiatal hernia, impaired oesophageal clearance, delayed gastric emptying and impaired mucosal defensive factors. Hiatal hernia contributes to gastro-oesophageal reflux disease by promoting lower oesophageal sphincter dysfunction. Impaired oesophageal clearance is responsible for prolonged acid exposure of the mucosa. Delayed gastric emptying, resulting in gastric distension, can significantly increase the rate of transient lower oesophageal sphincter relaxations, contributing to postprandial gastro-oesophageal reflux disease. The mucosal defensive factors play an important role against development of gastro-oesophageal reflux disease, by neutralising the back diffusion of hydrogen ions into the oesophageal tissue. While the pathogenesis of oesophageal symptoms is now well known, the mechanisms underlying extra-oesophageal airway manifestations are still poorly understood. Two hypotheses have been proposed: direct contact of gastric acid with the upper airway and a vago-vagal reflex elicited by acidification of the distal oesophagus, leading to bronchospasm. Gastro-oesophageal reflux disease can thus be considered as the result of a complex interplay of factors, all promoting the contact of gastric acidic contents with the oesophageal mucosa, leading to different degrees of structural oesophageal damage (Dent 2008; Bennett 1988).

2.3 Diagnosis

The cornerstone of the diagnosis is a detailed medical history, followed by an initial test period of medications, and a follow-up to confirm the diagnosis. In case further tests are required, endoscopy is the first test to undertake. Thereafter, in order to tailor therapy, stepwise evaluations can be done mainly to find out the severity of the disease.

2.3.1 Proton Pump Inhibitor Test

The proton pump inhibitor (PPI) test is a short course of high-dose PPI, used to diagnose gastro-oesophageal reflux disease (GORD). This diagnostic strategy is used globally for symptoms suggesting uncomplicated GORD, without additional symptoms suggesting complications or malignancy, primarily because of its availability, simplicity and high sensitivity. The PPI test has been proven to be a sensitive tool for diagnosing GORD in non-cardiac chest pain patients (Gasiorowska and Fass 2008).

2.3.2 Endoscopy

Oesophago-gastro-duodenoscopy is usually the first test a patient is sent to for evaluation whether or not he or she has manifestations of GORD, or in case another underlying disorder may explain the presented symptoms. The results of the endoscopy may show a normal endoscopy with or without a hiatal hernia, with or without erosive oesophagitis. Hiatal hernias are associated with reflux symptoms and are diagnosed in most patients with reflux. Hiatal hernias may add dysphagia due to a bolus temporarily stuck in the hernia between the oesophagus and the crural impressions of the diaphragm. However, patients without GORD symptoms with hernias are not uncommon.

Erosions in the oesophageal mucosa starting at the gastro-oesophageal junction are usually good indicators for GORD and the concept erosive oesophagitis (ERD) (Fig. 1) as compared to non-erosive GORD (NERD) is commonly used.

2.3.3 pH-Metry and Oesophageal Manometry

To further elucidate whether or not a patient has GORD, a pH study best discriminates between normal and pathological acid exposure to the oesophagus. A pH value of less than 4 has a corrosive effect on the oesophageal mucosa and has for several reasons been used as a cut-off level for determining whether or not reflux exists. To quantify the amount of acid exposure, ambulatory devices have been developed to quantify GORD by measuring the time during day and night the oesophagus is abnormally exposed to gastric acid contents (Fig. 2). An endoscopically placed probe that sends data to an external receiver for 2 days (Fig. 3) has now gradually replaced the cumbersome through-the-nose-placed catheter system (Fig. 3). Normally, a person without reflux symptoms or GORD exposes his or her distal oesophagus to acid gastric contents to a pH value of less than 4 up to 3.4% of a day (24 h). Values higher than this are associated with GORD.

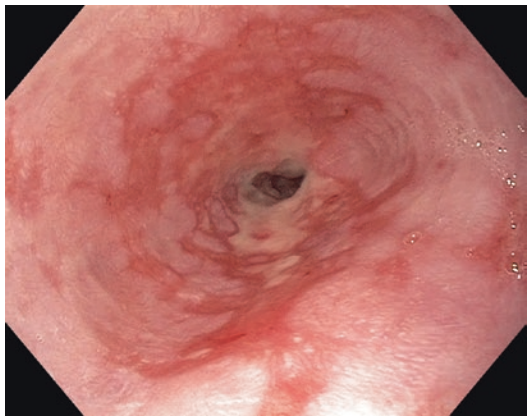

Fig. 1 Erosive oesophagitis as a manifestation of GORD is seen as white/yellow inflammation with red lining along a normal pale oesophageal mucosa. Image: *Jan Johansson*

Oesophageal manometry is used to exclude other motor disorders of the oesophagus that symptomatically may mimic GORD, to prove a structurally damaged lower oesophageal sphincter (LES), and to evaluate motility of the oesophagus. The LES can manometrically be recognised as a high-pressure zone that starts in the distal oesophagus and ends in the stomach. The high-pressure zone is mainly characterized by a total length, an intra-abdominal length, a resting pressure and the ability to open and close upon a swallow. The motor activity of the oesophagus cranially to the LES can be quantified by evaluating the propulsive activity of a bolus over time and by the pressure it generates. GORD patients usually have normal motor activity of their oesophagus, but in achalasia and other motor disorders of the oesophagus specific characteristics can be diagnosed by traditional manometry or by high-resolution manometry. When GORD is present a structur-

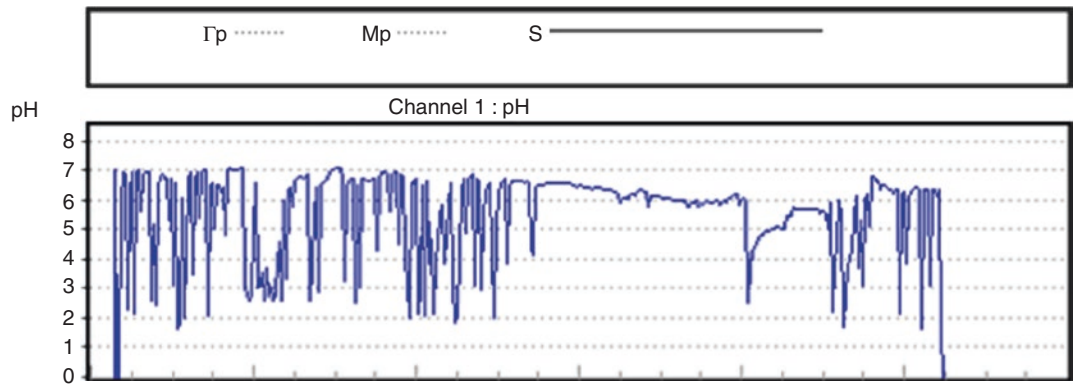

Fig. 2 A typical 24-h pH study of the distal oesophagus. On the *y*-axis the actual pH value is presented, and the *x*-axis presents the plot of the pH value over time. To quantify acid reflux to the oesophagus, the cumulative time that pH is below 4 is presented as the percentage time of the day that pH is less than 4 (not shown in graph). In this 24-h graph two meals and their initial postprandial period are noted (Mp) as well as the time when the patient was in a supine position (S) during night. A number of short daytime reflux periods are seen as spikes; however less nocturnal reflux is noted. Image: *Jan Johansson*

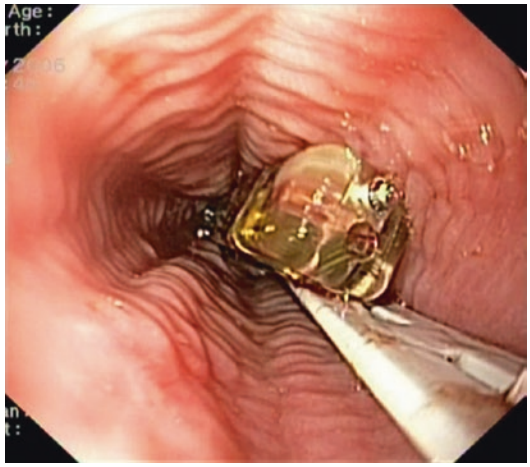

Fig. 3 The endoscopically placed pH capsule is fixed to the oesophageal mucosa, and falls off within a week. The distal part of the delivery device is seen in view. Image: *Jan Johansson*

ally damaged LES is seen, by virtue of one or more defect components of the high-pressure zone. Hiatal hernias, associated with GORD, can be recognised on manometry.

Radiology is seldom used as a primary diagnostic tool for diagnosing GORD, but may be of value in selected cases.

2.4 Differential Diagnoses

The most important diagnosis to rule out is premalignant and malignant lesions, especially in middle-age patients where the risk for cancer is increasing. Since intestinal metaplasia (Barrett's oesophagus) is a known long-term sequel to GORD, but usually goes without additional symptoms, patients with long-standing reflux symptoms usually are sent for an upper GI endoscopy to rule out this condition. Eosinophilic oesophagitis, achalasia and other motility disorders are less common conditions than GORD, but may initially be misdiagnosed as GORD.

2.5 Treatment

The goal of treatment is symptom relief, which can be achieved with medical or surgical therapies. The most prominent symptoms to relieve in most patients are heartburn, regurgitations and reflux.

Atypical reflux symptoms such as cough, asthma and hoarseness can be more difficult to treat only with PPIs. Contrary to the distal oesophagus that is used for physiologic gastric reflux, the larynx and the airways are not. Atypical reflux symptoms may manifest also after minimal exposure of refluxed contents and the diagnosis is more difficult to establish. These patients usually benefit from surgical therapy since it better protects the target organs from any reflux rather than just removing acid from the refluxate the way PPIs do.

2.5.1 Medical Treatment

Proton pump inhibitors block acid production of the stomach and have revolutionised GORD treatment because of a much better acid reduction than previous generations of drugs had. A majority of patients are completely relieved of their symptoms by using PPIs once or twice daily or on demand. Reflux symptoms or GORD usually persist over time, but may alter in intensity and the patients usually can adapt their medicines to this. The erosive effect of the refluxate in the oesophagus can usually be taken care of by PPIs, but reflux of a more neutral pH still exists. Since gastric contents physiologically contain bile, the potential for erosions still exists, but is uncommon.

2.5.2 Surgical Treatment

When it comes to surgical treatment for GORD, it is of outmost importance to select the proper patient for therapy, and to select the proper procedure for each patient. Patients should undergo endoscopy, pH-metry and oesophageal manometry to confirm the GORD diagnosis and to rule out other oesophageal disorders. Criteria for good surgical treatment results include persistent symptoms suggesting GORD in a patient who is willing to undergo surgical therapy, a response to given medical therapy and symptom relief, and objective tests suggesting GORD.

Open, laparoscopic or robotic surgery is the mainstay therapy for GORD treatment in patients with more advanced disease, and for patients with atypical manifestations of the disease.

Endoscopic suturing devices, thermal- or injection therapies to the LES as well as minimally invasive augmentations of the LES have been tried as alternative therapies to medical treatment in patients with less advanced disease. Some of these therapies are abandoned for poor effects or for side effects, and some are still investigational.

The laparoscopic fundoplication has for decades been the most used surgical therapy for GORD. Reflux is prevented by reducing a hernia, if present, pulling and securing the distal oesophagus to an intra-abdominal position, and by the augmentation of the distal oesophageal high-pressure zone with a wrap of the upper stomach around the distal oesophagus.

Reflux of gastric contents into the oesophagus is physiological, a way to clear the stomach from gas, and to vomit. A surrogate marker for physiological reflux can be measured by pH studies in the distal oesophagus. A couple of anatomical and physiological considerations may help to understand the pathophysiology of reflux and also the mechanism of how anti-reflux procedures prevent reflux. One should bear in mind the difference in pressure between the chest and the abdomen, and that the gastro-oesophageal junction is a transitional zone between these two compartments. As compared to the abdomen and the atmosphere the intrathoracic pressure is negative. This is intra-abdominally manifested as a constant suction from the chest. The chest with the intercostal muscles and the diaphragm are inelastic and stiff structures. Analogue to this the abdominal compartment is also a closed and relatively stiff compartment. The only naturally weak connection with some compliance and possibilities to exchange pressure differences between the chest and the abdomen is the area where the oesophagus enters the abdomen from the chest. This area, the gastro-oesophageal junction, contains the oesophagus and its relatively weak and soft supporting ligaments. This area thus slides a little bit with breathing, and is a natural exchange area for pressure differences when occurring, a phenomenon that probably facilitates physiological reflux, GORD and hiatal herniation. A normally placed intra-abdominal oesophagus with a normal high-pressure zone will prevent reflux. When a structurally damaged high-pressure zone is present reflux may occur. In case a hiatal hernia exists, with or without a defect high-pressure zone, the upper abdomen and the distal oesophageal high-pressure zone are positioned in the lower chest, a phenomenon that facilitates reflux and GORD to occur.

Following a successful anti-reflux procedure, patients usually are relieved of their symptoms, erosive oesophagitis disappears, pH studies reveal reduced acid exposure to normal or subnormal levels, and a longer total and intra-abdominal length of the high-pressure zone with normal resting pressures is usually found on tests. Oesophageal peristalsis however remains unchanged after an anti-reflux procedure.

Numerous variations of anti-reflux procedures exist, all with the aim to stop reflux, but with minimal side effects. An early experience after fundoplications was almost no measurable reflux at all, and sometimes dysphagia due to outflow obstruction at the site of the wrap. Full fundoplications (Figs. 4 and 5), as the original Nissen fundoplication, may have other side effects such as inability to belch and to vomit, effects of a super-

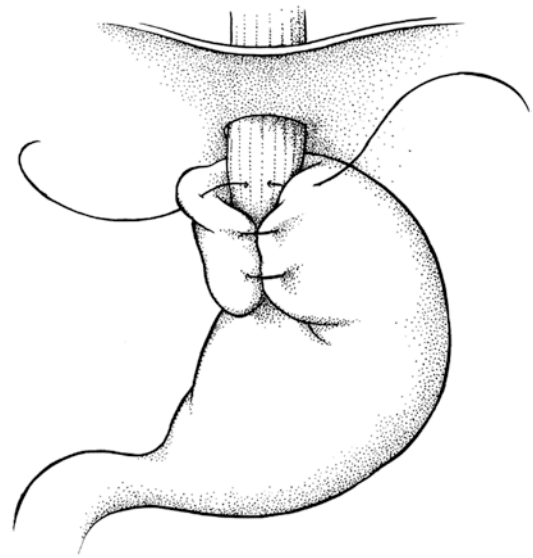

Fig. 4 Typical 360° (full) fundoplication placed inferior of the diaphragm where the upper part of the stomach is wrapped around the intra-abdominally secured distal oesophagus. Image: *Jan Johansson*

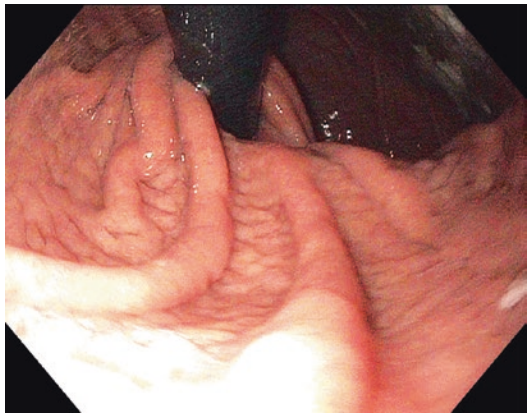

Fig. 5 Endoscopic view of a 360° fundoplication where the fundus is wrapped around the distal oesophagus. The endoscope is passed through the oesophagus into the stomach and a j-turn is made to visualise the anti-reflux wrap that appears as a continuous gastric fold that encircles the distal oesophagus and the endoscope. Image: *Jan Johansson*

competent high-pressure zone. These symptoms may be effects of a too tight anti-reflux valve that well protects the patient from reflux, but omits the ventilating function of the high-pressure zone. Nowadays a full but loose or 'floppy' fundoplication with good results is done to prevent this phenomenon. Anti-reflux procedures are nowadays tailored to minimise side effects of a full fundoplication and to allow some natural reflux to occur in order to minimise side effect. Partial fundoplications, where not the whole stomach is brought around the oesophagus, are sometimes used. Partial fundoplications usually result in less of the above-mentioned side effects following full fundoplications, but sometimes provide a less efficient anti-reflux procedure. Partial fundoplications favour in patients with compromised oesophageal peristalsis for better oesophageal clearance.

Depending on the magnitude of reflux, patient's preferences, expectations and other medical conditions the operating surgeon and the patient together need to select a proper procedure for each individual patient.

Patients with atypical reflux symptoms are a minority in comparison with traditional GORD patients, and respond well to surgical therapy. Anti-reflux procedures usually reduce any manifestation of reflux to subnormal levels irrespective of its content, while PPIs reduce acid only.

According to a systematic review of the literature surgical management of GORD is more effective than medical management with respect to patient-relevant outcomes in the short and medium terms. However, long-term studies still are needed to determine whether anti-reflux surgery is an equivalent alternative to lifelong medical treatment (Rickenbacher et al. 2014).

3 Barrett's Oesophagus

Patients with GORD in 3–5% (Ronkainen et al. 2006) diagnosed with metaplastic columnar epithelium, Barrett's oesophagus (Fig. 6). The new mucosal lining of the oesophagus endoscopically looks like an ordinary pink gastric mucosa in contrast to the white ordinary squamous oesophageal lining. Several risk factors for development of Barrett's have been identified including GORD, central obesity, *H. pylori* eradication and male gender. Nearly half of the patients with Barrett's are asymptomatic (Wood and Yang 2008).

As any metaplastic condition, Barrett's oesophagus may further develop into a malignant condition, cancer in Barrett's oesophagus, with symptoms identical to patients who develop squamous cell cancer in the oesopha-

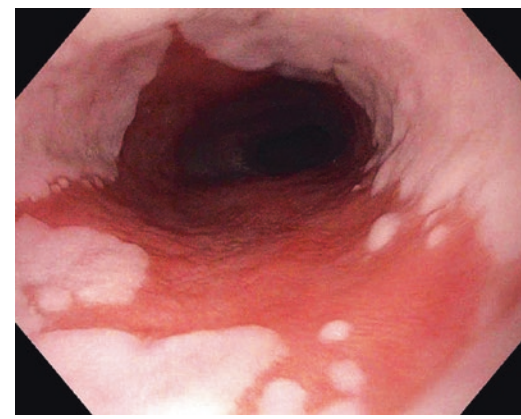

Fig. 6 Endoscopic view of a metaplastic Barrett's segment (pink) in the distal oesophagus as compared to a normal oesophageal mucosa proximal (white). Image: *Jan Johansson*

gus. The risk of developing cancer in patients with Barrett's oesophagus is approximately 0.5% per year (Spechler 2003). Since some subtypes of Barrett's oesophagus are recognised as a pre-malignant condition, patients with those forms of metaplasia at risk for cancer development are followed according to endoscopic surveillance protocols including biopsies for histological evaluations. Literature usually describes the clinical management of patients with Barrett's oesophagus with oesophageal tumours, which is why it is not further described in this chapter. At present, there is no support in the literature that anti-reflux procedures or continuous PPI medication prevents the development of cancer in metaplastic segments of Barrett's oesophagus.

4 Hiatal- and Para-Oesophageal Hernias

From a clinical point of view hiatal hernias are divided into four subgroups because of different symptoms and partially different treatments: sliding hernia (95%), para-oesophageal hernias (0.4%), a combination of these hernias (4.5%) and large hernias with additional viscera herniated (0.1%) (Krause et al. 2016).

4.1 Diagnosis

Sliding hiatal hernias (type I hernia) are frequently endoscopic and radiologic findings and consist of a herniation of the distal oesophagus and the upper part of the stomach into the lower mediastinum, with or without symptoms of dysphagia, with or without symptoms of reflux. Most hernias slide up and down between the chest and the abdomen and are inconsistent finding. The endoscopist's view of a hernia is an onion-shaped part of the zone between the oesophagus and the stomach, where the upper part is delineated by the start of the longitudinal gastric folds and the impression of the diaphragm determines the end of it (Fig. 7). A j-turn of the endoscope in the stomach confirms

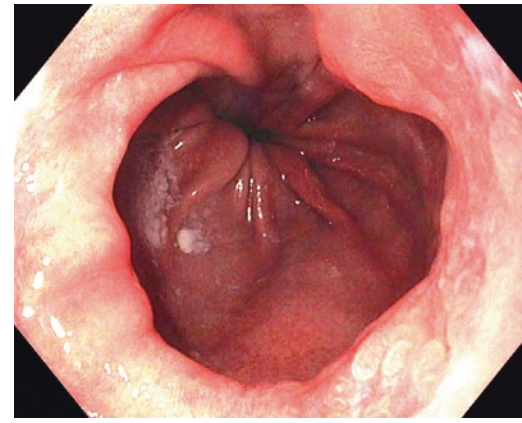

Fig. 7 Endoscopic view of a sliding hernia (type I) visualised from the oesophagus. The hernia looks like a dome that starts at the end of the oesophagus and ends where the left and right diaphragmatic crura encircle the upper stomach in this picture seen as a distal narrowing of the gastric folds with a central opening to the remaining stomach. Image: *Jan Johansson*

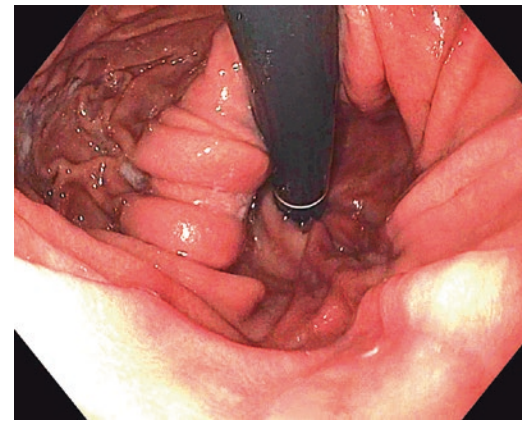

Fig. 8 The hernia endoscopically visualised from the stomach with the endoscope placed in a j-turn. Image: *Jan Johansson*

the findings with a herniated stomach looking like a dome-shaped hole between the diaphragmatic crura at the place where a normally sized oesophagus ends (Fig. 8). Since the oesophagus has a good and relatively fast motor activity, a property that a wide herniated stomach distally obstructed by the crura does not share, food is sometimes intermittently stuck inside a hernia with dysphagia as a result. Sometimes food is completely stuck inside a hernia and needs to be removed. Surgical repair for a sliding hernia by

itself is seldom indicated, but may be an indication for repair in case associated GORD exists or in case a mechanical obstruction exists from the hernia.

Para-oesophageal hernias or type II hernias are named so because a part of or the whole stomach slides up next to the oesophagus in the chest while the oesophagus remains in place all the way down through the crura, a feature that separates para-oesophageal hernias from sliding hernias. The stomach thus makes a 180° angulation at the gastro-oesophageal junction and is more or less completely in the chest. The condition is rare and has symptoms and treatment as described below for combined hernias.

Combined sliding hernias and para-oesophageal hernias (type III) are also relatively rare but the second most common type of hernia. Patient may be asymptomatic and the diagnosis is accidental or present with a variety of symptoms. Patients with this condition are often elderly thin ladies without much previous complaints who are admitted to the emergency room because of new-onset severe chest pain or sudden inability to swallow. Their medical condition may range from normal to a compromised condition. The diagnosis is obvious after a CT scan or suspected during endoscopy. Swallowing difficulties are usually secondary to the herniation of parts or the whole stomach where an angulation between the oesophagus and the stomach suddenly has become evident. Some patients admit prior swallowing difficulties and early satiety. Chest pain and a bad general condition may give signals of a compromised circulation to the stomach with ischemic parts or a complete gangrene of the stomach. In case the patient is diagnosed during endoscopy for less specific upper GI symptoms the endoscopist may become confused because the anatomy is deranged. Sometimes, due to the angulation of the distal oesophagus, it is almost impossible to pass the endoscope to the stomach. Sometimes this manoeuvre is easy but the anatomy of the stomach looks weird. The gastric impression of the diaphragm is at a wrong place and from inside the stomach it may be difficult to find and pass the endoscope to the duodenum.

4.2 Treatment

Treatment must be tailored to the severity of the condition, but in emergency patients it is important to decompress an often massively distended stomach by inserting a naso-intestinal tube to the stomach to drain it from gas and contents. The initial emergency symptoms are usually relieved by this manoeuvre. Haemorrhagic contents indicate ischemia and a surgeon should see the patient.

Surgical treatment must be tailored to the patient's general condition. In case the patient is in a good condition but the stomach is stuck in the chest, a laparoscopic or an open repair is required to re-establish swallowing. Following repositioning of the stomach into the abdomen, the huge hernia sac is excised to prevent re-herniation, and a mobilisation of the oesophagus facilitates a fundoplication after a proper closure of the diaphragmatic crura has been done.

In case the patient is compromised emergency surgery may be indicated (Fig. 9). Ischemic perforations may be present with fluid in the chest or in the abdomen that needs to be drained. The procedure may end up in a total gastrectomy or in case of a compromised but still viable stomach after reduction closure of the diaphragm and a simple fixation of the stomach in the abdomen

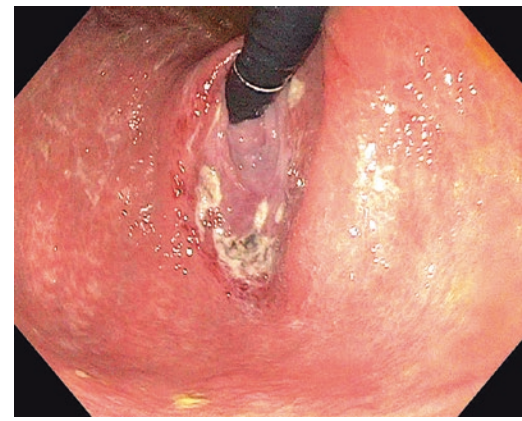

Fig. 9 Endoscopic view of an ischemic part of the stomach close to the oesophageal junction in a patient with a para-oesophageal herniation (black-grey-white area in the middle of the picture) of the stomach during emergency operation. Also the outside of the stomach was partly ischemic. Image: *Jan Johansson*

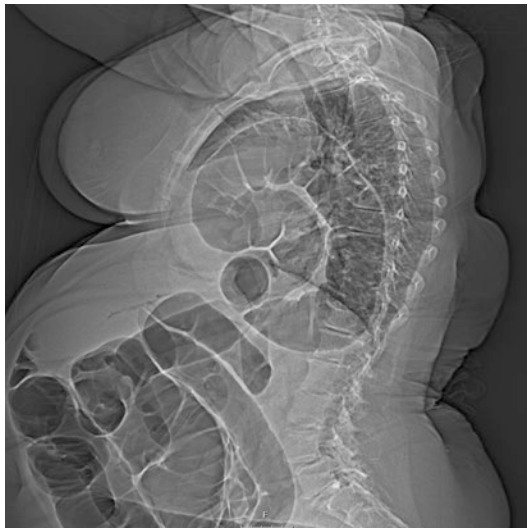

Fig. 10 Type IV hernia with the stomach and colon herniated into the chest and filled with gas. An outflow obstruction at the level of the diaphragmatic crura causes a backward intestinal obstruction of the small bowels also filled with gas. Image: *Jan Johansson*

with or without local excisions of parts of the stomach.

Type IV hernias, where additional viscera in the hernia sac are adding complexity to type III hernias, may include obstruction of the colon that needs to be addressed (Fig. 10). Evaluation and surgical principles are otherwise identical with type III hernias.

5 Strictures

Patients with progressive or solid food dysphagia suggesting a stricture should undergo a barium oesophagram or endoscopy to diagnose a potential stricture, and to further classify it as benign or malignant. The origin may be erosive oesophagitis in the distal oesophagus (Fig. 11), healing after radiation therapy to the chest, swallowed tablets, ingested lye or the result of a healing anastomosis (Johansson et al. 2009). The vast majority of benign strictures are acid related and short. Benign peptic strictures are best managed by oesophageal dilation and with acid-suppressing medications (Ferguson 2005). Strictures from caustic injuries are long-standing and often comprise longer segments of the oesophagus, and require repeated dilatations.

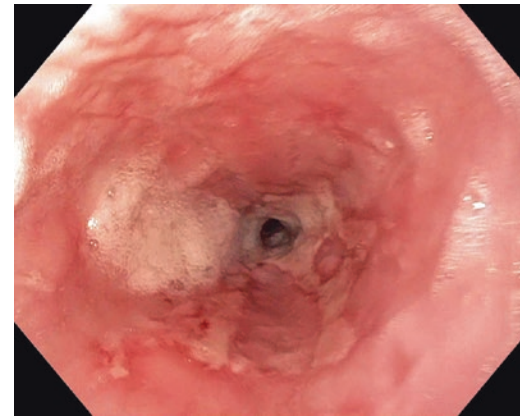

Fig. 11 Erosive oesophagitis (white–yellow fibrin) with a distal peptic stricture (circumferential fibrin deposits) immediately above a hiatal hernia in the distal oesophagus. Image: *Jan Johansson*

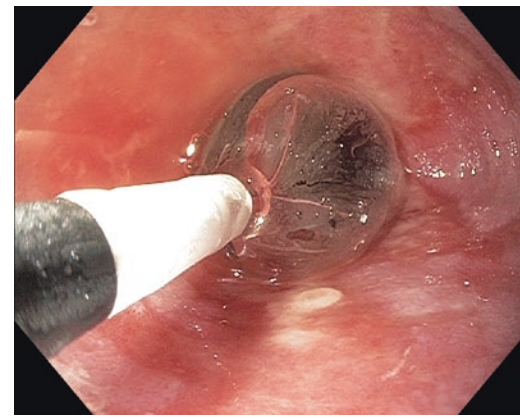

Fig. 12 Through-the-scope (TTS) endoscopic dilatation of a patient with a peptic oesophageal stricture. Image: *Jan Johansson*

5.1 Treatment

Irrespective of origin most oesophageal strictures can be dilated with through-the-scope (TTS) balloon catheter technique (Fig. 12) in light sedation in an outpatient setting, or using more rigid dilators during anaesthesia. The procedure is rapid and can be repeated as often as needed. With the exception of achalasia dilata-

tions where special dilators are used, ordinary endoscopic dilators range from approximately 7 to 20 mm in diameter. The catheters with the dilating balloon inside the patient are outside the patients filled with fluid to a certain pressure that corresponds to a certain predefined balloon diameter. Rigid plastic dilators (Savary) are placed on a through-the-stricture-placed guidewire and increasing sizes of dilators are used up to 15 mm. Savary dilators can be reused after proper sterilisation.

Complications to dilatations are perforations and sometimes bleeding. Perforations are usually minor and can be conservatively managed with nothing per mouth, antibiotics and careful monitoring of inflammatory parameters and sometimes with repeated CT scans. After a couple of days the patient may re-establish eating and can be sent home. Surgical treatment of perforations is described below.

A variety of interventions for refractory strictures exist and include injection of intralesional corticosteroids, temporary placement of self-expanding plastic stents and resectional surgery.

6 Eosinophilic Oesophagitis

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated disorder of the oesophagus characterized by the combination of upper gastrointestinal symptoms such as dysphagia and even food impaction. The cause of EoE is unknown; however dietary, environmental and immunological factors may contribute.

6.1 Incidence

The disorder was not described until in the 1990s (Attwood et al. 1993) and remains probably underdiagnosed. The incidence of EoE has increased and currently varies widely from 1 to 20 new cases per 100,000 inhabitants per year. Prevalence rates range between 13 and 49 cases per 100,000 inhabitants (Lucendo et al. 2017). There is often a history of allergy and an unexplained male predominance of 70% in adults (Remedios et al. 2011).

6.2 Diagnosis

The diagnosis is based on histological findings of >15 eosinophils/high-powered field found in endoscopic biopsy specimens.

Typical endoscopic features are longitudinal and vertical furrows (‘trachealisation’), oesophageal oedema and mucosal fragility (“crêpe paper oesophagus”). The presence of white exudates is an additional typical finding and these are thought to be clusters of eosinophils (Fig. 13).

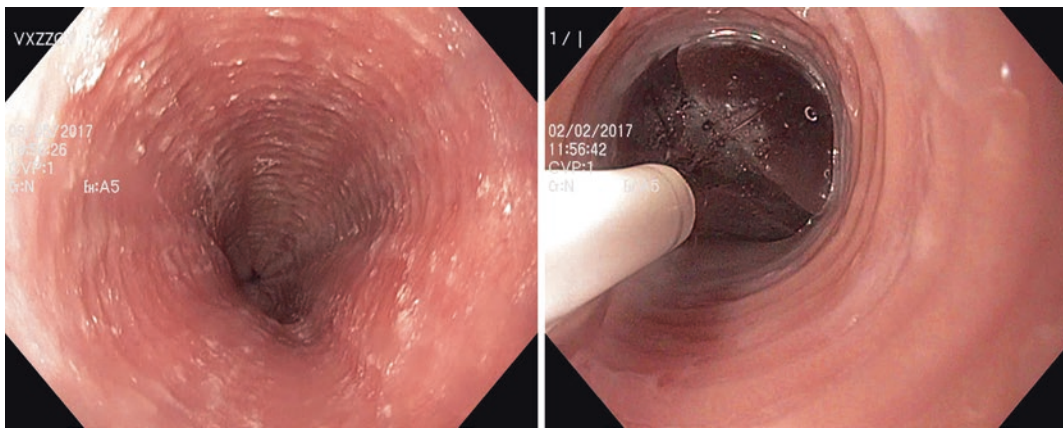

Fig. 13 Endoscopic view of a patient with eosinophilic oesophagitis undergoing dilatation. Note the multiple ring-formed webs, ‘trachealisation’, and the presence of white exudate spots of the mucosa. Image: *Jan Johansson*

6.3 Treatment

Current medical therapies include steroids, dietary manipulation, mast cell inhibitors, leukotriene receptor antagonists and immune modulators; however there is no universal approach to treatment (Elliott et al. 2010). Topical glucocorticoids are considered standard line of treatment, whereas endoscopic dilations are performed for patients presenting with treatment-resistant disease or manifestations of dysphagia and/or food impactions; endoscopic oesophageal dilation seems to be an effective and safe treatment option (Moole et al. 2017). Dilatations are performed as described in the stricture section.

7 Oesophageal Diverticula

Oesophageal diverticula are rare and traditionally divided into two types based on the aetiology: traction and pulsion diverticula. Traction diverticula may result from inflammatory reactions (tuberculosis) in neighbouring lymph nodes or as a result of embryonic malformation, and are composed of all layers of the oesophageal wall. Contrary to this, pulsion diverticula are the result of herniation of the mucosa through a weak point of the muscle layer, and are mainly of three types based on the location along the oesophagus. They may occur in the pharyngo-oesophageal area (Zenker's), in mid-oesophagus or distally (epiphrenic). A motility disorder is associated with oesophageal diverticula. An estimated ratio of epiphrenic to Zenker's diverticula is 1:5 (Zaninotto et al. 2011). Patients with mid-oesophageal diverticula seem to have a better prognosis than those with more distal disease (do Nascimento et al. 2006).

7.1 Diagnosis

Patients usually present with chest-related symptoms or oesophageal symptoms which are related to the underlying motility disorder, or to additional symptoms from the contents of the diverticulum that may compress, or unexpectedly empty its contents with aspiration as a result. Evaluation includes barium studies, gastrointestinal endoscopy, CT scans and oesophageal manometry.

7.2 Treatment

Surgery is the treatment of choice for symptomatic and large diverticula, although the outcome in asymptomatic patients is unknown (Sonbare 2015). According to a review of the literature asymptomatic diverticula or small diverticula do not need a specific treatment (Herbella and Patti 2012). The surgical options include diverticulectomy or diverticulopexy with an adequate myotomy.

7.2.1 Zenker's Diverticulum

Zenker's diverticulum is a relatively common cause of cervical dysphagia in elderly, and is the result of cervical muscular dysfunction at the cricopharyngeal muscle with a dorsal mucosal herniation through the muscular layers (Fig. 14).

Treatment is by either open, transcervical or transoral approaches. The common goal of all modalities is splitting of the septum between the oesophageal lumen and the diverticulum

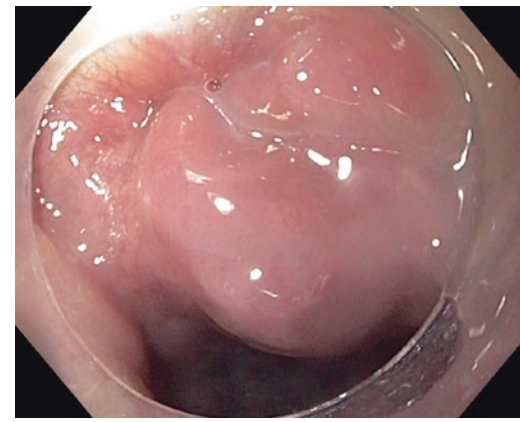

Fig. 14 Endoscopic view of a Zenker's diverticulum. Note the cup on top of the endoscope to facilitate visualisation. The opening of the diverticulum is seen at the bottom of the picture. The entrance of the normal oesophagus is closed but seen as a narrowing in the upper part of the picture with a minimal air bubble just at the oesophageal entrance. Image: *Jan Johansson*

containing the cricopharyngeal muscle. Over the past 20 years, transoral approach has mostly replaced transcervical approaches (myotomy with resection or pexi of the diverticulum) due to less pain, no scarring and a rapid recovery. Transoral approaches use either rigid access or flexible endoscopy. Today, the most common approach is transoral stapling using a 12 mm laparoscopic linear cutting stapler. This has the drawbacks of requiring extreme neck extension, the massive size of the stapler making visualisation mostly impossible and the current staple design that does not cut/staple all the way to the end of the blades, resulting in a residual pouch. Flexible endoscopy allows a more tailored approach under direct vision; the myotomy can even be extended beyond the diverticulum and onto the oesophageal wall to minimise the risk of incomplete myotomy (Beard and Swanstrom 2017).

7.2.2 Epiphrenic Diverticula

Most patients with epiphrenic diverticula (Fig. 15) are asymptomatic. When dysphagia or regurgitation is limited and respiratory complaints are absent, these patients usually can live with the diverticulum left in place. Fewer than one-third of the diverticula produce symptoms severe enough to seek medical attention or to warrant surgery (Zaninotto et al. 2011). An abnormal LES (hypertensive or non-relaxing) and/or abnormal peristalsis in the lower part of the oesophagus, with simultaneous contractions, are common findings. These motor abnormalities create a high-pressure segment that contributes to protrusion of the oesophageal wall, usually to the right side of the chest. The functional disorder may be treated by myotomy. It should start in line with the neck of the diverticulum and on the opposite side to the diverticulum to avoid interfering with subsequent pouch resection and muscle closure. Most surgeons extend the myotomy onto the gastric wall (Zaninotto et al. 2011). When myotomy is performed, partial fundoplication is recommended to avoid the risk of subsequent gastro-oesophageal reflux (GORD). Data in the medical literature on the prevalence of GER after surgery with or without fundoplication for epiphrenic diverticula are scarce. Since GER appears in more than 50% of achalasia patients

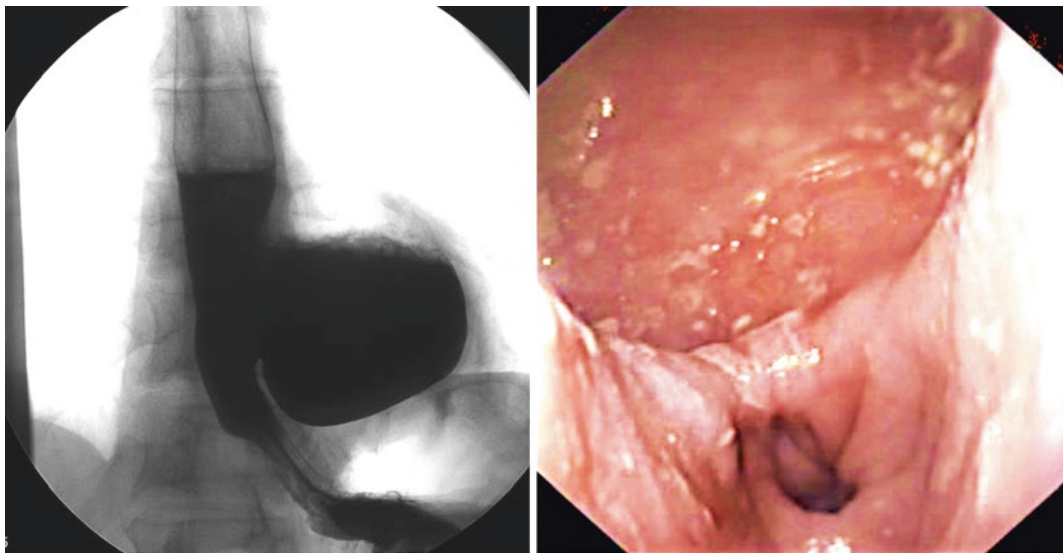

Fig. 15 Radiographic and endoscopic images of a patient with a left epiphrenic diverticulum resting on the diaphragm. The contents of the diverticulum may impinge on the distal oesophagus with swallowing problems, or may regurgitate to the throat. Both slides show a remaining septum between the diverticulum and the oesophagus, and a wide opening into the diverticulum. On the endoscopic picture the normal distal oesophagus appears as the smallest of the two openings. Image: *Jan Johansson*

when a myotomy-only procedure without fundoplication is done (Falkenback et al. 2003), the need for an additional anti-reflux procedure at the same time in patients operated on for epiphrenic diverticula seems justified. Because the motor disorder associated with epiphrenic diverticula is often characterised by abnormal peristalsis of the oesophageal body, partial and not full fundoplication is usually preferred to avoid excessive outflow resistance.

The most common complication following diverticulectomy is suture leakage, and the morbidity rate is nearly 20%. The overall mortality rate for surgery for epiphrenic diverticula is nearly 5% (Devaney et al. 2001).

The nonsurgical alternative of endoscopic pneumatic dilation has proved valuable in symptomatic patients who had an underlying motility disorder (achalasia or hypertensive lower oesophageal sphincter) but were unfit for or unwilling to undergo surgery.

8 Foreign Bodies

Patients with foreign-body ingestion typically present with odynophagia, dysphagia and sensation of having an object stuck, chest pain and nausea/vomiting. The majority of foreign bodies pass through the digestive system spontaneously without causing any harm or symptoms, or necessitating any further intervention, and occur more frequently in the paediatric population.

Impaction or obstruction often occurs at areas of physiological narrowing or angulations. Areas of physiological narrowing include the upper oesophageal sphincter, aortic arch, left main stem bronchus or lower oesophageal sphincter. Previous surgery of the oesophagus, bariatric surgery, surgery for GORD or achalasia requires special attention since the anatomical conditions can be altered. Underlying oesophageal pathology is found in more than 75% of patients presenting with food bolus impaction. The most frequently associated abnormalities are oesophageal strictures (more than 50%) and eosinophilic oesophagitis (about 40%). Less frequently, oesophageal cancer or oesophageal motility disorders, such as achalasia, are causes of food bolus impaction (Birk et al. 2016).

8.1 Diagnosis

A well-documented clinical history and thorough physical exam are critical in making the diagnosis. If additional modalities are needed, a CT scan and diagnostic endoscopy are generally the preferred modalities, but not barium swallow, because of the risk of aspiration and worsening of the endoscopic visualisation (Birk et al. 2016).

8.2 Treatment

In managing patients with ingested foreign bodies, it is essential to protect the patient's airways. Patients who have increased secretions are at an increased risk and require urgent management. Endotracheal intubation is recommended. A flexible endoscope has a greater than 95% (Ginsberg 1995) success removing foreign bodies, and is preferred when compared to rigid endoscopes because there is a lower risk of perforation (Gmeiner et al. 2007). Commonly used tools include polypectomy snares, grasping forceps, magnetic probes, retrieval snare net and transparent cap-fitting device. An overtube is beneficial in that it protects the airway and facilitates passage of the endoscope to be more effective in piecemeal removal of a food impaction. Depending on the type of impaction, different devices should be used. The European Society of Gastrointestinal Endoscopy (ESGE) suggests treatment of food bolus impaction in the oesophagus by gently pushing the bolus into the stomach. If this procedure is not successful, retrieval should be considered (Birk et al. 2016). However, especially after previous oesophageal surgery, altered anatomy may be present. The endoscopist should be aware that the bolus itself may be placed in a dilated or pouch-like part of the oesophagus where the lumen of the oesophagus is not in front of the bolus where expected, but more eccentrically positioned. A blind, forced push of a bolus under this condition will result in a perforation.

Recommended time frames for removal (Birk et al. 2016; Bekkerman et al. 2016).

Emergent (immediate)

1. Oesophageal obstruction
2. Disk battery in the oesophagus
3. Sharp-pointed objects in the oesophagus

Urgent (within 24 h)

1. Oesophageal objects that are not sharp and pointed
2. Oesophageal food impaction w/o complete obstruction
3. Objects >6 cm at or above the duodenum
4. Magnets within endoscopic reach

Recovery after endoscopic retrieval of a bolus is usually uncomplicated, and after a successful and uncomplicated endoscopic removal of ingested foreign bodies the patient can be sent home. The most critical complication is instrumental oesophageal perforation, and in case the patient has chest pain or experiences pain when drinking or eating after the procedure, individualised and immediate evaluations are mandatory to rule out a perforation. Since a vast majority of patients with food obstruction sooner or later are diagnosed with an underlying condition, diagnostic workup after extraction of foreign bodies is recommended.

9 Oesophageal Haemorrhage

Oesophageal haemorrhage may be acute or chronic (mainly from tumours). After admission to the hospital a structured approach to the patient with acute upper gastrointestinal bleeding that includes haemodynamic resuscitation and stabilisation is done. The clinical presentation of patients with acute oesophageal bleeding may range from a minor bleeding in a stable patient to massive upper gastrointestinal bleeding with immediate need for resuscitation. The vast majority of patients with acute non-malignant causes of oesophageal haemorrhage have bleeding from oesophageal varices. Other less common causes are Mallory-Weiss tears, Dieulafoy's lesions and other vascular deformations, aorto-oesophageal fistulas, and 'black oesophagus'. Endoscopy offers not only the localisation of the bleeding site but also a variety of therapeutic measures like band ligation, injection therapy, thermocoagulation or endoclips. The over-the-scope clip is a novel endoscopic clipping device designed for approximating larger amounts of tissue than ordinary endoscopic clips can incorporate with one or several clips. The device has been used in GI bleeding.

9.1 Oesophageal Variceal Bleeding

Oesophageal variceal bleeding is a severe complication of portal hypertension with significant morbidity and mortality. The clinical presentation varies according to the intensity of bleeding from occult bleeding to melena or hematemesis and haemorrhagic shock. The endoscopic treatment of choice for oesophageal variceal bleeding is band ligation of varices (Siersema 2006). A substantial portion of cirrhosis fails to respond to conventional medical therapy and band ligation, which is why self-expanding metal stent placement for acute refractory oesophageal variceal bleeding has been developed. Technical success for stent deployment endoscopically can be achieved in almost all patients, but with rebleeding ulceration and stent migration within 48 h in almost 40% (McCarty and Njei 2016). Transjugular intrahepatic portosystemic shunt (TIPS) is another second-line choice of therapy for the prevention of variceal rebleeding in liver cirrhosis (Qi et al. 2016), and has replaced open portosystemic shunt operations. The long-term outcome after therapy for oesophageal variceal bleeding depends on the severity of the underlying liver cirrhosis or portal vein thrombosis.

9.2 Mallory-Weiss Bleeding

Mallory-Weiss bleeding comes from a laceration in the mucosa at the junction of the stomach and

oesophagus caused by severe vomiting. It is strongly associated with heavy alcohol consumption, but can be caused by any conditions that cause violent vomiting and retching such as food poisoning or bulimia. In Mallory-Weiss lesions, the bleeding vessel is usually within the tear. To avoid the risk of perforation, the vessel is best grasped with both or at least 1 margin of the tear. Clipping should ideally start at the distal end of the tear; approximate the edges and proceed upward clip by clip in the fashion of clip suture. Endoscopic hemoclipping proved safe and effective in patients with Mallory-Weiss tears, even in patients with shock or comorbidity.

9.3 Dieulafoy's Lesion

Dieulafoy's lesion is a vascular abnormality consisting of a tortuous, dilated aberrant submucosal vessel that erodes the overlying mucosal layer without ulceration, and is at high risk for rebleeding. The oesophagus is a very rare location for the lesion.

Bleeding from Dieulafoy's lesion can be managed successfully by endoscopic mechanical methods, and these should be regarded as the first choice in the initial management; however, data does not support one mechanical method over another mechanical method (Tjwa et al. 2014).

9.4 Acute Oesophageal Necrosis

Acute oesophageal necrosis, sometimes named 'black oesophagus', is a rare clinical entity. Vascular supply to the body of the oesophagus comes from multiple short vessels from the thoracic aorta. The intrathoracic oesophagus can usually without ischemic side effects or dysfunction be completely dissected off the intrathoracic aorta. This may be a contribution to why this condition is rare but may arise in the setting of multiorgan dysfunction, hypoperfusion, vasculopathy, sepsis, traumatic transection of the thoracic aorta, thromboembolic phenomena, iatrogenic injury (Fig. 16) and malignancy. Clinical presentation is remarkable for upper gastrointestinal bleeding,

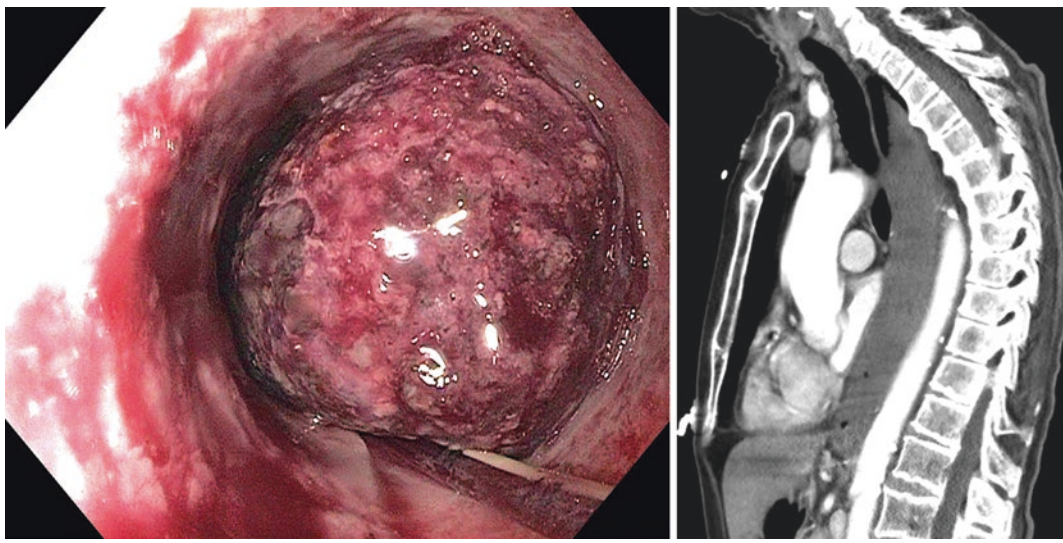

Fig. 16 Ischemic hematoma with bleeding in the oesophageal wall following a therapeutic coronary intervention. The patient complained about dysphagia and was slightly anaemic. The submucosal hematoma almost dissected off the whole oesophageal mucosa from the muscular layer and almost completely filled the lumen. Ischemic areas and bleeding were seen along the whole oesophagus. A CT scan confirmed the huge submucosal hematoma on the image seen as a grey widened oesophagus. The hematoma resolved completely after conservative treatment without stricture or dysphagia. Image: *Jan Johansson*

and symptoms may include epigastric/abdominal pain, vomiting, dysphagia, fever, nausea and syncope. Associated laboratory findings may reflect anaemia and leucocytosis. The hallmark of this syndrome is the development of diffuse circumferential black mucosal discoloration in the distal oesophagus that may extend proximally to involve variable length of the organ. Classic 'black oesophagus' abruptly stops at the gastro-oesophageal junction. Histologically, necrotic debris, absence of viable squamous epithelium and necrosis of oesophageal mucosa, with possible involvement of submucosa and muscularis propria, are present.

Treatment is directed at correcting coexisting clinical conditions, restoring hemodynamic stability, nil-per-mouth restriction, supportive red blood cell transfusion and intravenous acid suppression with proton pump inhibitors. Complications include perforation with mediastinal infection/abscess, oesophageal stricture and stenosis, superinfection and death. Outcome is related to the underlying medical comorbidities and diseases, but a high mortality rate is seen (Gurvits 2010).

9.5 Aorto-Oesophageal Fistulas

Aorto-oesophageal fistulas are rare but should be a suspected cause of bleeding in case a patient has undergone therapy to the thoracic aorta. The fistula itself may be only a couple of millimetres in diameter and may be overseen on an initial endoscopy and on imaging, or may present as an aortic graft replacing the oesophageal wall (Fig. 17). The cause of the fistula is probably a low-grade chronic graft infection.

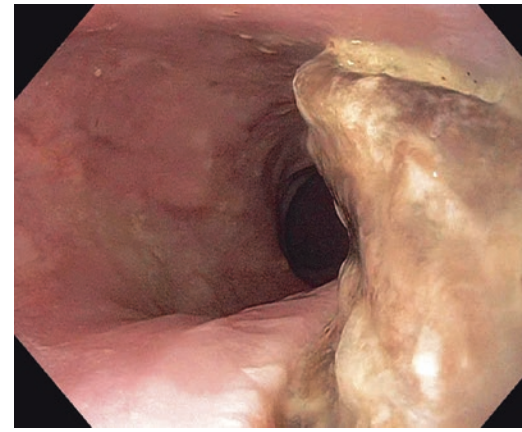

Fig. 17 Aorto-oesophageal fistula with a huge hole in the oesophageal wall with parts of an infected aortic graft seen to the right. To the left is the normal oesophagus. Image: *Jan Johansson*

10 Oesophageal Perforations

Clinical manifestations of oesophageal perforations range from almost asymptomatic to septic patients. Perforations of the oesophagus are nowadays mostly secondary to instrumental perforations, but may be caused by a full wall tear of the oesophagus usually after a through with a food-contaminated mediastinum and pleura (Boerhaave syndrome). As a consequence of the wide variety of the patient's conditions, therapy spans from expectation to immediate resuscitation and emergency surgery and has during the last decade benefited from newer technology in endoscopy and imaging.

Historically, outcomes appear to be highly affected by the ability to rapidly and accurately diagnose the site and severity of perforation and initiate treatment within the first 24 h; however referral to a tertiary care centre is as important as treatment within 24 h. The most common site for perforations is the distal oesophagus followed by the cervical oesophagus (Carrott Jr and Low 2011).

10.1 Pathogenesis and Pathophysiology

In a review including more than 500 patients, iatrogenic injury to the oesophagus was the most frequent cause of perforation, with instrumental perforations accounting for 59% of all patients. Spontaneous perforations accounted for 15% of all patients. Other injuries included foreign-body ingestion (12%), trauma (9%), operative injury (2%), tumour (1%) and other causes (2%) (Brinster et al. 2004).

10.1.1 Cervical Perforations

Cervical perforation of the oesophagus is generally less severe and more easily treated than intrathoracic or intra-abdominal perforation. Spread of contamination to the mediastinum through the retro-oesophageal space is comparably slow. Patients with cervical perforations can present with neck pain, cervical dysphagia, dysphonia or bloody regurgitation. Subcutaneous emphysema is commonly found on physical examination and appears often radiographically in cervical oesophageal perforation (Hermansson et al. 2010).

10.1.2 Intrathoracic Perforations

Intrathoracic perforations rapidly contaminate the mediastinum (Fig. 18). The rupture may immediately extend into the pleural cavity, or the pleura may withstand the injury. If the integrity of the pleura is maintained, gastric contents infiltrate the mediastinum and produce characteristic mediastinal emphysema and inflammation, and eventually cervical subcutaneous emphysema. This initial, chemical mediastinitis is followed by bacterial invasion and severe mediastinal necrosis. Rupture of the overlying pleura by mediastinal inflammation or by the initial perforation directly contaminates the pleural cavity, and pleural effusion results. As a result of negative intrathoracic pressure, gastric fluids and bacteria are drawn farther into the pleural space. Contamination disseminates, and sequestration of fluid and hypovolaemia result. Chest pain, tachycardia, tachypnoea, fever and leucocytosis occur during the ensuing inflammatory response, and systemic sepsis and shock develop often within hours. The first description of a spontaneous oesophageal perforation was by Dr. Hermann Boerhaave in 1723 who in detail described a barogenic oesophageal rupture suffered by a High Admiral of the Dutch Navy due to intense and prolonged vomiting following excessive ingestion of food and alcohol. The first successful surgical repairs following this condition were not reported until 1947, indicating the severity of the disease.

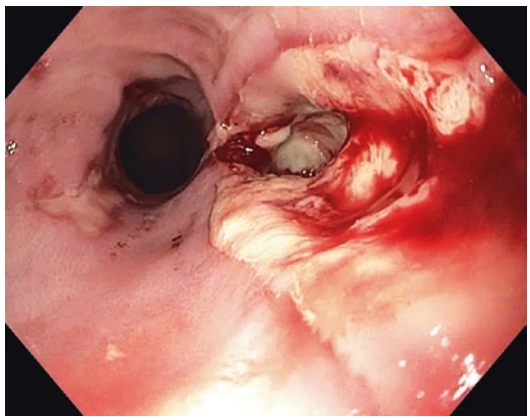

Fig. 18 A long oesophageal tear with perforation to the mediastinum and ongoing oozing bleeding. The perforation is approximately 24 h old and the edges are stiff and coated with fibrin as a manifestation of the ongoing severe inflammation. The penetration to the mediastinum is seen as a hole in the oesophagus in the middle of the picture. The ordinary oesophageal lumen appears to the left. Image: *Jan Johansson*.

10.2 Diagnosis

Common clinical manifestations of oesophageal perforation include chest pain, dysphagia, dyspnoea, subcutaneous emphysema, epigastric pain, fever, tachycardia and tachypnoea, but up to 50% of patients are atypical with delayed diagnoses. Any combination of these signs and symptoms following instrumentation of the oesophagus or respiratory tract implies perforation until proven otherwise. Flexible oesophagoscopy provides direct visualisation of the perforation in almost 100%. A plastic cup on top of the endoscope may be helpful to visualise a perforation, especially in the upper oesophagus or in case it is difficult to get an overview due to narrow conditions. CT scans with a special oesophageal leakage protocol have become standard imaging when suspicion of a leak is present (Liguori et al. 2016). The presence of pleural effusions, pneumomediastinum, subcutaneous emphysema, hydrothorax, hydro-pneumothorax or subdiaphragmatic air heightens suspicion of oesophageal perforation also in the absence of a visible perforation.

10.3 Treatment

Tailored and timed treatment is mandatory especially in the complex cases; however management decisions should be guided primarily by the degree of contamination. Other critical determinants of therapy for oesophageal perforation are the cause, location and severity of the perforation, as well as the interval between perforation and treatment. In addition to the age, general health of the patient, ASA score, damage to surrounding tissues and presence of concomitant oesophageal pathology or injury must be considered before initiating therapy (White and Morris 1992; Hermansson et al. 2010).

The objectives of treatment include elimination of infection, and prevention of further contamination from the perforation. Therefore, debridement of infected and necrotic tissue, drainage of contamination, closure of the perforation and total elimination of distal obstruction are essential to successful management. Therapy for oesophageal perforation should also include establishment of enteral or intravenous nutrition and initiation of systemic antibiotic therapy. Restoration of the integrity of the gastrointestinal tract depends on the general condition of the patient, and in septic patients this procedure may need to be delayed.

Treatment options include non-operative and operative management. Close monitoring is necessary in all patients septic or not, to detect persistence or reappearance of symptoms. Repeat CT scans and endoscopy are useful to guide changes in therapeutic policies. The decision regarding operative vs. non-operative therapy is best done by a dedicated surgical team with experience in all the surgical and endoscopic treatment options. Centralisation of low-incidence conditions such as oesophageal perforation to high-volume cancer centres provides a greater level of expertise and ultimately reduces mortality (Markar et al. 2018).

10.3.1 Non-operative Management

Non-operative management of oesophageal perforation is appropriate in selected patients with well-contained perforations and minimal mediastinal and pleural contamination, but should be active and aggressive.

The following criteria for selection of non-operative treatment are recommended from the literature (Brinster et al. 2004):

1. Early diagnosis or leak contained if diagnosis delayed
2. Leak contained within neck or mediastinum, or between mediastinum and visceral lung pleura
3. Drainage into oesophageal lumen as evidenced by contrast imaging
4. Injury not in neoplastic tissue, not in abdomen, not proximal to obstruction
5. Symptoms and signs of septicaemia absent
6. Contrast imaging and experienced thoracic surgeon available

Baseline non-operative management includes nothing by mouth for at least 48–72 h, at which time clear liquids can be initiated if the patient demonstrates clinical improvement. In addition, non-operative therapy should include administration of broad-spectrum antibiotics for at least 7–14 days and total parenteral nutrition as well as proton pump inhibitors to check associated acid reflux. Mediastinal or pleural fluid collections are drained with chest tubes, computed tomography or ultrasonography-guided drainage catheters or with suction guided by transluminal endoscopy. Intrapleural dornase and tissue plasminogen activator may help to resolve thick-walled remains of abscesses when chest drains alone fail to drain, and before surgical pleural debridement is considered. Drainage procedures may be repeated several times due to new abscesses or drain malfunction.

10.3.2 Additional Non-operative Management

Stents The goal of endoscopic insertion of endoprostheses covering the opening is to prevent continuing septic contamination, guide the re-epithelialisation of the mucosal gap and

allow early feeding. Most prostheses used in this indication are coated and extractible. Oesophageal stent can be considered as a treatment option in the management of patients who present early after oesophageal perforation or anastomotic leak with limited mediastinal or pleural contamination along with mediastinal or pleural drainage (Dasari et al. 2014). Extirpation should be performed between 4 and 6 weeks after insertion to avoid re-epithelialisation, haemorrhage or impaction of the stent. One disadvantage of oesophageal stenting is the risk for migration and insufficient closure of the tear, and stent failures in more than 20% have been reported (Wahed et al. 2014); another late disadvantage is strictures that develop at the proximal and distal parts of the stent (Fig. 19).

Clips Another not so well-documented method to close perforations is the use of endoscopic clips. Through-the-scope clips are more suitable for closing defects with a diameter less than 10 mm and over-the-scope clips perform well in closing perforations less than 30 mm (Li et al. 2016). Endoscopic clipping is difficult since the tissue around the perforation early on becomes oedematous and fragile and should be combined with drainage procedures. Endoscopic clipping is still under development.

Combined Endoscopic and Percutaneous Procedures Combined endoscopic and percutaneous procedures have been used accurately to place a percutaneous tube into the oesophagus without surgery. This allowed safe, controlled healing to occur by means of the oesophago-cutaneous fistula created with progress monitored by further radiologic and endoscopic assessment (Shenfine et al. 2001). Rendezvous endoscopy with one endoscope inserted through a previously placed chest drain hole and one from the inside of the oesophagus may facilitate removing debris, performing lavage and for drain placement (Fig. 20).

10.3.3 Operative Management

Primary repair has for decades remained the treatment of choice for oesophageal perforation in patients without diffuse mediastinal necrosis, including those seen more than 24 h after perforation (Brinster et al. 2004; White and Morris 1992; Sdralis et al. 2017). Successful reinforced primary repair requires meticulous suturing to avoid postoperative oesophageal leaks. The critical determinants of outcome following primary

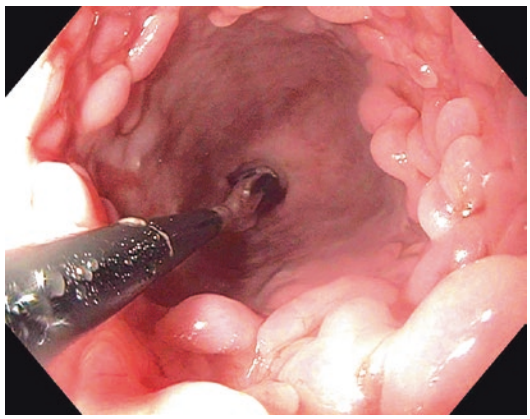

Fig. 19 Oesophageal stricture at the distal end of a previously placed oesophageal stent for perforation. Note the polyp-like granulation at the proximal end of the previously placed stent, and the through-the-scope-placed catheter ready to dilate the distal stricture. Image: *Jan Johansson*

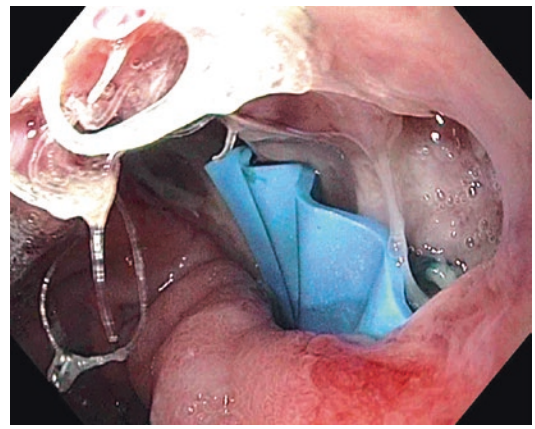

Fig. 20 The endoscope can be passed through an oesophageal tear into the mediastinum and pleura for lavage and adjustment of drains in the chest. The picture shows a blue drain with debris in the mediastinum just outside a poorly healed oesophageal perforation with some remaining sutures after previous attempt to suture the perforation. Image: *Jan Johansson*

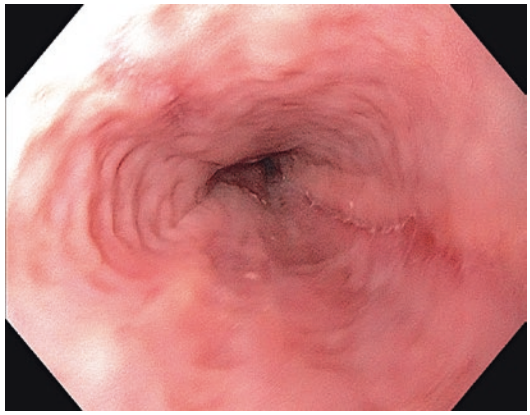

Fig. 21 The endoscopic view of a successful surgical repair of an oesophageal perforation after suturing. The suture line is seen to the right as a minimal linear scar after the perforation. No stricture developed postoperatively. Image: *Jan Johansson*

repair are the complete exposure and closure of the ruptured oesophageal mucosa and the elimination of distal obstruction, and placement of drains (Fig. 21). In case the tear cannot be closed with satisfaction, a T-tube can be placed in the oesophagus to form an artificial fistula to the skin to drain the oesophagus.

A modern alternative approach to open surgery is to combine laparoscopic and thoracoscopic approaches for lavage, drainage and suturing with or without endoscopic therapies as is described above.

Septic patients usually have a delayed diagnosis more than 24 h after perforation, and may present with diffuse mediastinal and oesophageal necrosis, and with a large deficiency of the oesophageal wall. These patients are usually beyond primary repair therapy, and following debridement of mediastinal and pleural contamination and placement of drains, an emergency resection of the oesophagus with a separate oesophagostomy and a gastrostomy is necessary. A delayed reconstruction of the gastrointestinal continuity is best done not earlier than after 3 months.

Early diagnosis of oesophageal perforation reduces the rate of complication and mortality significantly. The overall mortality rate associated with oesophageal perforations in modern studies is between 13 and 20%, and a delay in treatment of more than 24 h after perforation can result in a doubling of mortality (Brinster et al. 2004; Sdralis et al. 2017). Rehabilitation is long after advanced perforations, and strictures at the site of perforation or at both ends of the stent are not uncommon (Fig. 19).

11 Achalasia

Achalasia is a rare motility disorder of the oesophagus that usually starts with a gradual onset of dysphagia. Contrary to tumour dysphagia that usually develops within a couple of months achalasia dysphagia may slowly progress over the years, and includes problems to swallow both solid foods and beverages. The hallmark of achalasia is abnormal relaxation of the lower oesophageal sphincter (LES) and aperistalsis of the body of the oesophagus. A consequence of this is stasis of ingested food that gives rise to dysphagia, regurgitation, chest pain and sometimes weight loss. It is not uncommon that the patients seek medical attention more than a year after the onset of their swallowing problems, and subsequently they have adapted their eating habits to their new condition. Sometimes patients vividly describe how they need to leave the dinner table to vomit, or more common while eating, standing up from a sitting position to stretch or to pressurise the chest to facilitate the food to pass from the oesophagus to the stomach.

11.1 Incidence

Although uncommon, achalasia is the most common disease among the motility disorder of the oesophagus with an incidence of 0.3–1.6/100,000 (Sadowski et al. 2010; Boeckxstaens et al. 2014). Achalasia occurs in both sexes, but is less common in children (Marlais et al. 2011).

11.2 Pathogenesis

In achalasia, the oesophagus has lost the enteric neurons leading to impaired relaxation of the

lower oesophageal sphincter (LES), and absence of peristalsis in the oesophageal body. Chagas disease, a parasitic disease by *Trypanosomes* that destroys the neurons of the oesophagus, gives rise to achalasia. For the majority of patients with achalasia the cause remains unknown, but ganglionitis resulting from an aberrant immune response triggered by a viral infection has been proposed to underlie the disease (Boeckxstaens et al. 2014).

11.3 Diagnosis

Conventional or high-resolution manometry (HRM) is the single most important diagnostic tool for achalasia. Other diagnostic cornerstones are endoscopy and radiological imaging (barium oesophagram or CT scan).

Endoscopy is usually the first study a patient with dysphagia is referred to. Endoscopy favours over X-ray barium oesophagram studies for immediate biopsy taking in case a tumour or other abnormality is seen. Endoscopic visualisation of the oesophagus depends on insufflation of gas. An endoscopist may miss a patient with early achalasia due to the endoscopic view of the diameter of the oesophagus which is harder to determine as compared to a barium oesophagram study or a CT scan. Normally the oesophagus is empty and endoscopic signs of retained liquid or food inside the oesophagus raise the suspicion, but is not alone diagnostic, for achalasia. Some achalasia patients have an endoscopically noted whitish papules of the mucosa that can be misinterpreted as a fungal infection, but are instead adhered contents from previous stasis of the oesophagus.

Radiological findings characteristic of achalasia are a widened oesophagus without peristalsis and a classical narrowing of the LES that is sometimes described as a bird's beak on a barium oesophagram in an upright position (Fig. 22). A CT scan cannot provide the swallow dynamics that barium oesophagram can, and is done with the patient in a supine position. Retained fluid in the oesophagus on a CT scan can raise suspicion of achalasia, but the most important finding a CT scan provided is the information that no other conditions such as tumours explain the patients' actual symptoms.

Conventional manometry in achalasia reveals absence of peristalsis, sometimes with increased intra-oesophageal pressure owing to stasis of food and saliva, and incomplete relaxation of the LES on deglutition, with an increased LES pressure (residual pressure >10 mmHg). Additionally, the resting tone of the LES may be raised.

The Chicago Classification of oesophageal motility disorders (Kahrilas et al. 2015) based on HRM has during the last decades allowed a re-evaluation of the classification of achalasia. On conventional manometry for achalasia, incomplete relaxation of the LES on deglutition and absence of peristalsis are seen (classic achalasia). HRM adds more detailed information that has led to the definition of three subtypes of achalasia, all with incomplete LES relaxation and absence of peristalsis (Kahrilas et al. 2015; Pandolfino et al. 2008). Each of the subtypes has somewhat different treatment and prognosis.

Type I (classic achalasia): 100% failed swallows

Type II (achalasia with oesophageal compression): >20% of swallows with pan-oesophageal pressurisation

Type III (spastic achalasia): >20% of swallows with premature (spastic) contractions

For illustrations of type I–III achalasia please see Fig. 9, oesophageal achalasia subtypes in chapter "High-Resolution Manometry of the Pharynx and Oesophagus" in this book (Rommel).

11.4 Differential Diagnoses

New-onset dysphagia especially in adults may indicate cancer of the oesophagus, a condition that always should be ruled out before achalasia is considered. Since gastro-oesophageal reflux disease (GORD) is a more common disease, it is not uncommon that patients later diagnosed with achalasia initially were treated as if they had GORD and the correct diagnosis was made first after more thorough evaluations were done following treatment failure with proton pump inhib-

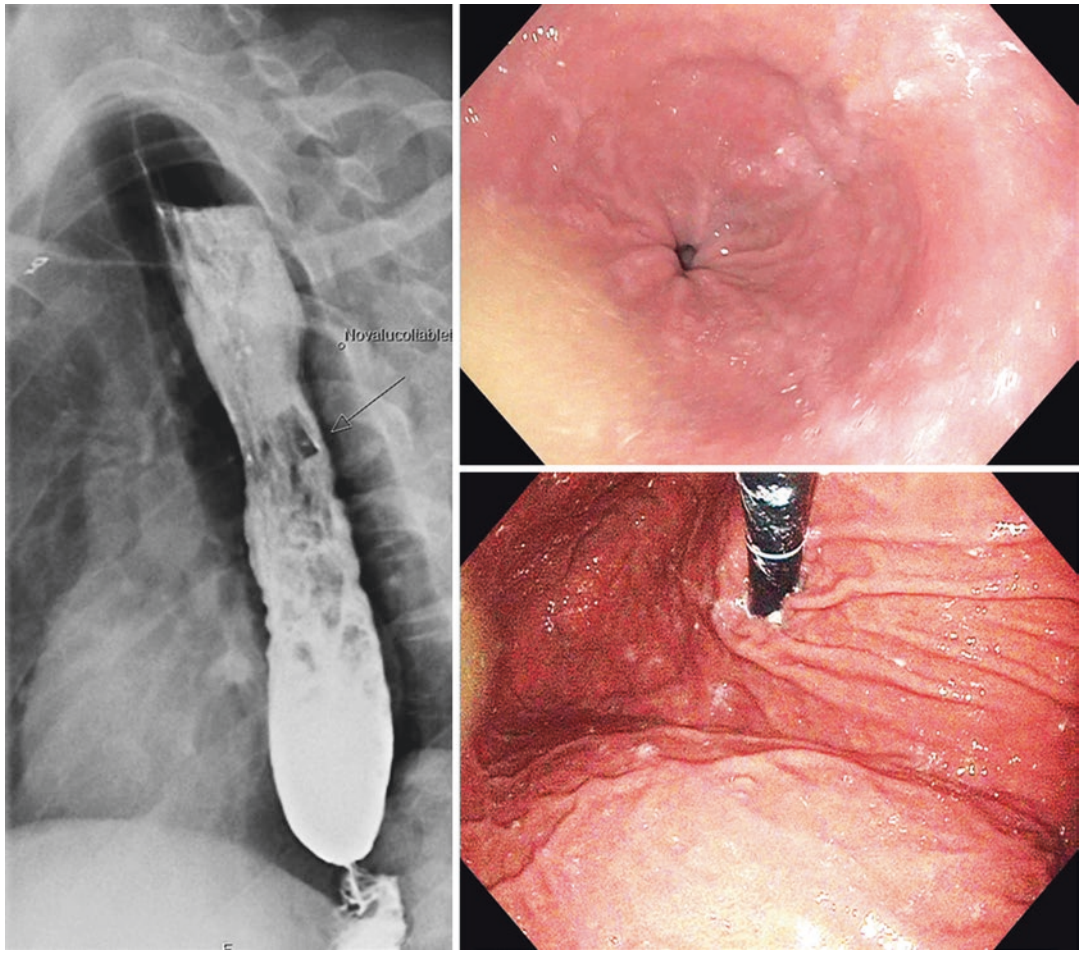

Fig. 22 Achalasia. The barium oesophagram shows a patient with the characteristic bird's beak indicating a non-relaxing lower oesophageal sphincter. A widened aperistaltic oesophagus with retained food and contrast is seen. The endoscopic picture shows a widened distal oesophagus with some retained fluid. The oesophageal opening is in the middle and is usually easy to pass with the endoscope, a phenomenon that indicates a physiologic outflow obstruction of the LES rather than a structural tissue stricture that is impossible to pass with the endoscope. A j-turn of the endoscope in the stomach confirms the tight LES in achalasia with a narrow oesophageal opening into the stomach. Image: *Jan Johansson*

itors. Eosinophilic oesophagitis is a sometimes missed diagnosis and may present with dysphagia. Fungal infection of the oesophagus may give rise to swallowing difficulties, and is more common in patients with diabetes or with a compromised immune system.

11.5 Treatment

No causative curative treatment for achalasia exists, and thus symptom relief is the goal of the treatment. Successful management of achalasia can be complex and may require more than one treatment modality. Dysphagia is the most prominent symptom to palliate in most patients; however also chest pain, regurgitations and aspiration may need to be addressed. Patients with achalasia seek medical attention sometimes early on, sometimes at advanced stages. The more advanced achalasia, the more trouble for the patient. The majority of patients are diagnosed with mild or moderate achalasia and are usually good

responders to therapy. Contrary to this, end-stage achalasia with a completely atonic, tortuously widened oesophagus where only gravity with difficulty empties the oesophageal contents to the stomach is usually resistant to most traditional treatment.

Treatment comprises medical, endoscopic pneumatic dilation (PD), laparoscopic or open Heller myotomy (LHM) and per-oral endoscopic myotomy (POEM).

11.5.1 Medical Treatment

The effects of systemic medical treatments of achalasia are limited. The most often used pharmacological drugs are nitrates and calcium channel blockers (Wen et al. 2004). Endoscopic injection of botulinum toxin into the LES temporarily improves the emptying of the oesophagus, and gives symptom relief. The effect of the injection is not immediate, lasts approximately up to 6 months and can be repeated. Injection therapy is less efficient than pneumonic dilatation (Leyden et al. 2014) evaluated at 6 months. Botulinum toxin injections may best be used as a bridge to other therapies or in frail patients since it can be done with slight sedation at the outpatient endoscopy unit.

11.5.2 Pneumatic Dilatations

Pneumatic dilatations are usually done under general anaesthesia. The procedure usually starts with an endoscopy, where a through-the-scope-inserted guidewire is placed in the stomach or duodenum. The level of the LES is endoscopically noted or in case fluoroscopic guidance is used a marker is placed at the level of the LES. A 30, 35 or 40 mm in diameter achalasia balloon is introduced on the remaining guidewire and placed at the LES. In case fluoroscopic guiding is used a characteristic waist is seen while inflating the balloon (Fig. 23). The disappearance of the waist indicates a complete dilatation (Fig. 24). The dilatation tears the LES muscles and can for best effect be repeated after a couple of weeks. There is approximately a 2% risk for a complete oesophageal tear that in 50% of the cases can be managed conservatively (Katzka and Castell 2011).

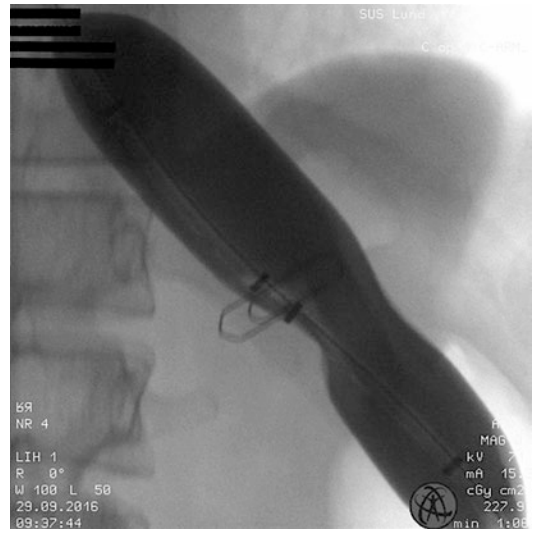

Fig. 23 Pneumatic balloon dilatation of the LES in a patient with achalasia. The paperclip is placed on the patient to indicate the fluoroscopic view of the endoscopically located LES. Following a fluoroscopically guided placement of the balloon catheter with the paperclip approximately in the middle, a controlled dilatation can be done. Initially during dilatation a waist-like impression of the hypertrophic LES is noted. Image: *Jan Johansson*

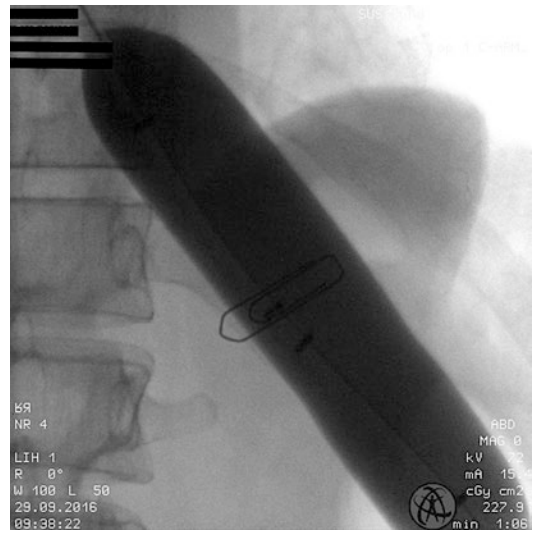

Fig. 24 After a complete dilatation the waist-like impression of the balloon has disappeared. Image: *Jan Johansson*

11.5.3 Per-Oral Endoscopic Myotomy

Per-oral endoscopic myotomy (POEM) is a recently developed endoscopic technique for treatment of achalasia (Fig. 25). The operation is

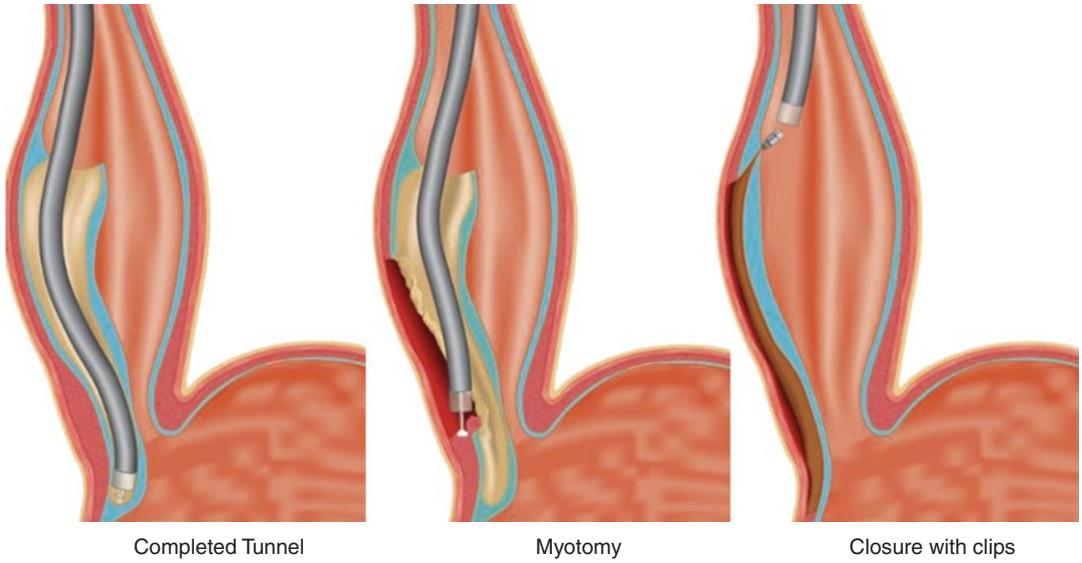

Fig. 25 Per-oral endoscopic myotomy (POEM) for achalasia. Image: http://www.achalasia.ca/poem.html

labour intensive, and performed in general anaesthesia. After an endoscopic mucosal incision in the middle of the oesophagus the endoscopist creates a submucosal tunnel to reach the LES to cut the muscle fibres. High success rates are seen even after several previous pneumatic dilatations, but long-term results are lacking (Boeckxstaens et al. 2014; Awaiz et al. 2017). Because no anti-reflux procedure is included in this technique, the risk of gastro-oesophageal reflux is substantial and might represent an important drawback.

11.5.4 Heller Myotomy

A Heller myotomy (Fig. 26) is a muscular incision of the longitudinal and circumferential muscular layers of the LES, leaving an intact mucosa as the only remaining part of the oesophageal wall. The procedure is nowadays usually done with laparoscopy. Sometimes a hypertrophic LES can be identified during surgery, but not always. Therefore, especially in the absence of a hypertrophic LES as landmark to operate on, the extent of the myotomy has been discussed. In order to prevent dysphagia from recurring, and to facilitate oesophageal emptying, most surgeons extend the myotomy a couple of centimetres up

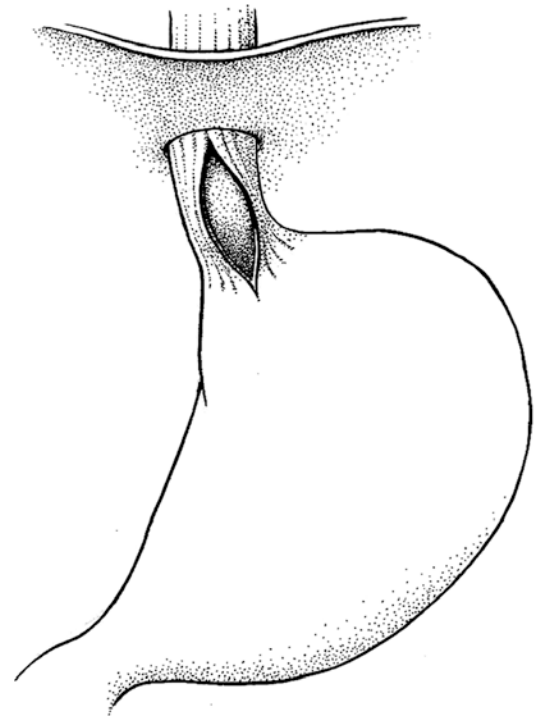

Fig. 26. Heller myotomy. The muscle wall of the oesophagus is surgically divided, and the mucosa is left intact. A fundoplication can be added to prevent reflux (not shown). Image: *Jan Johansson*

to the distal oesophagus and down to the upper stomach. A drawback of the myotomy is that it induces severe reflux, which is why the myotomy usually is combined with a fundoplication to restore the competence of the LES, but without creating a new outflow obstruction in the distal oesophagus.

11.5.5 Treatment Strategies

Nearly 90% of patients with achalasia can return to near-normal swallowing and good quality of life with present treatments (Vela et al. 2004). Success rates are significantly higher for type II achalasia (96%) than for type I (56%) and type III (29%) achalasia. Type III disease might be best treated by laparoscopic myotomy (Rohof et al. 2013). At present, pneumatic dilatation and Heller myotomy combined with an anti-reflux procedure are the treatments of choice and have comparable success rates (Boeckxstaens et al. 2014) (Fig. 27). The strategy of treating achalasia starting with pneumonic dilatations appears to be the most economic approach (Moonen et al. 2017).

During the years some patients undergo escalating therapies with less invasive procedures first and invasive laparoscopic surgery at a later stage. This should be regarded as a consequence of a tailored therapy focused on the patient's actual swallowing problems and not as failed therapy.

12 Failed Open or Minimally Invasive Surgery

Some patients are dissatisfied with the results of their previous open or laparoscopic surgery for benign disease. Symptoms vary but dysphagia is usually present. Other prominent symptoms may be weight loss, vomiting, pain, reflux and inability to swallow. Irrespective of previous surgery for GORD, achalasia, bariatric surgery and failed reconstructions after malignant surgery, a majority have complaints related to outflow obstruction with or without poor peristalsis. Patients without any objective manifestations of these symptoms seldom improve after revision surgery. Sometimes the patient is misunderstood or has an overconfidence in surgery. Before any new discussion of revisional surgery takes place, an updated set of evaluations are mandatory to pinpoint the actual problem. The surgeon must inform the patient of the limits of revisional surgical therapy, and the fact that second- or third-time surgery seldom completely resolves the patient's problem.

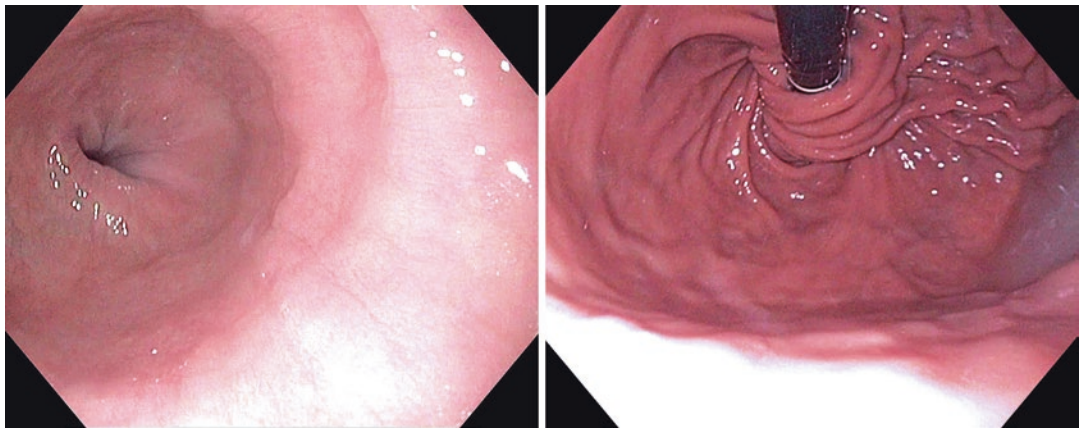

Fig. 27 Endoscopic view of the distal oesophagus following a successful Heller myotomy with a 360° fundoplication. The patient has no dysphagia and the distal oesophagus has a normal appearance without retained fluid or food, and is without dilatation. This is confirmed by the placement of the oesophageal lumen in the middle of the oesophagus, and not lateral as in a dilated distal oesophagus. The anti-reflux wrap protects from reflux secondary to the myotomy. Image: *Jan Johansson*

12.1 Outflow Obstruction

Outflow obstruction is usually diagnosed at the site of a failed anti-reflux procedure, myotomy, or at the site for an oesophagointestinal anastomosis. Irrespective of this, the patient is usually on radiographs diagnosed with a diverticula or a pouch cranial to the obstruction as a manifestation of increased pressure secondary to indigested food and beverages. The endoscopist's view of this phenomenon is usually a fluid and sometimes food-containing oesophagus where the oesophagus seems to end blindly in a sac-like formation. After withdrawing the instrument a couple of centimetres from the end of the sac the continuity of the oesophagus appears (Fig. 28). If in achalasia dysphagia recurs within months after previous surgery, a dilatation or later a re-myotomy may be needed. In case an anti-reflux procedure was added to the myotomy, fibrosis around the LES may be the cause of dysphagia, and a take-down of the anti-reflux procedure together with a new myotomy may be indicated.

12.2 Poor Peristalsis

Achalasia patients who have undergone surgery of the LES are usually relived of their outflow obstruction, but not of their poor oesophageal peristalsis. A relatively moderate outflow obstruction may in some patients with extremely poor peristalsis result in dysphagia, which is why it is important to select a partial anti-reflux procedure in case revisional surgery is considered. If end-stage achalasia is diagnosed, oesophagectomy may resolve the patient's problem with regurgitations and aspirations and other side effects secondary to oesophageal retention. In older or frail patients a feeding gastrostomy or jejunostomy may temporarily or permanently solve at least the nutritional aspects of the patient's problem.

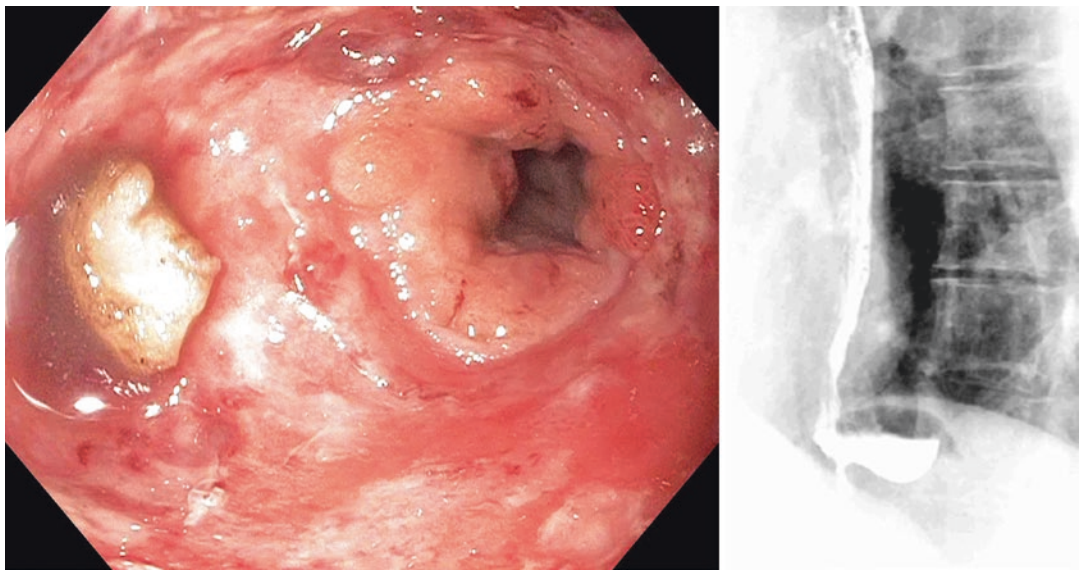

Fig. 28 Endoscopic and radiological view of a patient operated on twice with Heller myotomy and a partial fundoplication. The patient has eating problems and dysphagia with a combined partial outflow obstruction at the level of the gastro-oesophageal junction and poor oesophageal peristalsis. Both images show a diverticulum-like pouch in the distal oesophagus at the site of the myotomy with some retained fluid and food on the endoscopy image. The radiograph with the patient in an upright position shows gas in a widened oesophagus and a contrast level distally in the pouch-like ending of the oesophagus. The oesophageal opening has been lateralised, and is not, as expected, in the centre of the images. The endoscopy shows no short distal stricture, but rather a delayed emptying over the segment of the distal oesophagus where the myotomy and the wrap are placed and together with scar tissue cause the outflow obstruction. The radiograph shows poor peristalsis with some contrast passing slowly to the stomach. Image: *Jan Johansson*

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The Postoperative Pharynx and Larynx

Anita Wuttge-Hannig and Christian Hannig†

Contents

Abstract

Dysphagia is often seen in patients following surgery to the pharynx and larynx. It may be due to altered anatomy, altered physiology, or altered function. Dysfunction may be due to sensory disturbances or altered biomechanics due to resection of muscles or repositioning of muscles. Radiotherapy with or without chemotherapy often contributes substantially to dysfunction. Mucosal abnormalities are best evaluated during endoscopy while extraluminal abnormalities including tumor recurrence are evaluated with MR or CT.

1 Introduction

Considerable progress has been made in the past few years in the diagnosis and treatment of swallowing disorders of neurological, anatomic, or vascular origin. The treatment has been expanded to include patients with cancer and others with a rather limited time prognosis (Cantarella 1998; Denk et al. 1997; Groher 1992; Hannig and Wuttge-Hannig 1987, 1999; Hannig et al. 1989; Wuttge-Hannig and Hannig 1999; Lazarus et al. 2000; Leonard et al. 2001; Logemann et al. 1994).

This chapter deals with patients who have undergone ear, nose, and throat (ENT) surgery, minor or extensive and/or radio-, chemo-, and the more recent use of radioimmunotherapy and gamma-knife therapy, etc., including the sequelae of therapy (Eisbruch et al. 2002; Furia et al. 2000).

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The development in recent years of newer diagnostic and therapeutic modalities, including combined surgical and chemotherapeutic and radiotherapeutic schemes resulting in cure or remission even in advanced tumor stages, prompted the urgency to be aware and recognize swallowing complications before sequelae such as aspiration pneumonia become apparent (Hannig et al. 1995a, 1991; Jung and Adams 1980; Walther et al. 1990).

The differentiation between anatomical causes and functional origins related to sensory disturbances which often occur a year or two following the original treatment requires precise analysis in order to initiate appropriate therapy (Hannig and Wuttge-Hannig 1999; Wuttge-Hannig and Hannig 1995). It is also important to exclude submucosal spread of tumor, which may escape endoscopic detection (Wuttge-Hannig et al. 2001). Late consequences of subcutaneous and muscular fibrosis may occur resulting in the restriction of the anterosuperior movement of the larynx during swallowing (Hannig 1995).

1.1 Altered Anatomy

Dysphagia is often the result of the altered anatomy following surgery such as laryngectomy, whereby separation of the larynx from the anterior pharyngeal wall produces a so-called pharyngeal tube seen especially in wider resections of pharyngeal structures. The configuration and diameter of the pharyngeal tube can vary with different surgical and sewing methods producing wide morphological variations in the radiological appearance (Hannig et al. 1994, 1996; Hannig 1995; Jung and Adams 1980; Martin et al. 1993) (Fig. 1).

The medical literature reports 15–20% of dysphagia in partial and total laryngectomized patients (Di Santis et al. 1983; Hannig 1995). In our own series of 312 patients treated for laryngeal cancer, 37% complained of dysphagia and 19% of an annoying globus sensation. The higher incidence in our patients is probably due to stricter preselection of our interdisciplinary group, a heightened awareness, as well as better patient education and compliance.

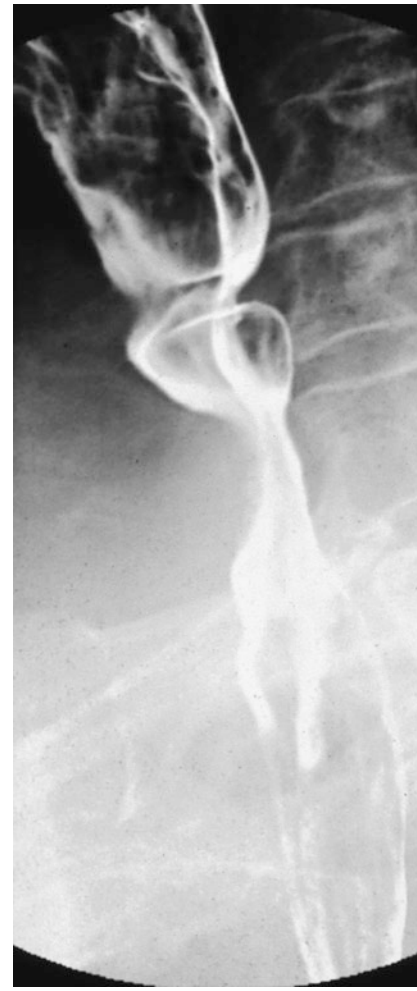

Fig. 1 Normal postsurgical anatomy of the pharyngeal tube after total laryngectomy. The pseudoglottis is seen as a circular narrowing

Post-therapeutic dysphagia following laryngectomy may be caused by the following pathology:

- Tumor recurrence (Fig. 2)
- Scarring and benign stenosis (Fig. 3)
- Functional disorder of the "pharyngeal tube" and the pharyngoesophageal transit zone (pseudoglottis) (Fig. 4)

Functional disorders are difficult to diagnose with video endoscopy or conventional radiological procedures but require observation of the dynamics of swallowing and analysis of the altered motility

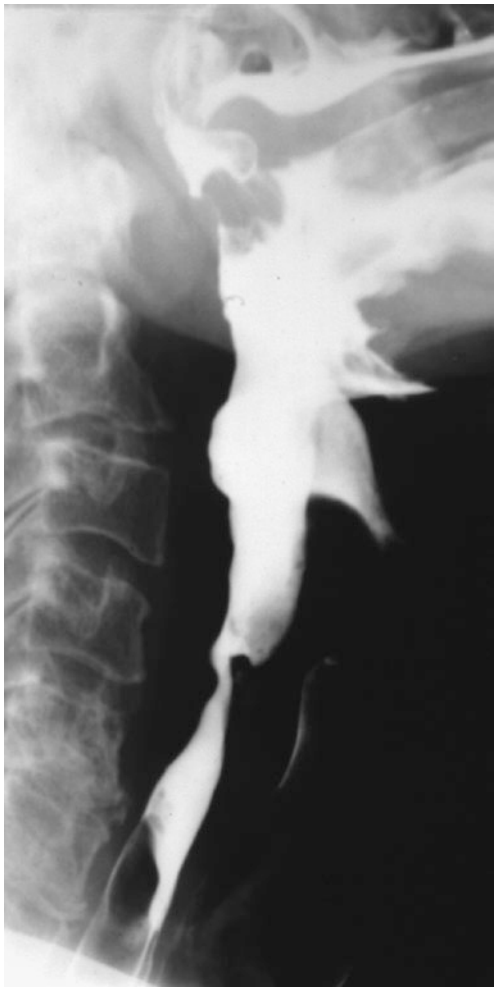

Fig. 2 Laryngectomy. Tumor recurrence with stenosis of the pharyngeal tube

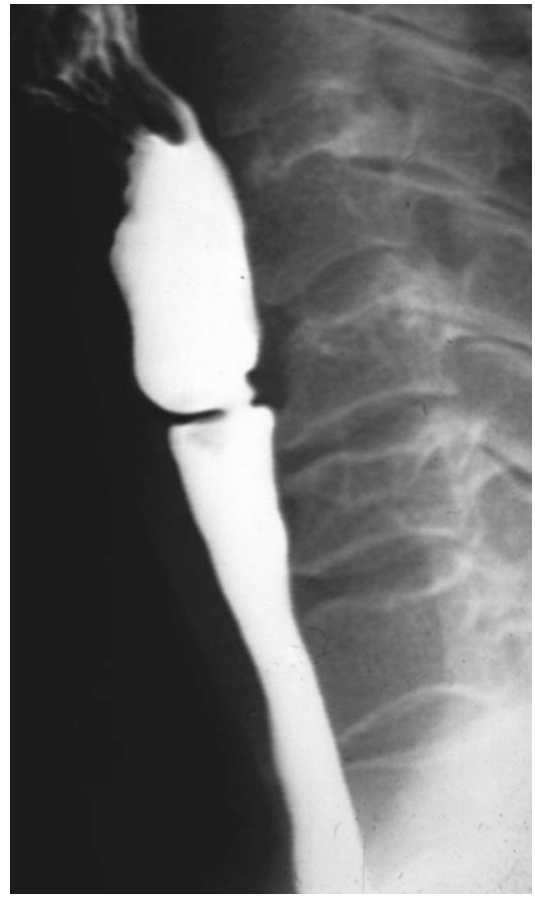

Fig. 3 Web due to scarring after radiation therapy

of the postsurgical laryngopharynx. This is the only way to differentiate among functional changes due to tumor recurrence or scarring.

1.2 Adapted Physiology of Swallowing

During the pharyngeal phase of swallowing, the force of the dorsal and lateral wave, the counterbalance of the larynx, and the tongue base combined with the occlusion of the soft palate maintain the pressure needed to compress and move the bolus of food. The anatomic loss of soft tissue material causes important disturbances in the propulsion of the bolus (Dodds et al. 1975; Gates 1980; Gay et al. 1984; Hannig 1995). Surgical resection of part of the tongue base or floor of the mouth is a frequent cause of poor bolus preparation and compression in the oral cavity, thus hindering the trigger for an adequate swallowing reflex. The normal swallowing reflex is effected by an "input summation" needed to reach a critical limit (Kennedy and Kent 1988). This limit is rarely reached in patients treated for an oral cavity carcinoma, therefore delaying the trigger in the secondary (valleculae) or tertiary area (piriform sinuses) or even quaternary area (laryngeal vestibule). Mucositis and mucosal atrophy due to radiation treatment can also cause trigger delay or absence. The restoration of the mucosal tissue integrity in the pharynx may

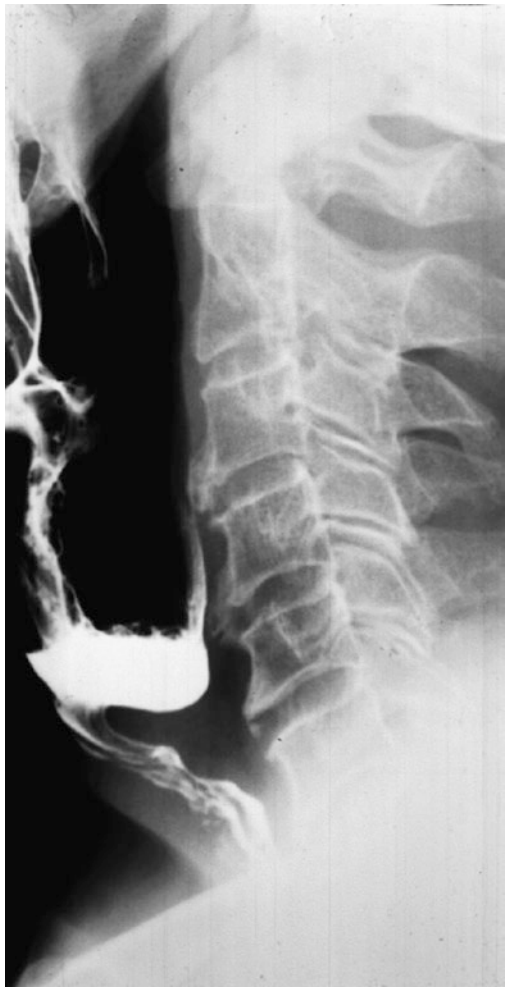

Fig. 4 Laryngectomy. Hypertrophic pseudoglottis with obstruction of the bolus transport

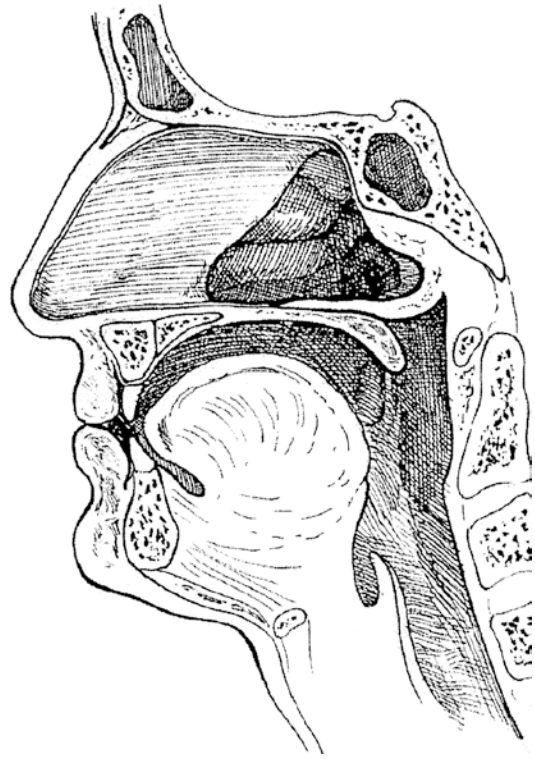

Fig. 5 Adult pharynx

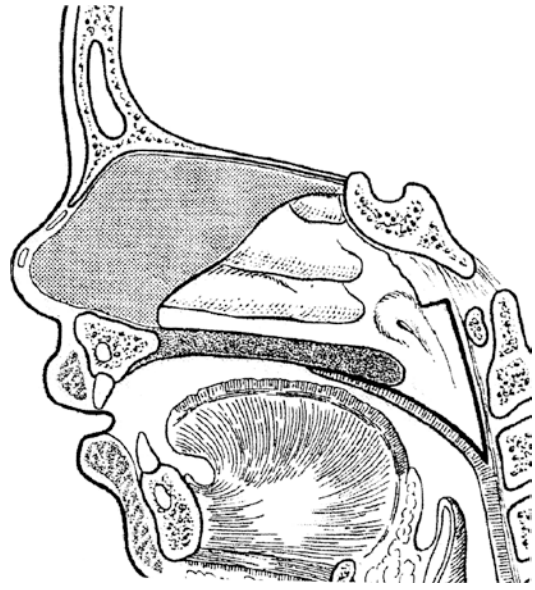

Fig. 6 Infantile pharynx with short distance between the base of the tongue and the laryngeal vestibule

restore the normal trigger but is frequently incomplete because of the rather permanent xerostomia. It may take 2–3 years of post-radiological treatment for restoration of the integrity of the mucosa. After combined radio-chemo treatment it may never be restored. In the latter patients, lesions in the trigger system occur in the receptors rather than the afferent limb of the loop (Fig. 5).

Children with a cleft palate present a special group of patients (Bosma et al. 1966; Isberg 1990; Ren et al. 1993; Rubesin et al. 1987) (Fig. 6). The maturation of the swallowing reflex,

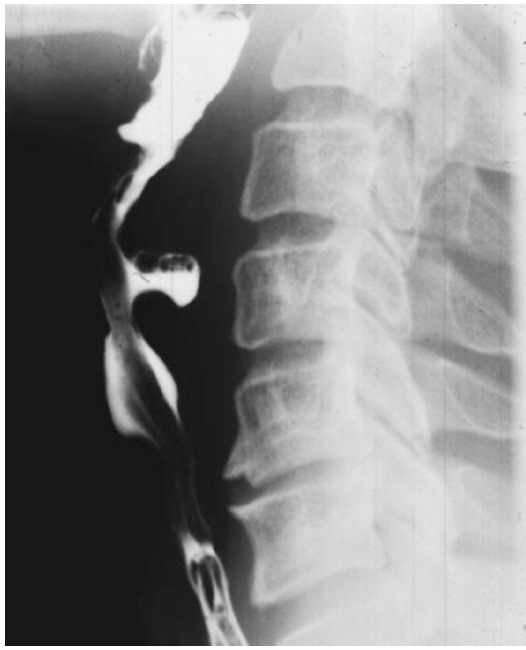

Fig. 7 Laryngectomy. Motor disturbance of the dorsal pharyngeal wall with diverticulum between the middle and inferior constrictors

which in nursing children occurs in the secondary area (the valleculae), cannot be brought up in time to the first area as is the case in adults, namely the arch of the fauces and dorsal pharyngeal wall, because the pressure generation in the oropharynx is inadequate. The lack of counterbalance of the soft palate during swallowing may cause a compensatory downward movement by the tongue base in order to propagate the bolus into the pharynx.

A unilateral incision of the pharynx causes likewise lack of propagation and transport of the bolus retaining part of the bolus in the ipsilateral vallecula and piriform sinus. The most serious motility change occurs as a result of resection of the larynx and the resulting motility changes of the "neopharynx" referred to as the "pharyngeal tube" (Fig. 7). In such patients, even a hypertonic dorsal wave is incapable of producing a competent peristaltic wave. The pharyngeal pressure generation is not sufficient to passively open the upper esophageal sphincter (UES). We demonstrated that in patients with a hypotonic wave and a normal UES at least 40 mmHg manometric pressure is needed for the passive opening of the dissected pharyngoesophageal segment.

1.3 Adaptation Methodology

In our swallowing-impaired patients we use an iso-osmolar iodine solution (Isovist®-Iotrolan) which causes no lung damage in case of aspiration (the hyperosmolar preparations may cause pulmonary edema) (Hannig et al. 1994; Hannig 1995). The contrast medium is mixed with the type of food that causes the swallowing difficulty. This can be solid, semisolid, crumbly, or liquid.

In patients after surgery for a cleft palate or following partial or complete laryngectomy we also have the patient perform different sounds and vocals, such as "coca-cola," "in the garden grows an apple tree," and "kakadu." The elasticity of the pharynx and larynx is tested by the use of Valsalva (Fig. 8) and Mueller maneuvers producing a maximal distension or collapse of the pharynx. This allows us to check for an occult neoplastic process of scarring.

1.4 Morphological and Functional Swallowing Abnormalities

A wide variety of morphological and functional swallowing abnormalities can be seen following ENT neoplasm surgery. The causes vary with the different types of surgery. Oral, pharyngeal, laryngeal, and thyroid neoplasms are treated with a variety of procedures ranging from laser excision, wide resection, horizontal and transverse pharyngeal resection, partial or total laryngectomy, or thyroidectomy, including combinations of therapy with or without hyperthermia present with different forms of dysphagia. Post-therapeutic changes related to vascular surgery of the neck and combinations of chemo- and radiation treatment may also result in dysphagia.

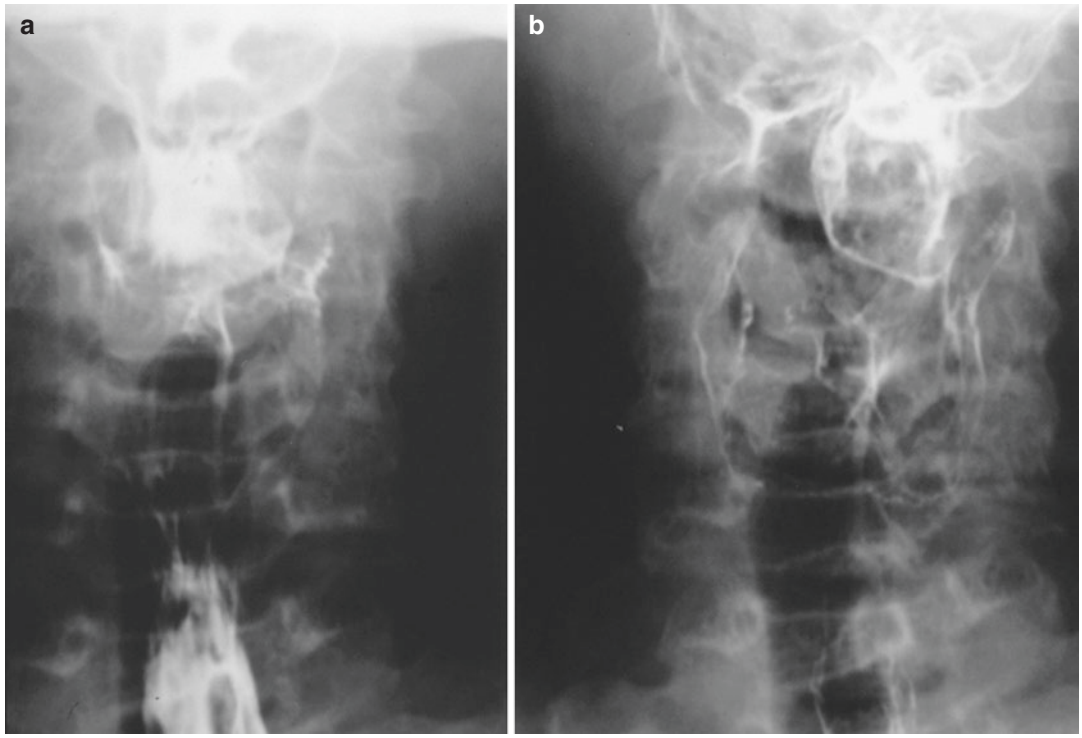

Fig. 8 (**a**, **b**) Oro-hypopharyngeal neoplasm of the posterior wall best demonstrated by Valsalva maneuver

1.5 Laryngectomy

The incidence of dysphagia and globus pharyngis following total laryngectomy is around 50% and rises with additional radiotherapy. Radiotherapy alone causes less of the latter but causes more frequently loss of sensation resulting in "trigger" delay. The displacement of the larynx results in loss of compression of the anterior pharyngeal wall, resulting in a hyper-competent dorsal wave of the reformed pharyngeal tube. Lateral compression during peristalsis is also deficient. The propulsion force is accomplished by the rotation of the tongue base which can result in hyper-excursion compensating for the dorsal pharyngeal wall (Hannig et al. 1994; Jung and Adams 1980; Mills 1973; Pauloski et al. 2002). A too large resection of the tongue base may cause severe dysphagia. A deficient opening of the reconstructed pharyngeal wall and the sphincter sleeve results in dysphagia. Hypotonicity of the pharyngeal tube may prevent the passive opening of the reconstructed sphincter. A hyperactive sphincter could also be responsible for solid-state dysphagia. Since voice prosthesis users form sounds with the reconstructed sphincter sling, a perfect voice quality correlates frequently with the degree of dysphagia. Our own patients favored sacrificing the discomfort for a better voice quality (Hannig et al. 1993a, 1994).

Another cause of dysphagia is displacement of a voice prosthesis, particularly a too high implanted or a too steeply inclined prosthesis, causing food impaction and both solid and liquid dysphagia. Table 1 lists the changes in the area of the UES and pharynx in relation to the associated clinical symptoms. In one-third of patients the dysphagia could be related to functional disorders. Post-radiation and post-therapeutic scar stenosis or membranous stenosis is quite frequent but a recurrence is rare. In two-thirds of our patients with dysphagia, dysfunction of the

Table 1 Dysphagia present in laryngectomies

	Causing dysphagia (%)	Not causing dysphagia (%)
Delayed opening of the UES	51	49
Premature closure of the UES	65	35
Incomplete opening of UES	70	30
Hypopharyngeal diverticula	52	48
Web	54	46
Reduced contractility/ scarring of the pharyngeal tube	80	20
Tumor recurrence	31	69

n = 246, male: female = 77%: 23%, median age 61.5 aa

Table 2 Dysphagia present in laryngectomy alterations in pharyngeal timing in relation to dysphagia

	Causing dysphagia	Not causing dysphagia	Normal value
Dysphagia	Dysphagia	Value	
Time of pharyngeal peristalsis	1047 ms	763 ms	617 ms
Time of pharyngeal passage	868 ms	721 ms	615 ms
Depth of constriction wave (quotient)	0.60	0.69	0.47

n = 246, male: female = 77%: 23%, median age 61.5 aa

motility of the pharynx or the UES could be identified. In asymptomatic patients slight dysmotility of the UES is still seen but is much less than in the symptomatic patients. The obstruction during a delayed opening of the UES was less than 20% in those patients. UES function was assessed using planimetry and frame-by-frame analysis. The median delay caused by the dysmotility of the UES was 47.5 ms, considerably longer than the 24.5 ms in the asymptomatic patients. Two-thirds of our symptomatic patients had dysphagia and one-third only globus sensation. We were interested to see that there was a correlation between the extent of swallowing symptoms and the hypercontraction of the neopharynx. Table 2 shows the median values of time of peristalsis, the time of pharyngeal passage, and the constrictor ratio (maximal protrusion of the dorsal pharyngeal wave in relation to the sagittal diameter of the C3 vertebral body). The median obstruction of the area of the pharyngoesophageal segment due to a dysfunction of the sphincter was 35% in the symptomatic group. It is remarkable how the time of peristalsis and time of pharyngeal passage were absolutely abnormal in the dysphagic patients. In Table 2, the motility disorders of the pharyngeal tube and the UES are presented in relation to the time measurements. As expected, due to the altered anatomy after laryngectomy, the constriction ratio was quite high in both the symptomatic and asymptomatic patients. Due to the loss of the laryngeal counterpressure, the dorsal peristaltic wave gets unusually prominent. In addition to the dysfunction of the neoglottis (formed by the UES) we see a second constricted area in the cervical esophagus just below the UES. This "second sphincter" showed a functional pattern comparable to the UES. The exact pathomechanism of this second hypercontractile zone is yet unknown. It might be the effect of regulation of the airflow during the esophageal voice production.

In a large number of patients with a delayed emptying of the pharynx due to insufficient peristalsis we were able to observe a marked compensation by the tongue-base, a virtual "tongue pump" (Hannig 1995).

This tongue pump consists of an accentuated caudo-dorsal movement of the floor of the mouth together with the tongue base moving the bolus through the pharynx and the UES. In some patients, an additional hyper excursion of the Passavant cushion and the region of the superior constrictor pharyngis was noted (a temporary long contact of the dorsal pharyngeal wall and tongue base). Quite often, scarring resulted in reduced contractility of the reconstructed pharynx or of a narrow pharyngeal canal. In Fig. 9 the scar was caused by radiotherapy. In other patients, it could be the result of chronic inflammation or a poor healing of a postoperative fistula.

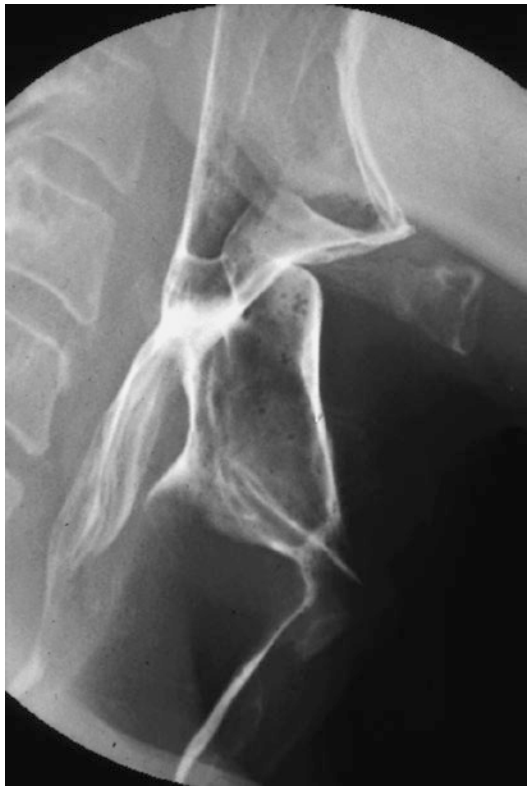

Fig. 9 Supraglottic pharyngolaryngeal resection

1.6 Hemi-Pharyngectomy

There are two main types of partial pharyngeal resections. The horizontal resection (Fig. 9) is uncommon today, due to long-term complications from the interruption of the constrictor muscles resulting in deficient bolus propulsion. The more common longitudinal resection includes resection of the unilateral vallecula and piriform sinus and reconstruction of the pharyngeal tube by means of suturing the dorsal and anterior pharyngeal wall, often in combination with a myocutaneous flap. This reconstructed pharyngeal structure does not participate in the normal constriction due to relative weakness of the muscles. The bolus often remains on the resected side and can be cleared out of the pharynx only through the healthy hemi-pharynx (Hannig and Wuttge-Hannig 1999; Hannig 1995).

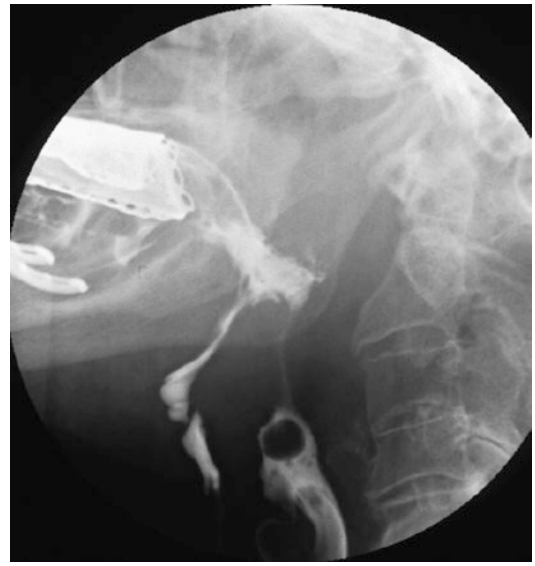

Fig. 10 Fistulation to the residual tongue base after partial tongue resection and radio-chemotherapy

1.7 Post-therapeutic Pharyngeal Cancer

In cancers of the oral cavity, the floor of the mouth, tongue, tonsils, pharynx, and UES, the morphological and functional changes correspond to the type and extent of therapy (Hannig and Wuttge-Hannig 1999; Rosen et al. 2001; Zuydam et al. 2000). This may include simple resection, and additional radio- or combined radio-chemotherapy. Less frequent forms of therapy such as combinations with hyperthermia are rare and will not be considered in our comparative studies (Fig. 10).

Table 3 summarizes the functional disorders. Combined radiation and chemotherapy and surgery alone present similar problems, whereas radiation therapy alone presents the least. The most severe problems occur when surgery is followed by radiotherapy whereby in addition to the trigger problem related to the surgery additional fibrosis related to the radiotherapy occurs. Differences in the severity and type of aspiration related to the different treatment modalities are illustrated in Table 4. Aspiration turns out to be most fre-

Table 3 Functional alterations due to ENT cancer therapy

	Surg *n* = 37 (%)	Rth *n* = 47 (%)	Surg + Rth *n* = 92 (%)	Rth + Chemo *n* = 145 (%)
Bolus formation	46	11	87	25
Premature leaking out of the oral cavity	85	37	77	44
Delayed trigger of the swallowing reflex	49	78	88	81
Penetration in the laryngeal vestibule	40	19	76	72
Aspiration	75	71	79	75
Reduced coughing reflex	–	6	32	8
Laryngeal antero-cranial movement	24	22	73	43
Dysfunction of the UES	65	9	86	56

n = 321, male: female = 67:33, mean age = 55.7 aa

Table 4 Type and severity of aspiration due to ENT cancer therapy

	Surg 27/32 82%	Rth 36/45 80%	Surg + Rth 78/92 79%	Rth + Chemo 112/145 77%
Predeglutitive	16	24	36	47
Grade I	4	9	10	21
Grade II	4	6	9	9
Grade III	6	5	9	9
Grade IV	2	4	8	8
Intradeglutitive	3	0	13	21
Grade I	–	–	2	3
Grade II	2	–	4	7
Grade III	1	–	3	9
Grade IV	–	–	4	2
Postdeglutitive	8	12	29	44
Grade I	2	3	12	15
Grade II	2	2	9	13
Grade III	4	5	5	10
Grade IV	–	2	3	6
Combined forms	15	7	51	49

n = 321, male: female = 67:33, mean age = 55.7 aa

quent in radiotherapy in combination with chemotherapy in which the negative effects of receptor destruction, hypo-stimulation, and mucosal damage are added to the radiation and chemotherapy combination. Nevertheless, surgery alone causes the highest incidence of aspiration followed by radiotherapy alone and surgery plus radiotherapy. The high number of aspiration complications related to radiotherapy alone could be due to the fact that it usually involves older patients who could not tolerate a combined protocol. Table 5 lists the morphological alterations relative to the therapeutic protocol. As expected radiotherapy alone, surgery alone, and radio-chemotherapy cause less problems.

Table 5 Morphologic alterations due to ENT cancer therapy

	Surg *n* = 20 (%)	Rth *n* = 47 (%)	Surg + Rth *n* = 92 (%)	Rth + Chemo *n* = 145 (%)
Fibrosis of the subepidermal tissue	11	62	72	48
Fibrosis of muscles	–	52	82	58
Adhesions skin-larynx	15	49	74	48
Adhesions larynx-prevertebral fascia	–	48	72	27
Stenosis by scarring	12	42	66	53
Oral defects	78	–	58	18
Pharyngeal defects	29	11	61	7
Laryngeal defects	32	–	48	–
Recurrence	–	07	11	21

n = 321, male: female = 67:33, mean age = 55.7 aa

1.8 Cleft Palate

A palatal cleft causes social stigma due to the external aesthetic image, the palato-rhinolalia, and the nasal penetration of the bolus during swallowing (Engelke et al. 1991; Engelke 1994; Hannig et al. 1993b). The anatomical shortening and the functional restriction of the soft palate include the post-therapeutic scar after closure of the defect. The above can lead to a velopharyngeal insufficiency.

An analysis of the velopharyngeal closing mechanism should be done before and after surgery (Thumfarth et al. 1996; Bergeron et al. 1984; Croft et al. 1981; Dalston et al. 1985; Engelke et al. 1991; Engelke 1994; Hannig and Wuttge-Hannig 1992; Hannig et al. 1993b, 1995b; Hartmann et al. 1972; Hess et al. 1994, 1995, 1996a, b; Herzog et al. 1993). The early use of surgical occlusion and/or prosthesis may help achieve proper maturation from the infantile to the adult swallowing reflex pattern. The nursing infant adapts safely to the anatomical changes. The first segment of the nearly horizontal aditus laryngis, which remains very narrow to the base of the tongue, together with the large valleculae and the long soft palate, permits a two-chamber separation of the pharynx. The infant is, thus, able to fill up the valleculae with usually three suctions during breathing. Only after three stimulations of the tongue base can the swallowing reflex, located very deep in the pharynx, be triggered. Mastication assists in the development of the orally directed swallowing reflex. Tactile stimulations are also helpful in this process. According to Croft et al. (1981), four types of velopharyngeal occlusion mechanisms can be identified: sagittal, coronal, circular, and circular with a Passavant cushion (Fig. 11).

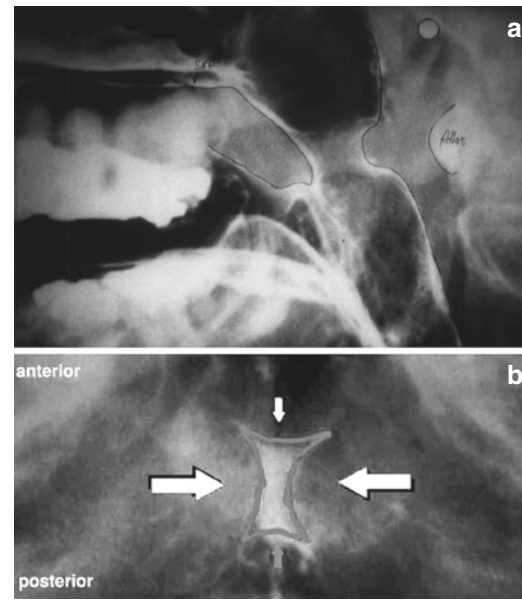

Fig. 11 Cleft. (**a**) Insufficient nasopharyngeal closure with attempt of a Passavant compensation. (**b**) Circular compensation with major action of the lateral pharyngeal constrictors in hemiaxial projection

The commonly used tools are lateral radiography of the cranium, a pantogram of the dental arcade, videofluoroscopy, and the 16-slice helical CT already separated in spatial but not temporal resolution in the electron beam tomogram. In the future, MRI will be the imaging modality of choice especially in infants and young adults in whom the radiation dose is critical and where many radiograms in different planes have to be used. A very accurate appreciation of the velum motility and the swallowing competence allows one to decide which therapeutic approach would be most favorable: simple augmentation of the dorsal wall (Hynes) or the more complicated velopharyngoplasty (Sanvenero-Roselli) (Horch et al. 1993; Sader et al. 1994, 1995, 1997, 2001; Skolnick 1989). Post-therapeutic evaluation of the velum performance assists in the decision whether a reoperation or a conservative program is to be pursued.

2 Posttraumatic, Post-lesional, and Postsurgical Brain Lesions

A large spectrum of damage to the CNS and peripheral nervous system can result in dysphagia (Hannig 1995; Wuttge-Hannig and Hannig 1995). In neurologically impaired patients, conservative rehabilitative methods are the procedures of choice. Surgery might cause further damage to the trigger area. The Munich rehabilitative strategy is generally adopted for such patients. Therapy is planned based on dynamic swallowing analysis. A division and grading analysis into pre-, intra-, and post-deglutitive aspiration and its severity is done. The accurate study of the multiple pathomechanisms allows us to design a program individually tailored for each patient, which gives the best results and is most cost effective (Hannig et al. 1995a; Hannig and Wuttge-Hannig 1999).

A unilateral functional defect or hypotonicity suggests a unilateral cerebral event, whereas a bilateral defect suggests a neuromuscular disorder (Wuttge-Hannig and Hannig 1995). Dilatation of the hypopharynx is common in trumpet players and singers and is bilateral. The study can identify neurogenic, myogenic, and reflux-induced disorders. The reflux episodes could be due to the tenth cranial nerve. The differentiation is important since in myogenic dysfunction simple drug use might solve the problem, which is not the case in vagal dysfunction where not only the UES but also the esophageal clearing function is compromised. A myotomy of the UES should only be performed in rare cases. Esophagopharyngeal and tracheal aspiration would result from a surgical dilatation of the PE segment. The passive opening of the UES can be influenced by the Mendelsohn maneuver, but if there is a spasm of the UES conservative therapy is rarely adequate. Further reconstructive surgery should be undertaken only after a long-term rehabilitative trial. In the latter patient, the separation of the alimentary and respiratory canal should only be a last choice. If the patient possesses good cognitive capacity the use of alternative positional maneuvers could be used. This is especially important in the planning of a laryngo-hyoidomentopexy procedure planned via dynamic imaging. This surgical technique necessitates deglutition in the upright position (Hannig 1995). In 1996 Mahieu described a similar method as “laryngeal suspension,” which was performed in a large number of aspirating patients but which excluded the tracheal stabilization (Fig. 12). ENT and neurologists use botulism toxin injections. Newer applications of the latter may cure esophageal motility disorders causing dysphagia. Within Thumfart’s

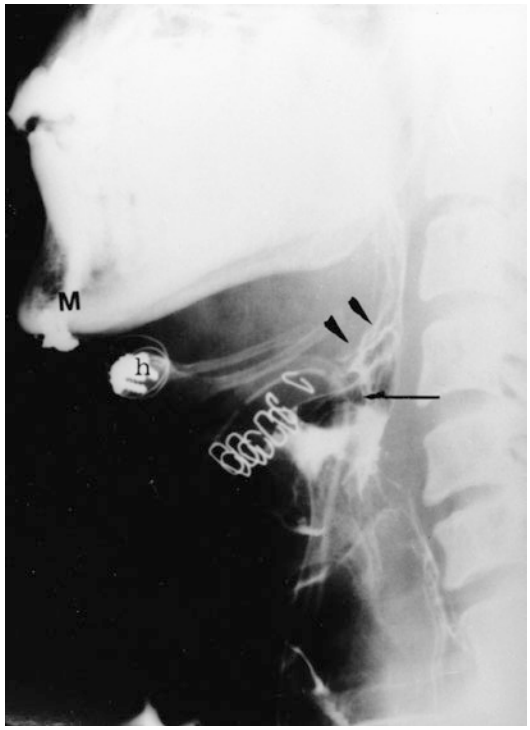

Fig. 12 Laryngo-hyoido-mentopexy in a patient with an intradeglutitive aspiration due to a resection of an ependymoma of the IVth ventricle

group in Innsbruck and at the ENT departments in Turin and Milan Botox injections are frequently used (Cantarella 1998; Pastore et al. 1997; Thumfarth et al. 1996).

3 Scarring and Postsurgical Instabilities of the Pharynx

Dysphagia is quite frequent as a result of muscular dissection in vascular (Fig. 13) and orthopedic surgery of the cervical spine area (Hannig and Wuttge-Hannig 1999; Hannig 1995). In surgical unilateral procedures, an outpouching of the weaker hemi-pharynx may occur due to a less effective lateral constrictor wave. The therapeutic approach in such cases depends on the extent of weakness of the unilateral pharynx. If there is a relatively weak pharyngeal wall the bolus will end up in this weak hemi-pharynx and will not be cleared out of it. If there is a scar or hypertonicity of the surgical side, the contralateral side will transport the bolus well. A trial of the best maneuver by means of dynamic imaging will yield the best results. The raising or inclination of the head may result in a different preload to the external laryngeal musculature. The swallowing disorder may get even more complex by adhesions of the skin of the neck to the larynx frequently after surgery for thyroid tumors (Fig. 14).

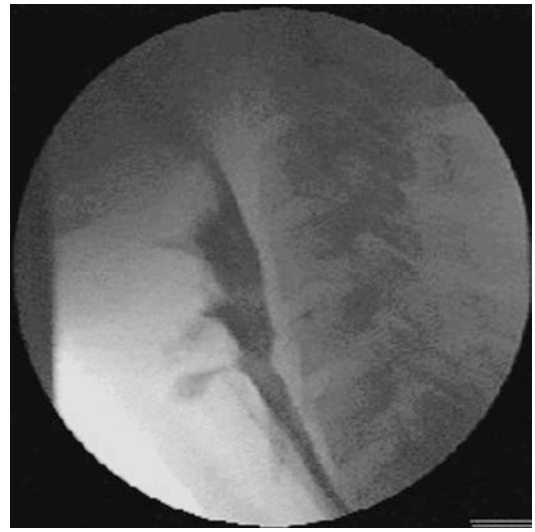

Fig. 13 Patient after surgery and radiotherapy for a thyroid cancer 25 years previously. Fistulation below the level of the arytenoid cartilages

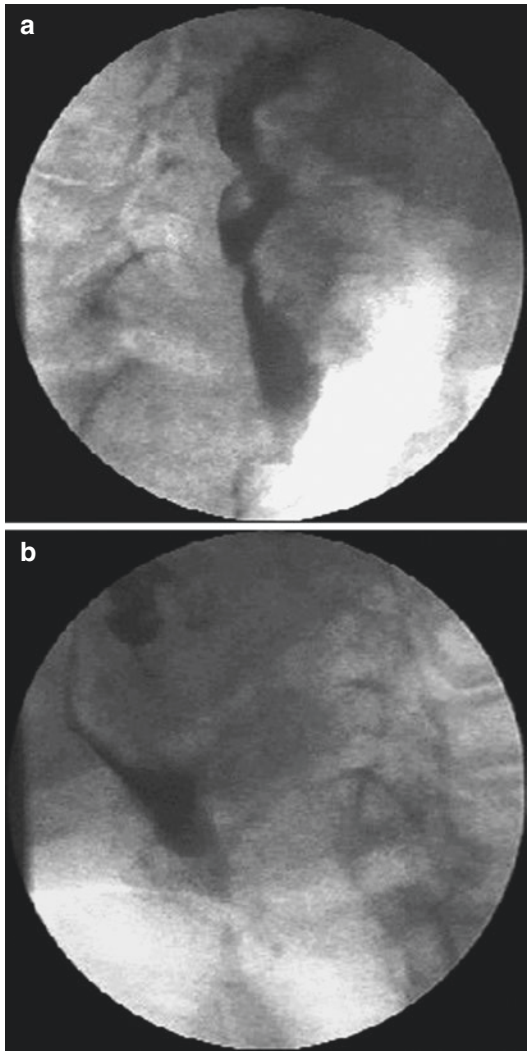

Fig. 14 Patient with dysphagia due to a patch insertion in the right carotid artery. (**a**) By turning the head to the left side the bolus passage is obstructed. (**b**) By turning the head to the right side a good clearance of the pharynx can be achieved

Conclusion

Dynamic imaging in swallowing disorders defines the pathophysiology of the disorder and determines the method of rehabilitation of the post-therapeutically impaired deglutition. Myo- or neurogenic disorders can be identified. The oral and pharyngoesophageal interaction can be studied. The advantage of this method of study lies in its ability to produce the high spatial and temporal resolution of the very fast motility between the oral cavity and entrance into the esophagus. This procedure may also provide hints as to the localization of the neurological focus, although the nature of the underlying disease is rarely identified by this technique alone. The studies permit individual tailoring of rehabilitation and the most cost-effective method.

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Dysphagia Evaluation and Treatment After Head and Neck Surgery and/or Chemoradiotherapy of Head and Neck Malignancy

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Contents

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Abstract

Tumors of the head and neck represent 3.2% of newly diagnosed cancer; both surgery and chemoradiotherapy are valid treatment options for head and neck cancer. In many head and neck cancer patients dysphagia, malnutrition, and aspiration pneumonia are found and significantly impact the quality of life. Dysphagia is related to the tumor itself or its treatment consequences.

A large number of surgical procedures according to tumor site and extension, patient age, and general conditions have been developed and are reviewed in this chapter. Swallowing disorders are related to both the surgical approach (open or endoscopic) and the tissue removed; while surgery of oral and oropharyngeal cancers mainly impact the oral control, oral peristalsis, and mastication, partial laryngeal surgery interferes with airway protection mechanisms, and complete laryngeal removal may be complicated with hypopharyngeal strictures. Different chemoradiotherapy protocols are available nowadays and are here reviewed; dysphagia may arise in the first 2 years as well as many years afterwards and is mainly related to increased oropharyngeal transit time, reduced tongue and pharyngeal strength, restricted laryngeal and hyoid elevation, poor vestibule and true vocal fold closure, and possibly abnormal upper esophageal sphincter function.

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The primary treatment goal of dysphagia in head and neck cancer patients is to maintain functional oral feeding and prevent aspiration and thoracic complications. All patients treated for a head and neck cancer should have access to a dysphagia specialist and to an instrumental investigation in order to establish adequate treatment.

1 Introduction

Tumors of the head and neck are not rare, representing 3.2% of newly diagnosed cancer (Curado and Hashibe 2009). Incidence and prevalence may vary because of several factors: area of the world, district within the head and neck region, age, and treatment. Both surgery and chemoradiotherapy are valid treatment options for head and neck cancer and the role of these two approaches has changed considerably during time; in fact, the evolution of head and neck cancer treatment can be divided into three main eras. The first was focused on curing patients using radical surgical procedures; the second era developed with the goal of speech preservation, using sound oncological principles. The final and current era is of organ-sparing protocols utilizing a combination of radiation, chemotherapy, and surgery (Genden et al. 2007; Haigentz Jr et al. 2009; Genden et al. 2010).

In many of the patients with head and neck cancer dysphagia as well as its complications (malnutrition and aspiration pneumonia) are commonly found and significantly impact the health and quality of life (QOL) (Gallo et al. 2009; Manikantan et al. 2009; Schindler et al. 2006). Different factors may contribute to the presence of dysphagia: the tumor itself, the treatment, and, in a small percentage of patients, associated diseases, such as Parkinson's disease or stroke. Swallowing study in patients with head and neck cancer revealed signs of dysphagia prior to treatment in up to 59% of the population; pharyngeal tumors appeared more often associated with dysphagia compared to oropharyngeal or laryngeal tumors and swallow function worsened significantly with increased tumor stage (Pauloski et al. 2000; Stenson et al. 2000; Van der Molen et al. 2009a, b). Appropriate management of dysphagia in this nonuniform population requires a team approach, with strict collaboration between different professions including surgeons, oncologists, radiotherapists, dentists, phoniatricians, speech and language pathologists, and dieticians; a precise knowledge of the disease, the treatment protocols, and the patient's will is necessary before swallowing assessment and rehabilitation planning (SIGN 2006). In this chapter only the main treatment options, both surgical and nonsurgical, for head and neck cancers are reviewed with the aim to describe the impact on swallowing and the dysphagia management of these patients.

2 Surgical Options of Head and Neck Malignancy

Head and neck malignancy may occur in different regions: oral cavity, oropharynx, larynx, hypopharynx, and salivary glands (Table 1). A large number of surgical procedures according to tumor site and extension as well as patient age and general conditions have been developed over time to treat head and neck malignancies. Head and neck cancers are often treated with curative intent despite frequent presentation with advanced-stage disease, an intent which must be balanced with the potential for long-term morbidity following aggressive local and regional therapies. Head and neck cancers are classified as either "resectable" or technically "unresectable" due to regional invasion of critical structures; while "unresectable" tumors are often best treated with chemoradiotherapy, several curative-intent treatment options currently exist for resectable tumors. The advantages of surgery as primary therapy include complete pathological staging for determination of patient prognosis as well as potential for sparing some patients subsequent radiotherapy with or without chemotherapy with its attendant toxicity. However, possible disadvantages of primary surgery include morbidity of the procedure, postoperative functional impair-

Table 1 Regions and sites of head and neck malignancy

Region	Site
Oral cavity	Lip Gingival Hard palate Buccal mucosa Floor of mouth Anterior 2/3 of tongue Retromolar trigone
Larynx	Supraglottis Glottis Subglottis
Nasopharynx	Lateral nasopharyngeal walls Posterior nasopharyngeal wall Superior nasopharyngeal wall
Oropharynx	Base of the tongue Inferior surface of the soft palate and uvula Anterior and posterior tonsillar pillars Glossotonsillar sulci Pharyngeal tonsils Lateral and posterior pharyngeal walls
Hypopharynx	Pyriform sinuses Lateral and posterior hypopharyngeal walls Postcricoid region
Salivary glands	Parotid Submandibular gland Sublingual gland Minor salivary glands

ment, or, when the patient is not able to avoid postoperative treatment, toxicity of both surgical and subsequent adjuvant therapy.

In most surgical procedures of the oral cavity, pharynx, and larynx a tracheotomy is performed in order to prevent respiratory failure in case of edema, upper airway obstruction, or perioperative bleeding. Appropriate management of the tracheotomy and of the cannula is required in order to achieve swallowing in the best possible way.

2.1 Surgery of the Oral Cavity Malignancy

The oral cavity extends from the lip to the junction of the hard and soft palate above and to the line of the circumvallate papillae below; therefore, the regions of the oral cavity include buccal mucosa, upper and lower alveolar ridges, retromolar trigone, anterior two-thirds of the tongue, floor of the mouth, and hard palate. Surgical procedures for tumors of the oral cavity vary according to the site and the dimension of the tumor; while for tumor <4 cm surgery can be the only treatment options, for larger tumors chemoradiotherapy is usually associated. The challenge of surgery for malignancies of the oral cavity is to perform an adequate resection and then to provide the best functional reconstruction (de Bree et al. 2008). In fact, extensive surgical resections are often required, leading to major physical defect that cannot be repaired by primary mucosal closure or skin grafting. Surgical reconstruction aims to repair the physical deficit while restoring functional deficits. Reconstruction techniques are diverse and vary by anatomical region. Split-thickness skin grafts are the mainstay for small, superficial defects of the oral cavity (Fig. 1); the pectoralis major myocutaneous flaps provide soft tissue for large floor-of-mouth and tongue resections, while myocutaneous or osteomyocutaneous free flaps are the reconstructive methods of choice for oral cavity defects. The radial forearm flap is the most widely used free flap, while if bone is required for mandibular reconstruction fibula iliac crest or scapula free flaps can be used.

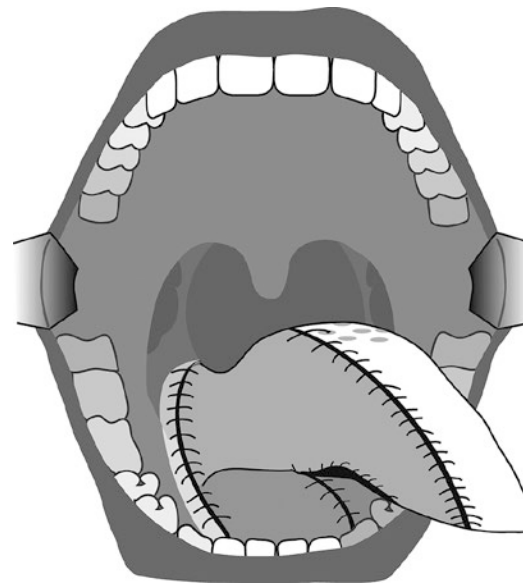

Fig. 1 Schematic drawing of split-thickness brachial flap after resection of half of the tongue and mouth floor

2.1.1 Glossectomies

Tongue cancer surgery may vary depending on three main variables: extension of tongue resection, access to the tumor, and reconstruction. Depending on the site and extension of the tumor the possible tongue resections are marginal glossectomy (resection of ¼ of the tongue), hemiglossectomy (resection of half of the tongue along the midline), hemiglossomandibulectomy (resection of half of the tongue and portion of the mandible), and near-total glossectomy.

After marginal glossectomy of hemiglossectomy swallowing disorders are usually temporary and are mainly related to clumsiness in tongue movement difficulties in triggering the swallowing reflex. Clumsiness in tongue movement may impact both control of material in the mouth and lingual peristalsis. When lingual resection exceeds 50% of the tongue, effects on swallowing are more severe. In particular lingual peristalsis and oral control may be severely reduced (Fig. 2a, b); patients' diet may be restricted to liquids and thinned paste, and tilting of the head backward allowing gravity to carry material into the pharynx is often required.

2.1.2 Commando Procedures

The commando procedure (COMbined MANDibulectomy and Neck Dissection Operation) is a surgical procedure for malignant tumors of the floor of the oral cavity, involving resection of portions of the mandible in continuity with the oral lesion and radical neck dissection. Segmental mandibulectomy is considered only when there is gross invasion of the cancellous part of the bone by oral cancer, for primary bone tumors of the mandible, metastatic tumors to the mandible, invasion of inferior alveolar nerve or canal by tumor, and for massive soft-tissue disease around the mandible. In the other cases, since there are no lymphatic channels traversing through the mandible, there is no need to perform an in-continuity composite resection of the uninvolved mandible; in order to gain access to the large primary oral cancer a mandibulotomy can be performed without the need to sacrifice the normal intervening mandible (Shah and Gil 2009).

Reconstructive surgery following resection for oral cancer is considered when there is functional or aesthetic loss of structures in the oral cavity. Superficial surgical defects of the mucosa and underlying soft tissues can be adequately reconstructed using a skin graft, while larger defects of

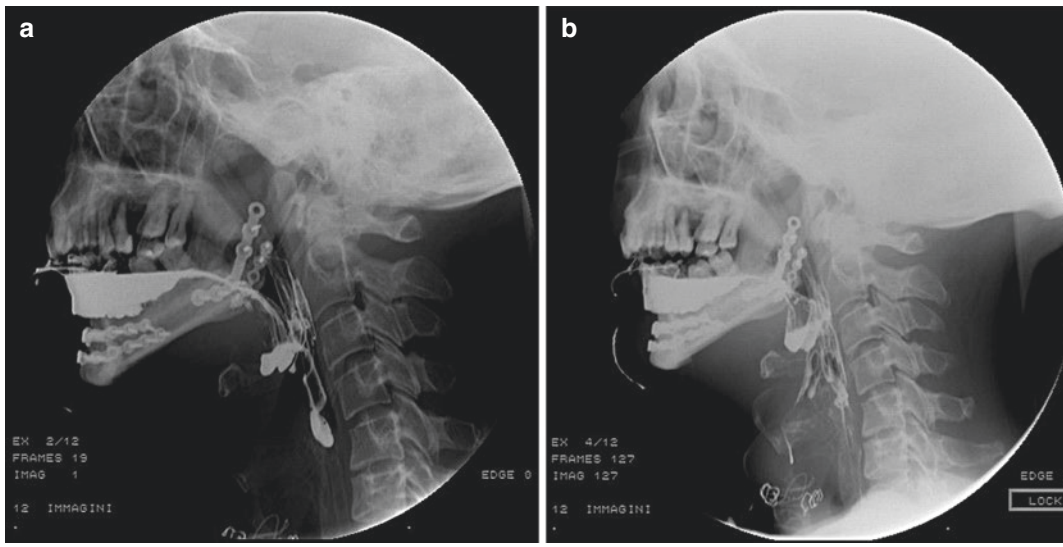

Fig. 2 Videofluoroscopic images of a patient after hemiglossectomy; poor oral control with stasis in the floor of the mouth and spillage in the hypopharynx (**a**), as well as aspiration (**b**), are visible

the tongue exceeding one-half of the tongue or large surface areas of the floor of the mouth, gum, and buccal mucosa require a free tissue transfer. A radial forearm free flap provides excellent tissue for resurfacing mucosal defects and underlying soft-tissue deficiencies. The radial forearm flap is also an excellent choice for reconstruction of any substantial resection of the tongue. The anterolateral thigh flap represents another optimal flap which is now considered the ideal soft-tissue flap for reconstructing defects in the tongue, as numbness at the donor site is minimal and patients are satisfied (Chen et al. 2016). Fibula free flap reconstruction is currently the choice of reconstruction for defects following segmental mandibulectomy in any part of the mandible. While other free flaps are available (from iliac crest, scapula, and radial forearm), the fibula provides the maximum length and bone stock to achieve a satisfactory reconstruction of the lower jaw.

After anterior floor of the mouth resection, swallowing is strictly related to surgical closure technique, but it is usually preserved. If the tongue is sutured into the surgical defect, however, impairment in control of the bolus, lingual peristalsis, and mastication will arise. After lateral floor of the mouth resection, severe swallowing impairment may arise if the base of the tongue is involved in the surgical procedure; lingual propulsion and oral transit time will be reduced and material will collect in the lateral sulcus and/or in the crevices.

2.2 Surgery of the Oropharyngeal Malignancy

The oropharynx consists of four sites: soft palate, tonsil, base of the tongue, and pharyngeal wall. The survival outcomes of therapy for these tumors remain essentially the same regardless of the treatment combination employed. The most important factor which affects long-term outcome following initial treatment of oropharyngeal cancer is the disease stage at the time of presentation. In the past, surgery followed by radiotherapy was the standard of care. However, at present concurrent chemoradiotherapy appears to be the preferred choice of therapy. Surgical intervention would be considered for tumors of minor salivary gland origin or squamous cell carcinoma which remains persistent after chemoradiotherapy or recurs after chemoradiotherapy. Surgical access to neoplasms of the oropharynx can be obtained via a mandibulotomy (Fig. 3), lateral pharyngotomy, or transoral robotic surgery (TORS) (Weinstein 2007). Early-staged tumors offer excellent cure rates; however once regional lymph node metastases have taken place a significant drop in the cure rate is to be expected. Early diagnosis and implementation of appropriate surgical treatment based on tumor and patient factors, selective management of regional lymph node metastases at risk, and involvement of multidisciplinary teams for implementation of adju-

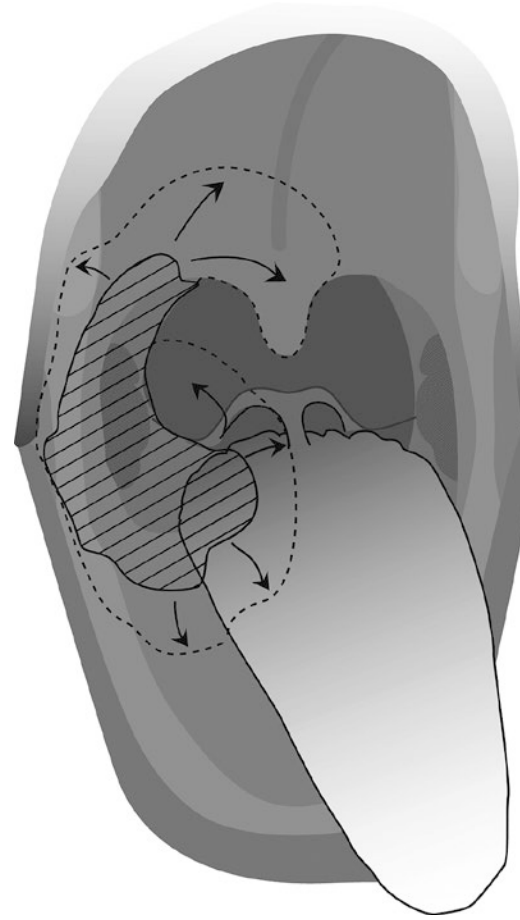

Fig. 3 Schematic drawing of transmaxillary-oropharyngectomy; the arrows indicate possible diffusion of the tumor

vant radiotherapy or chemoradiotherapy have all contributed to improvements in survival of patients with oral cancers in these last decades. Contemporary surgical techniques of tumor resection and reconstruction are essential to improve the QOL of patients following surgical resection of oropharyngeal cancer.

Surgery of oropharyngeal tumors impact both oral and pharyngeal stages of swallowing. Tongue propulsion will be reduced; nasal regurgitation may also be present as well as delayed or reduced triggering of the swallowing reflex and pharyngeal peristalsis, leading to oral and pharyngeal residue. Occasionally, cricopharyngeal sphincter difficulties may also arise.

2.2.1 Mandibulotomy Access

Surgical access to the posterior oral cavity and oropharynx can be accomplished via a multitude of approaches, including pull-through glossotomy and pharyngotomy. In the pull-through technique, once the hypoglossal and lingual nerves are identified, the floor of mouth mucosa and the extrinsic tongue muscles are divided and the tongue is dropped into the neck (Fig. 4); when pharyngotomy is performed, neck dissection is associated and resection of the upper portion of the thyroid cartilage is necessary, before the incision of the pharyngeal wall. The most widely used access is the mandibulotomy, in particular the lip-splitting mandibulotomy approach (LSMA). This latter involves a lower lip-splitting incision, followed by a mandibular osteotomy, which is fixated at the end of the operation. It provides the widest and most reliable access to the deep anatomy of the posterior oral cavity and oropharynx and lends exposure to virtually any site in the upper aerodigestive tract, including the nasopharynx, hypopharynx, parapharyngeal spaces, and clivus.

2.2.2 Lateral Pharyngotomy Access

Lateral pharyngotomy access is useful for small tumors of the base of tongue and pharyngeal walls. The pharynx is entered posterior to the thyroid ala on the least diseased side. Once in the pharynx, the larynx is retracted to the opposite side. This allows a good view of the posterior pharyngeal wall, opposite lateral wall, and base of tongue. If more superior exposure is needed, the pharyngotomy can be extended across the vallecula or this approach can be combined with a lateral mandibulotomy.

2.2.3 Transoral Robotic Surgery

Robotic surgery is performed utilizing the da Vinci surgical system. The surgeon sits at the console and controls micromanipulators, which in turn are connected to a robotic cart at the patient's bedside. In transoral robotic surgery (TORS), three arms are routinely utilized (Genden et al. 2009). TORS is nowadays applied for the management of tongue-base carcinoma, squamous cell carcinoma of the posterior pharyngeal wall, hypopharynx carcinoma, and supra-

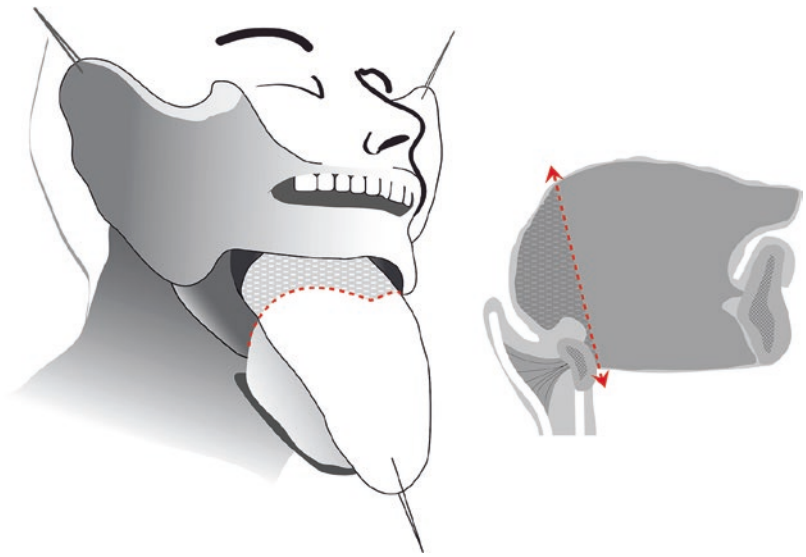

Fig. 4 Schematic drawing of pull-through glossotomy

glottic and total laryngectomy (Lombard and Ceruse 2017). This non-open approach is associated with faster and better recovery compared to the corresponding open approaches.

2.3 Surgery of the Laryngeal Malignancy

The era of surgical treatment for laryngeal cancer started in 1873 when Billroth first described the surgical procedure of total laryngectomy (TL), the "gold standard" for advanced-stage laryngeal carcinoma. Despite its efficacy as an oncologic procedure, complete loss of the larynx is a devastating event that results in significant diminution of QOL for many individuals. The consequences of TL include loss of nasal function, poor cough, swallowing difficulties, lung function changes, and above all the loss of normal voice. Therefore, the challenge for the head and neck surgeon has not been significantly improving the cure rate for laryngeal cancers, because the survival data for the radical laryngectomy have remained quite constant when adjusted for tumor site and stage, but reducing the morbidity associated with the treatment (Dworkin et al. 2003; Levine et al. 1997). Not surprisingly, the evolution in the management of laryngeal cancer has been to establish surgical as well as nonsurgical protocols with overall survival equivalent to TL but better QOL (Genden et al. 2007).

2.3.1 Partial Laryngectomies

Several surgical options for treating laryngeal carcinoma can be used, allowing the resection of the tumor with oncologically safe margin and preserving laryngeal function. While frontolateral partial resections have been used in the past, partial horizontal laryngectomies are currently more popular; open partial horizontal laryngectomies (OPHL) include supraglottic partial laryngectomy (type I OPHL), supracricoid laryngectomies (SCL, type II OPHL), and supratracheal laryngectomies (type III OPHL) (Succo et al. 2014).

Frontolateral vertical laryngectomy consists of a vertically laryngectomy with removal of the anterior commissure; a lateral thyrotomy is performed on both sides, the vocal fold with the anterior commissure is removed, and the remaining vocal fold is sutured to the thyroid cartilage. SGL consists in resecting the whole supraglottic portion of the larynx, including both ventricular folds and epiglottis (Fig. 5).

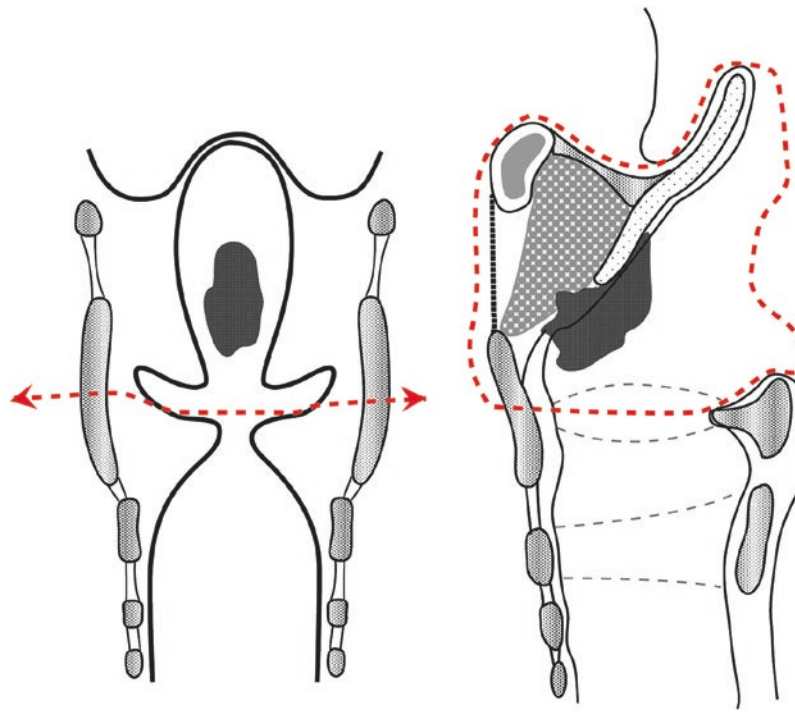

Fig. 5 Schematic drawing of horizontal supraglottic laryngectomy

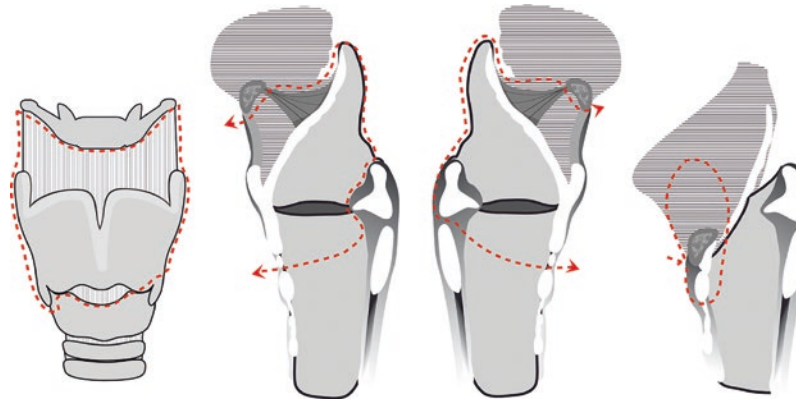

Fig. 6 Schematic drawing of supracricoid laryngectomy with crico-hyodo-pexy (CHP)

Depending on the size and site of the tumor, type I OPHL may be extended into the base of the tongue or may include one arytenoid (Marandas et al. 1987). Type II and III OPHL are conservative surgical techniques for the treatment of selected laryngeal carcinomas; two reconstruction techniques, cricohyoidoepiglottopexy (CHEP) and cricohyoidopexy (CHP), are used depending on whether the epiglottis is preserved or not (Adamopoulos et al. 2000; Brasnu 2003; Labayle and Bismuth 1971; Laccourreye et al. 1987, 1990, 1995, 1996; Levine 1997; Piquet et al. 1974, Piquet and Chevalier 1991). In type II and III OPHL both ventricular and vocal folds as well as the entire thyroid cartilage are resected, while at least one arytenoid cartilage is spared; in type II and III OPHL with CHP (Fig. 6) the epiglottis and preepiglottic space are also resected, while in type II and III OPHL with CHEP they are spared (Fig. 7). Preliminary data did not seem to show significant difference in swallowing outcome in type II and type III OPHL (Schindler et al. 2015a, b; Schindler et al. 2016a, b). In the last years in addition to open type II OPHL, endoscopic CO_2 laser SCL has been developed; this surgical approach reduces anterior neck muscle and nerve involvement (Weinstein et al. 2007; Jong-Lyel et al. 2008). Volitional sphincteric approximation of the mobile arytenoid cartilage and base of tongue, in the case of CHP, or epiglottis, in the case if CHEP, allows neoglottal closure and airway protection (Fig. 8) (de Vincentiis et al. 1996, 1998; Luna-Ortiz et al. 2004; Naudo et al. 1997, 1998).

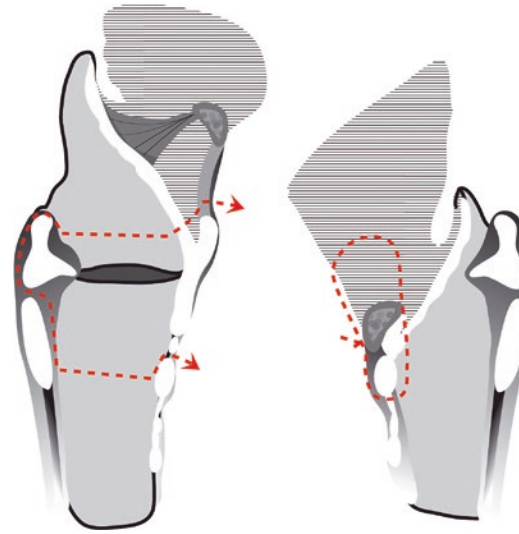

Fig. 7 Schematic drawing of supracricoid laryngectomy with crico-hyodo-epiglottopexy (CHEP)

The advantage of partial laryngectomies over TL is that a permanent tracheostoma is not required, since the main laryngeal functions (respiration, phonation, and swallowing) are preserved, when at least one functioning cricoarytenoid joint is maintained, facilitating neoglottal competency (Bron et al. 2000). Compensatory mechanisms with reorganization of the stepwise sequence of neuromuscular events, lasting several months, are necessary to restore swallowing (Woisard et al. 1996; Yuceturk et al. 2005). Satisfactory functional results of both voice and swallowing after partial laryngectomies have been reported by different authors (Crevier-Buchman et al. 1995,

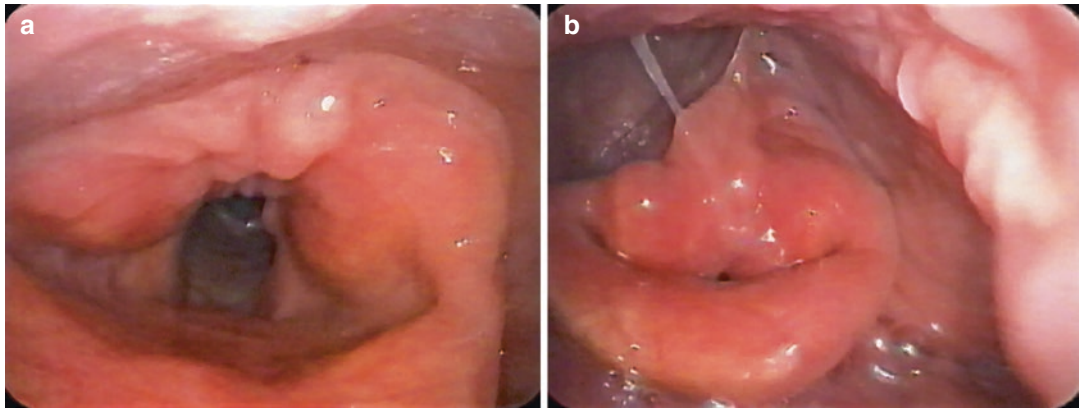

Fig. 8 Videoendoscopic laryngeal images of a patient who underwent supracricoid laryngectomy with crico-hyodo-pexy (CHP); larynx during respiration (**a**) and phonation (**b**)

1998; Zacharek et al. 2001); however, significant alterations have appeared inevitable and long-term outcome showed mild-to-moderate dysphagia in the majority of patients (Schindler et al. 2006, 2009).

While vertical partial laryngectomy usually does not impact swallowing, horizontal partial laryngectomies are associated with dysphagia mainly due to airway protection impairment and require appropriate management by a swallowing therapist; in all the reported case series a small but significant percentage of patients developed aspiration pneumonia and few patients did not achieve by mouth feeding. Severity of dysphagia and recovery time are mainly related to amplitude of resection: after type I OPHL swallowing recovers sooner than after type II OPHL with CHP, but OPHL I extended to the tongue base is associated with more severe dysphagia compared to type I OPHL (Schindler et al. 2016a, b). Insufficient laryngeal vestibule and/or glottis closure during the pharyngeal phase of swallowing is seen in all these patients and appropriate laryngeal closure needs to be acquired after surgery (Rademaker et al. 1993). While upper airway protection deficit is the main cause of dysphagia, other factors should be considered: superior laryngeal nerve function is often impaired, leading to a reduced laryngeal sensation; laryngeal elevation could also be damaged and upper esophageal sphincter opening reduced. Finally,

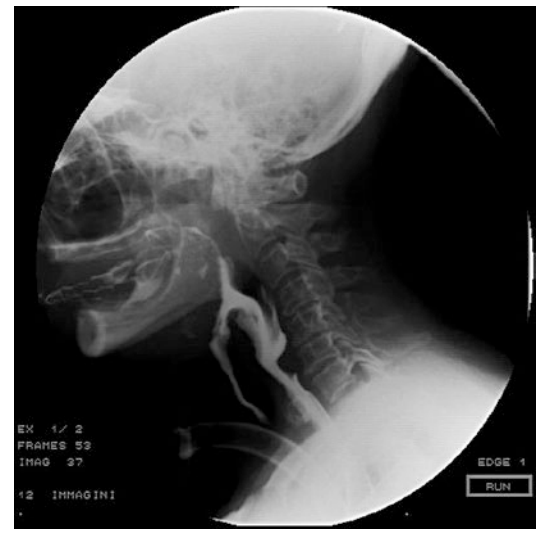

Fig. 9 Videofluoroscopic image of aspiration after supracricoid laryngectomy with crico-hyodo-pexy (CHP); an incomplete opening of the upper esophageal sphincter is also visible

a delayed swallowing reflex is found in a significant percentage of patients (Fig. 9).

In the long term aspiration is found in about 40% of patients who underwent type II and III OPHL and who are mouth fed (Fig. 10); nonetheless, pulmonary CT scan fails to find significant differences compared to COPD patients, suggesting that in this population a mild chronic aspiration is well tolerated (Simonelli et al. 2010).

2.3.2 Total Laryngectomy (TL) and Laryngopharyngectomy

Total laryngectomy (TL) is the gold standard for surgical treatment of advanced laryngeal and hypopharyngeal tumors. TL includes removal of all laryngeal and associated structures, from the hyoid bone and the epiglottis superiorly to the tracheal rings inferiorly with varying amounts of the hypopharynx and thyroid gland. It can be extended to the tongue base, pharynx, and trachea as well as prelaryngeal soft tissues including the skin (Fig. 11). When the tumor originates in the hypopharynx or there is a hypopharyngeal extension of laryngeal carcinoma, a partial or total laryngopharyngectomy may be needed. If the extension is limited, partial pharyngectomy is performed, while with extensions of more than 50% of the hypopharynx it is advisable to do a total pharyngectomy. In case of extension to the esophagus, total laryngopharyngectomy with esophagectomy can be performed; the most frequently used techniques are a tubed jejunum free flap, tubed pectoralis major flap, and gastric pull-up (Remacle and Eckel 2010). After TL there is a significant modification of aerodigestive tract, and the respiratory and digestive tracts are entirely separated: the mouth, pharynx, and esophagus act as digestive system, while the trachea, directly attached to the neck skin, is the first part of the respiratory system.

Even if swallowing is usually well preserved and aspiration is not possible after TL, two complications may lead to dysphagia: pharyngoesophageal stenosis/stricture and esophageal motility disorders. Pharyngoesophageal stenosis/stricture may occur after large resections or as a consequence of adjuvant radiotherapy (Fig. 12).

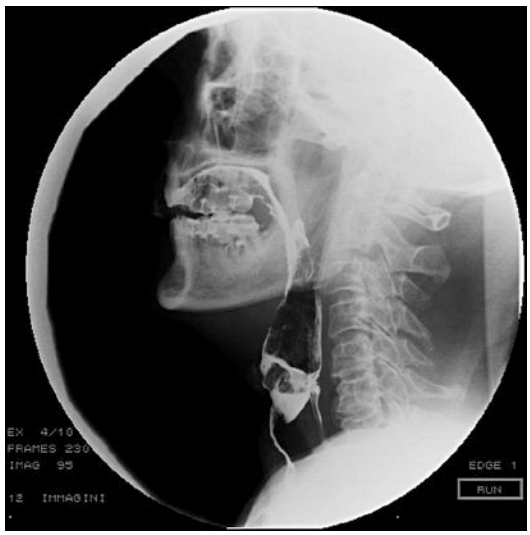

Fig. 10 Videofluoroscopic image of aspiration after supracricoid laryngectomy with crico-hyodo-pexy (CHP) several years after the surgical procedure

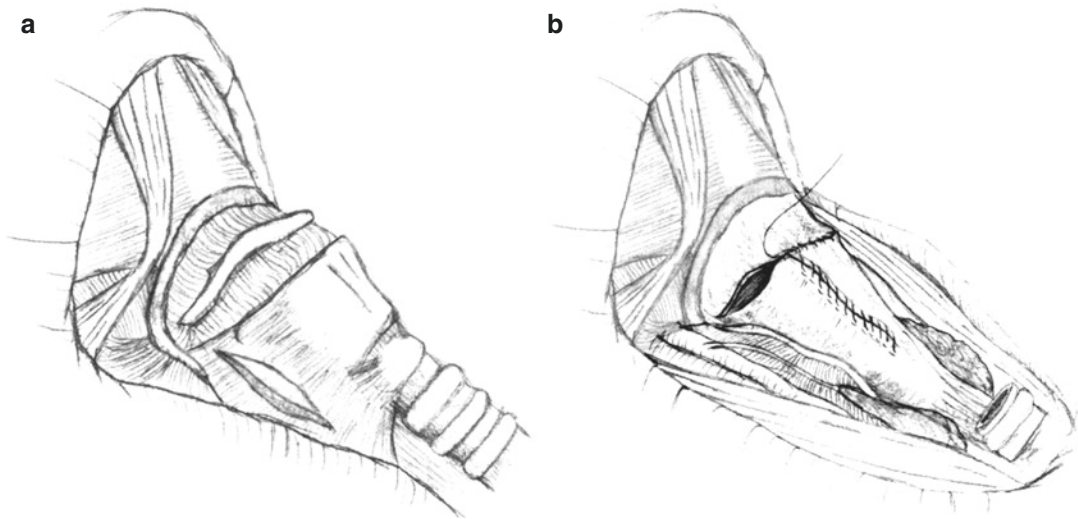

Fig. 11 Schematic drawing of total laryngectomy; incision of the muscle (**a**); suture of the pharynx (**b**). Taken from Remacle and Eckel 2010

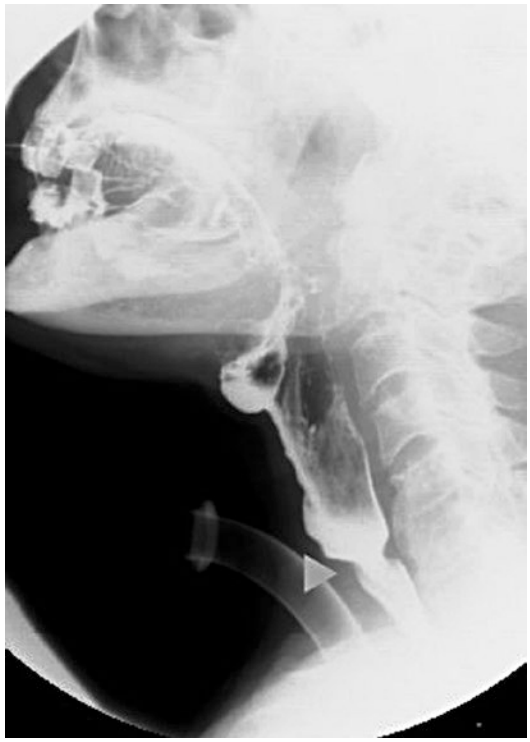

Fig. 12 Videofluoroscopic image of a mild stenosis after total laryngectomy

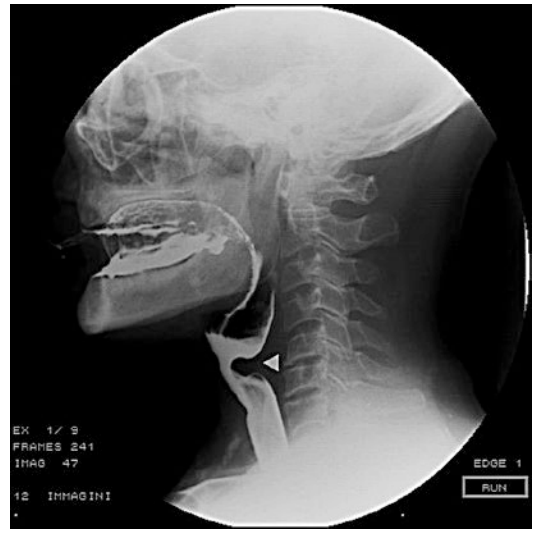

Fig. 13 Videofluoroscopic image of a hypertone of the upper esophageal sphincter after total laryngectomy

Outpatient dilatation is usually effective in restoring swallowing, even if the dilatation procedure might be repeated over time. In the unlikely situation that dilatation is unsuccessful, flap augmentation (e.g., pectoral major or jejunal free flap) may be necessary. Esophageal motility impairments have been found in patients after TL (Fig. 13): the amplitude of contractions is lower and the number of nonperistaltic contractions is higher; besides, the duration of lower esophageal sphincter relaxation is shorter and the upper esophageal sphincter pressure is lower in laryngectomized patients than in control subjects (Dantas et al. 2002, 2005).

2.4 Surgery of Neck Metastasis

Metastasis of head and neck malignancies to the neck lymph nodes is common and appropriate management of neck metastasis is as important as tumor treatment. Both surgical and nonsurgical options are available; only surgical options will be considered in this paragraph. Several cervical lymph node dissections are currently used for the surgical treatment in patients with head and neck cancer. Neck dissections are classified taking into account the lymph node groups (submental, submandibular, jugular, supraclavicular, paratracheal nodes) that are removed and the anatomic structures that may be preserved (spinal accessory nerve, sternocleidomastoid muscle). Based on this assumption, there are three anatomic types of neck dissections: radical, selective, and extended. In radical neck dissection en bloc removal of the lymph node-bearing tissue of one side of the neck, from the inferior border of the mandible to the clavicle and from the lateral border sternohyoid muscles to the anterior border of the trapezius, is performed. Included in the resection are the spinal accessory nerve, intrajugular vein, and sternocleidomastoid muscle. In selective neck dissection only the lymph node groups at highest risk of containing metastases are removed. Extended neck dissections are neck dissection that may include lymph node that are not routinely removed (retropharyngeal, upper mediastinal) or other structures that are not routinely removed (skin of the neck, carotid artery, vagus, or hypoglossal nerve).

Even if neck dissection is considered not to impair swallowing, several important muscular and nerve structures for swallowing may be damaged during neck dissection and there is evidence that swallowing modifications arise (Hirai et al. 2010). In particular, a lower rest position of the hyoid bone and a decreased hyoid bone elevation have been described, together with penetration in a percentage of patients; no residue or pharyngeal transit time modifications were found. Recurrent laryngeal nerve injury and suprahyoid muscle resection are the most likely elements involved in the pathogenesis of swallowing impairment. Even if dysphagia is unlikely to develop following neck dissection, there is evidence that feeding tube is prolonged in patients with head and neck cancer who underwent neck dissections besides tumor treatment (Lango et al. 2010).

3 Chemoradiotherapy for Head and Neck Malignancy

Chemoradiotherapy can be delivered with curative intent (radical chemoradiotherapy), in order to improve local control following surgery (adjuvant chemoradiotherapy) or to provide symptomatic relief only (palliative chemoradiotherapy). Chemotherapy is administered in combination to locoregional therapy to improve survival. The chemotherapeutic agents most widely used are cisplatin (100 mg/m^2 on days 1, 22, and 43) and 5-fluorouracil, 5-FU (1 g/m^2 in day 1 and 4). Radiotherapy uses ionizing radiation to treat malignancy. Ionizing radiation may be delivered as an external radiation beam targeting the tumor (external beam radiotherapy), or by directly implanting radioactive sources within the tumor (brachytherapy). External beam radiotherapy (RT) is usually fractionated which means that the total dose is delivered over time in smaller doses or fractions. The dose of radiation that can be delivered to a tumor is limited by the tolerance of the surrounding normal tissues, which are also unavoidably irradiated during treatment. Generally, the dose of radiation per day is 1.8–2 Gy for 5 days in a week for 6–7 weeks for a total of 70 Gy. Altered radiation fractionation regimens that incorporate acceleration and/or hyperfractionation have also been proposed; acceleration involves a reduction in overall treatment time, while hyperfractionation involves the use of multiple smaller dose fractions delivered at an increased frequency. These latter improve locoregional control but also increase acute toxicities for head and neck cancer patients (Harari 2005). The role of chemoradiotherapy in head and neck cancer treatment increased significantly after the introduction of intensity-modulated RT (IMRT) (Liu et al. 2010). IMRT is an advanced mode of high-precision radiotherapy that utilizes computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3-D) shape of the tumor by modulating the intensity of the radiation beam in multiple small volumes. IMRT also allows higher radiation doses to be focused to regions within the tumor while minimizing the dose to surrounding normal critical structures. Typically, combinations of multiple intensity-modulated fields coming from different beam directions produce a custom-tailored radiation dose that maximizes tumor dose while also minimizing the dose to adjacent normal tissues.

3.1 Effects of Chemoradiotherapy on Mucosa, Cartilages, and Muscles

Concomitant chemoradiotherapy protocols for locally advanced oropharynx carcinoma increase the overall survival rate but can cause significant and severe swallowing problems secondary to anatomic and functional changes occurring in the mucosa, cartilages, and muscles that are involved in swallowing. In particular radiotherapy (RT) may induce edema, erythema, decreased acuity of taste buds, decreased production of the salivary glands, and desquamation of the skin which may eventually lead to atrophy and fibrosis of the connective tissues (Fig. 14).

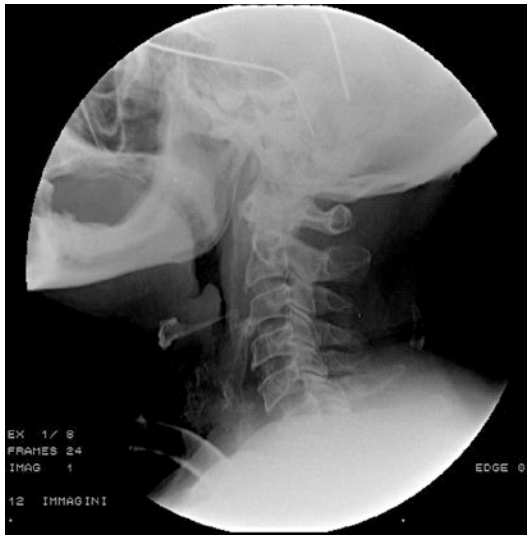

Fig. 14 Videofluoroscopic image of a thickened epiglottis after radiotherapy

Xerostomia which results in oral dryness may impair the normal oral functions (speech, chewing, and swallowing) because of insufficient wetting, and decreased lubrication of the mucosal surfaces and of ingested food. Furthermore, the oral mucosa can become dry and atrophic, leading to frequent ulceration and injury. Finally, the shift in oral microflora towards cariogenic bacteria, reduced salivary flow (oral clearance), and changes in saliva composition (decreased buffer capacity, pH, immunoprotein concentrations) may result in rapidly progressing radiation caries. In addition, concomitant chemoradiotherapy affects the neuromuscular mechanism of swallowing resulting in multiple swallowing measure abnormalities, including increased oropharyngeal transit time, incoordination of bolus movement through the oropharynx, reduced tongue-base contact with the posterior pharyngeal wall, restricted laryngeal and hyoid elevation and movement, poor vestibule and true vocal fold closure, possibly abnormal upper esophageal sphincter function, and persistent pharyngeal residue and aspiration. These disorders are most likely the results of neuromuscular fibrosis and of increased apoptosis (Smith et al. 2000) and play the most important role in the genesis of dysphagia.

3.2 Effects of Chemoradiotherapy on Swallowing

Swallowing function after chemoradiotherapy is receiving increasing attention, as it has been shown that long-term survival is severely affected in patients with optimal locoregional cancer control (Forastiere et al. 2013). Chemoradiotherapy plays a critical role in producing swallowing disorders in head and neck cancer patients (Eisbruch et al. 2002). A number of variables determine the incidence of late complications: total radiation dose, fraction size, radiated volume, interfraction interval, treatment techniques, use of IMRT and tissue-dose compensation, and site and size of the primary tumor (Dornfeld et al. 2007). Even if most widely described impairments occur in the first 2 years after chemo-RT, also after many years after treatment a number of oropharyngeal motility disorders can be found (Jensen et al. 2007). Mechanisms underlying late-onset dysphagia have been studied (King et al. 2016); different patterns of swallowing dysfunction have been identified: low persistent, intermediate persistent, severe persistent, transient, and progressive. Patients with high dose to the upper pharyngeal, laryngeal, and lower pharyngeal region had the highest risk of severe persistent swallowing dysfunction (Christianen et al. 2015).

During RT and in the first weeks afterwards patients experience oral mucositis which severely impacts oral intake. When oral and pharyngeal mucositis heals a significant improvement in oral diet is seen and a correlation between healing from oral mucositis and oral intake is visible (Pauloski et al. 2011); nonetheless, oropharyngeal deficits are still visible. Oral phase impairment includes reduced mouth opening, reduced range of lingual motion, reduced lingual strength, impaired bolus formation, impaired bolus transport through the oral cavity, prolonged oral transit times, and increased oral residue. As for the pharyngeal phase several defects are found: reduced tongue base posterior movement, defective velopharyngeal closure, delayed triggered swallowing reflex, reduced pharyngeal contraction, reduced laryngeal elevation, reduced glottis and laryngeal vestibule closure, and reduced opening of the upper esophageal

sphincter. Impairments are limited to not only motor function but sensibility as well; several authors found reduced laryngeal sensibility, defective or absent laryngeal adductor reflex, and silent aspiration in patients who underwent RT. Motor and sensibility impairment leads to reduced bolus clearance, residue, and silent aspiration (Lazarus 2009); it is not surprising, therefore, that weight loss and malnutrition are commonly found in patients after RT for a head and neck cancer.

Dysphagia may occur even many years after RT (Smith et al. 2000); even if the precise cause is not known, most authors agree that tissue fibrosis, peripheral neuropathy, and sensibility impairment are responsible for late-onset dysphagia development. Xerostomia is usually found even years after chemoradiotherapy and significantly impact patient's perception of dysphagia and diet choices; however, there is no correlation between saliva weight and swallow function (Logemann et al. 2003).

4 Evaluation of Swallowing and Swallowing Disorder Complications After Surgery and/or Chemoradiotherapy of Head and Neck Malignancy

Swallowing evaluation in a patient after head and neck cancer treatment relies on the same principles of dysphagia of other origin: bedside clinical assessment and subsequent instrumental examination, either videofluoroscopy or fiber-optic endoscopic evaluation of swallowing (FEES). Before patient assessment, it is critical to have detailed information on the surgical procedure and the chemoradiotherapy protocol; in fact it is crucial to know which structures have been sacrificed or involved in a RT protocol. Clinical and instrumental examinations aim to understand the functions of the spared structures; in particular motion range, strength, and timing of the remaining structures in swallowing and non-swallowing tasks are critical to understand bolus transit impairment.

Clinical examination is important for the understanding of tongue and mouth structures and functions; in patients with oral cancer, surgical and nonsurgical treatment protocols may have seriously modified the anatomy and physiology of oral structures (Fig. 15). FEES is recommended for a better definition of mucosal status, velopharyngeal and laryngeal motility, as well as saliva and food residue (Fig. 16). In particular in the early phases after treatment, when tracheotomy is still in place, laryngeal assessment in retrograde vision through stoma access (Fig. 17) gives important information on laryngeal sensibility and aspiration mechanisms; besides, FEES may be repeated several times in order to establish when oral diet may be initiated, avoiding exposure to X-rays. FEES with sensory testing (FEESST) is recommended if available, as laryngeal sensibility deficits are found in many patients

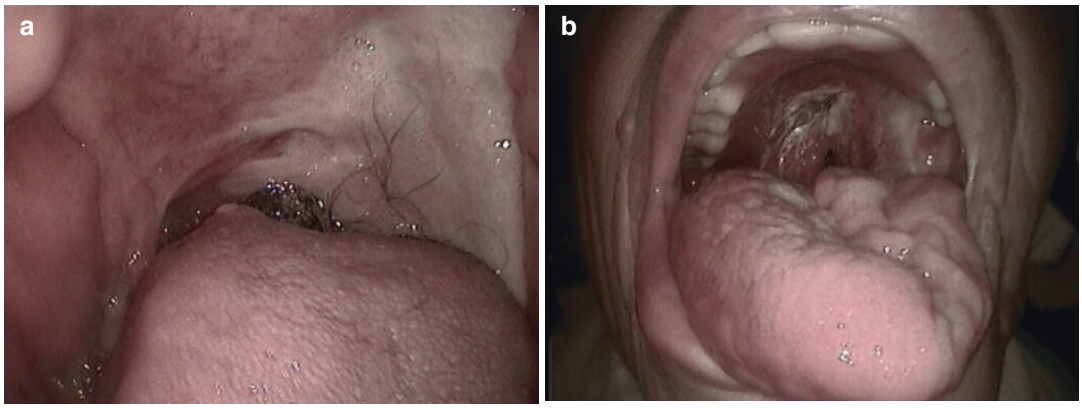

Fig. 15 Images of oral cavity after surgery. (**a**) Pectoralis major myocutaneous flap after left oro-pharyngectomy; (**b**) left tongue atrophy due to hypoglossal nerve damage

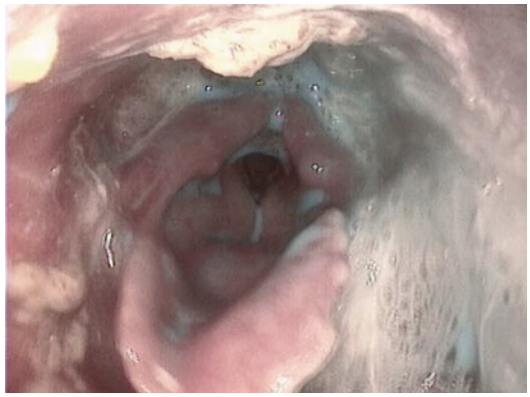

Fig. 16 Videoendoscopic image of a patient who underwent buccopharyngectomy following a (chemo)radiotherapeutic treatment; diffuse residues and penetration are visible

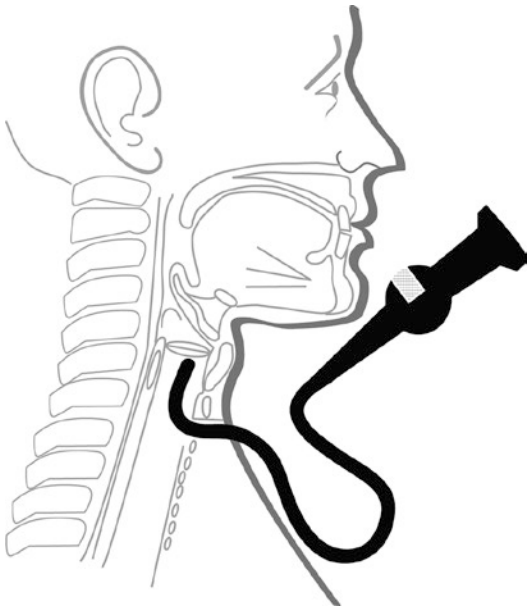

Fig. 17 Laryngeal assessment in retrograde vision through a stoma access

(Schindler et al. 2010). Videofluoroscopy plays a critical role in establishing oral phase modification, severity of pharyngeal motion defects, and mechanisms of pharyngoesophageal segment dysfunctions.

The application of functional rating scales and dysphagia-specific QOL measures, such as the M.D. Anderson Dysphagia Inventory (MDADI) or the SWAL-QOL, provides important information on the patient's perception of swallowing (Chen et al. 2001; McHorney and Robbins 2005). Use of these tools helps in identifying patient concerns, and helps to define therapy goals (Speyer et al. 2011).

Assessment of dysphagia complications (malnutrition and pulmonary complication) in head and neck cancer patients does not differ from that of patients with dysphagia of different origin. Since the risk of malnutrition is very high, all head and neck cancer patients should be screened for nutritional status using a validated screening tool, appropriate to the patient population, such as the malnutrition universal screening tool (MUST).

5 Treatment of Swallowing Disorders After Surgery and/or Chemoradiotherapy of Head and Neck Malignancy

All patients treated for a head and neck cancer should have access to a dysphagia team and to an instrumental investigation, if needed, in order to establish adequate treatment (Schindler et al. 2015a, b). The primary treatment goal is to maintain functional oral feeding and prevent aspiration and thoracic complications (SIGN 2006); QOL improvement should be considered as second yet not less important goal (Gillespie et al. 2004; Kulbersh et al. 2006).

Treatment mainly relies on swallowing rehabilitation, an emerging subspecialty (Gamble et al. 2011) of rehabilitation. Swallowing rehabilitation can be divided into three main areas: preventative, compensatory, and therapeutic exercises. While preventative rehabilitation after head and neck cancer surgery has been little explored but seems to reduce time recovery (Cavalot et al. 2009), there is a growing interest in prophylactic swallowing exercises prior to commencing RT (Mittal et al. 2003; Rosenthal et al. 2006; Van der Molen et al. 2009a, b). These exercises focus on maintaining tongue, jaw, and pharyngeal constrictor movement; hyolaryngeal elevation; airway closure; and upper esophageal sphincter opening; typically prescribed exercises are tongue range of motion, tongue strengthening, tongue base motion

(effortful swallow, tongue-hold maneuver, gargle), jaw range of motion, Mendelsohn maneuver, Shaker exercise, and super-supraglottic swallow. While prophylactic treatment seems to have positive effect, reactive treatment does not seem to improve swallowing function (Paleri et al. 2014). Efficacy and compliance data are emerging, but are not yet definitive; preliminary data suggest however that full adherence is far less than 30% of the population (Shinn et al. 2013). Compensatory strategies include postural changes (chin-tuck, head back, head tilt, head rotation, lying down), swallowing maneuvers (super-supraglottic swallow, Mendelsohn maneuver), and change in food consistency, temperature, and taste; compensatory strategies are well developed in the field of swallowing rehabilitation and their rationale and application do not differ in head and neck cancer patients from patients with other dysphagia-related diseases. Therapeutic exercises include a variety of exercises designed to increase motion range and/or muscle strength of specific muscle groups such as jaws, lips, tongue, closure of the airways, and laryngeal elevation; these exercises include effortful swallow, Shaker exercise, Mendelsohn maneuver, and tongue-hold maneuver and may be applied according to the residual swallowing deficit after cancer treatment. Efficacy of both compensatory strategies and therapeutic exercise has been object of investigation, showing preliminary positive effects (Nguyen et al. 2007; McCabe et al. 2009).

Other treatment options for selected patients include application of prosthetic devices, surgery, and enteral feeding. Prosthetic devices should be designed to provide maximum functional rehabilitation, as in the case of palatal obturators to prevent velopharyngeal insufficiency after oropharyngeal tumor resections. Surgical options include pharyngeal or cervical esophageal dilatation for hypopharyngeal or esophageal strictures, cricopharyngeal muscle myotomy for upper esophageal sphincter spasm, and application of fillers to reduce glottal insufficiency or tongue-base deficits (Bergamini et al. 2010). Tube feeding is frequently adopted in the early phase after head and neck cancer treatment and a percentage of these patients remain on enteral feeding, even if there is not enough evidence to decide the optimal feeding method (PEG or nasogastric tube); criteria to stop enteral feeding are mainly related to severity of aspiration, even though there are differences in different centers (Logemann et al. 2008; Nugent et al. 2010).

Tracheostomy is frequently adopted in head and neck cancer patients for prevention of complication due to postoperative edema or hemorrhage, or where supraglottic and glottic edema may occur during chemoradiation. Management of tracheostomy tube and removal timing differ in different centers and there is no consensus at the moment. However, the effect of tracheotomy and the tracheotomy tube have been objects of several investigations. It is reported that the presence of an inflated cuff may impact the range of laryngeal motion and, thus, airway protection and cricopharyngeal opening (Ding and Logemann 2005). The possible causes of aspiration after tracheostomy may be divided into mechanical and neurophysiological factors. The mechanical factors are decreased laryngeal elevation and stasis of secretions in the upper airway and cervical esophagus due to local compressive forces exerted by the inflated cuff. The neurophysiologic factors were desensitization of the protective cough reflex and a loss of coordination of laryngeal closure. Nonetheless, in most cases swallowing deficit in tracheostomized patients is not related to the tracheotomy itself, but to the underlying disease which required the tracheotomy (Leder et al. 2005; Leder and Ross 2010). Therefore, increased aspiration risk or improvement in swallowing function after decannulation seems a clinical impression rather than a scientific evidence. Besides, it has to be underlined that an inflated cuff is not protective against aspiration in tracheostomized patients. It is key that prior to decannulation, the supraglottic airway should be evaluated to ensure successful removal of the tube; patients should undergo instrumental evaluation of swallowing in both a cuff-inflated and -deflated condition, thus returning those with adequate swallow function to oral intake.

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Behavioral Treatment of Oropharyngeal Dysphagia

Renée Speyer

Contents

Abstract

This chapter gives an overview of the most common behavioral techniques for treating oropharyngeal dysphagia, namely, bolus modification and management, motor behavioral techniques, sensory and neurophysiologic stimulation, postural adjustments, and swallow maneuvers. Each intervention is described along with its rationale. Furthermore, in light of the literature, the effects of dysphagia treatment are discussed as well as some methodological issues that emerged from a review of outcome studies.

1 Introduction

Evolution has endowed humans with an aerodigestive tract that facilitates the combined functions of breathing, vocalizing, and swallowing. The system poses a risk of aspiration and choking, however, as a result of the large supralaryngeal space created by the rather low position of the larynx in adults. Any dysfunction in this system may lead to swallowing problems, a condition known as dysphagia.

The effect on a person's health may be severe, as dysphagia can lead to dehydration, malnutrition, and aspiration pneumonia. It also affects people on a social and psychological level, making mealtimes stressful and taking the pleasure out of going to a restaurant. The possibility of suffocation, severe coughing, and vomiting may

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also heighten one's anxiety and lower self-esteem. All these consequences have a strong impact on quality of life as experienced by dysphagic patients (McHorney et al. 2002). Yet studies on the effects of therapy in oropharyngeal dysphagia give little attention to the effects on quality of life (Speyer et al. 2010). In contrast, the literature on the effects of dysphonia or voice problems suggests that quality-of-life questionnaires are essential to multidimensional voice assessment (Speyer 2008).

Dysphagia can be caused by a variety of diseases (e.g., neurological etiologies such as cerebrovascular accidents or degenerative diseases). But it can also manifest itself as a side effect of treatment, for example, of radiation or surgical intervention in patients with head and neck cancer. Usually, a team of specialists will be involved in the diagnosis and treatment. Within a multidisciplinary context or interdisciplinary setting, each caregiver will focus on a particular aspect of the swallowing problems. In general, after the initial assessment and treatment by medical specialists, nurses may be the first to perform any screening focused on dysphagia (Bours et al. 2009). Subsequently, mostly speech therapists take charge of any further assessment of the swallowing mechanism, the choice of behavioral intervention, and the follow-up evaluation. In the event of malnutrition or dehydration, or if facing severe nutritional risk, dieticians are drawn in to assure a sufficient caloric intake and provide the patient with nutritional supplements if necessary. Additionally, occupational therapists, physiotherapists, social workers, or psychologists may be involved in the multidisciplinary management of dysphagia.

Depending on the dysphagic findings, swallowing treatment may include medical, surgical, and/or behavioral options (Crary and Groher 2003). The medical option could entail dietary modifications to address underlying disease (e.g., diabetes or hypertension) or pharmacological treatment (e.g., antireflux medication or mucolytics). The surgical option covers a range of interventions: to improve glottal closure by medialization thyroplasty or injection of biomaterials; to enhance airway protection (e.g., total laryngectomy); or to optimize the pharyngoesophageal segment opening by stretching the lumen of the segment by dilation, surgical myotomy of the cricopharyngeal muscle, or chemodenervation using botulinum toxin injection. This chapter focuses on the third option: treatment by speech therapists using behavioral techniques.

Langmore (2001) describes three patterns of dysphagia: the ineffective swallow or incomplete bolus clearance; the misdirected swallow or impaired airway protection due to incomplete valving; and the delayed or mistimed swallow. Regarding the motor control of swallowing, the physiological parameters are intact sensation, briskness of initiation of movement, speed of movement, force or strength of movement, and amplitude of movement, as well as precision, timing, and coordination of movement. Therapeutic strategies used in swallowing therapy can be classified as rehabilitative and/or compensatory (Huckabee and Pelletier 1999). Interventions that are mainly intended to restore or improve the actual swallowing physiology are referred to as rehabilitative techniques. Compensatory techniques, in contrast, are intended to improve the ability to adapt and cope with the problem. Laryngeal adductor exercises to improve laryngeal valving are among the rehabilitative interventions, whereas strategies—such as the chin tuck posture—to improve laryngeal protection or the use of bolus modification are considered compensatory techniques.

Behavioral treatment of oropharyngeal dysphagia as carried out by speech therapists may include a range of interventions: (1) bolus modification and management; (2) motor behavioral techniques; (3) sensory and neurophysiologic stimulation; (4) postural adjustments; and (5) swallow maneuvers—or any combination of these (Speyer et al. 2010). Bolus modification refers to adjusting the viscosity, volume, temperature, and/or acidity of the bolus. Oral motor exercises may address different features of motor function, including strength, muscle tone, or coordination. Facilitation techniques cover a variety of interventions, ranging from surface electrical stimulation to thermal application at the anterior faucial pillars. Behavioral techniques

commonly used to modify the swallow physiology are postural adjustments and swallow maneuvers. Postural adjustments involve whole-body and head-position strategies. Swallow maneuvers include the (super) supraglottic swallow, the Mendelsohn maneuver, the effortful swallow, the Masako maneuver, and the Shaker exercise, among others. Adjunctive biofeedback may be used to facilitate processes of complex motor learning. In the following sections, these techniques will be described in detail.

It is now widely accepted that medical treatments should be scrutinized by scientific methods. This implies that allied health therapies should also be evaluated according to current standards of evidence-based medicine. An evaluation of therapy in oropharyngeal dysphagia thus falls squarely into this area of growing interest (Speyer et al. 2010). Besides describing the behavioral techniques commonly used in dysphagia therapy, studies should provide information on the effects of therapy in oropharyngeal dysphagia and the methodological issues that arise in the literature. Moreover, outcome studies are essential in order for caregivers to adjust and improve therapy for patients with oropharyngeal dysphagia.

2 Choice of Intervention Techniques

After medical and swallowing assessment, there may be a need for further intervention by speech therapists. However, many considerations may influence which intervention techniques are indicated for a particular patient.

First of all, many strategies require a patient's full cooperation as well as the capacity to follow complex instructions under the supervision of a therapist. It may be almost impossible to explain and teach certain strategies to patients with severe cognitive limitations. Furthermore, a patient has to be internally motivated or else have support from close relatives in order to keep trying. Having family support or motivated caregivers is essential, especially to implement newly learned swallowing behaviors or compensation strategies in daily life.

When making decisions about oral feeding, the patient's general health will have to be taken into account. The estimated safety of oral intake must be set off against the risk of aspiration pneumonia. Concerns about malnutrition or frailty, particularly among the elderly (Rofes et al. 2011), may call for additional tube feeding combined with nutritional supplements. Oral feeding may be fatiguing and thus place a burden on the patient. But the taste and smell of food or drink may also be rewarding and motivating, allowing the patient to enjoy family meals. In fact, participating in daily dining routines might have a huge impact on his quality of life. It is important to take a patient's food preferences and cultural background into account when advising on the possibilities of oral intake and on the use of food or liquid boluses in therapeutic settings. It should be realized that even when physicians and therapists consider oral intake no longer safe, a patient may still refuse tube feeding because of the reduced quality of life associated with such an intervention.

Obviously, the choice of interventions is also determined by the medical diagnosis and corresponding prognosis for a disease. For example, for someone diagnosed with neuromuscular disease, rehabilitative techniques may result in fatigue and exhaustion instead of increased muscle strength. Also, if spontaneous recovery of the swallowing functions can be expected during the acute period after a recent cerebrovascular accident, compensatory techniques may suffice to achieve sufficient oral intake. On the other hand, in palliative care, intervention will be restricted to minimize the effects of the dysphagia and optimize a patient's quality of life during the dying phase (Veerbeek 2008).

Finally, cultural aspects may influence the way swallowing disorders are treated. Basically, care for dysphagia may be organized differently in different countries. National health systems may differ in the ratio of therapists to patients being hospitalized and treated, or the training provided for therapists may differ with respect to the material being taught or the level of education required for certification. Besides national differences, the preferences or expertise of individual

therapists will also influence the treatment. Decisions on therapy frequency, length of therapy sessions, and treatment period, as well as the behavioral techniques applied, all play a role in the outcome of swallowing therapy.

3 Behavioral Treatment of Dysphagia

Regarding the range of behavioral interventions used in oropharyngeal dysphagia, various strategies may be found in the literature. The most common techniques and therapeutic approaches that can be applied by speech and language therapists are covered in the following six subsections.

Bolus modification and management will be considered first, followed by motor behavioral techniques, then sensory and neurophysiologic stimulation. Next, postural adjustments to facilitate swallowing will be presented. This fourth category includes general body positions such as lying down or side-lying. It also includes head positions, particularly adjustments like head extension, flexion, rotation, or tilt. The fifth category consists of a variety of swallow maneuvers: the supraglottic and super supraglottic swallow; the Mendelsohn maneuver; the effortful swallow; the Masako maneuver; and the Shaker exercise. Finally, the application of biofeedback will be discussed in the sixth subsection.

3.1 Bolus Modification and Management

Bolus modification and management is an approach that amounts to adjusting parameters such as viscosity, volume, temperature, and/or acidity of the bolus (Speyer et al. 2010). Modifying the rheologic properties of food and liquids may be one of the most common strategies applied by therapists. Ways to modify a food's consistency may vary from the use of commercial agents for thickening liquids to the blending of solid foods. By thickening thin liquids, clinicians seek to decelerate the bolus transport into the pharynx. By giving the patient more time to handle the bolus, the risk of penetration or aspiration may be reduced. Thicker liquids may be helpful in case of a delayed or mistimed swallow (Langmore 2001). Solid foods can be modified with a blender or masher. This reduces the need for chewing by smoothing the particulate nature of certain boluses or by blending foods of a mixed consistency. Patients who fatigue easily and are at risk of malnutrition may benefit from such a modified diet because of the diminished amount of effort required for swallowing. Those patients who have difficulty clearing a bolus may also show improved swallow behavior when managing boluses of smoothed consistencies compared to handling crumbly or noncohesive foods. In the latter case, when food consistencies do not allow easy bolus-forming or preparation for swallowing, adding liquids may be considered. Smoothened bolus consistencies reduce the amount of pharyngeal residue, thereby reducing the risk of delayed aspiration as well. There is great variety in the clinical terminology used for different bolus consistencies, and consensus is lacking. However, in order to determine the effectiveness of modifying food and liquids in patients with oropharyngeal dysphagia and compare study outcomes, uniform definitions for the rheologic properties of foods and liquids should be used (e.g., Dealy 1995).

To determine the appropriate volume of food or liquid boluses, the caregiver must know the patient's capacity to control and secure a safe oropharyngeal bolus transit with minimal postswallow residue. Larger quantities may require optimal alertness of the swallow mechanism, whereas boluses that are too small may provide insufficient sensory stimulus to initiate the swallowing act, as seen in patients with Parkinson's disease (Baijens and Speyer 2009). Swallowing may also be influenced by temperature; colder boluses are thought to trigger a quicker onset of the swallowing reflex. Improved timing has also been found when using acid boluses (Logemann et al. 1995). Naturally, when applying bolus modification, it should be kept in mind that achieving an optimal taste and

smell—that is, adjusted to an individual's preference—will provide rewarding and motivating factors, which can improve the oral intake and in turn the health status of a patient.

3.2 Motor Behavioral Techniques

Swallowing is the result of combined forces producing bolus passage through the pharynx and avoiding the larynx or airway (Langmore 2001). Lips, tongue, palate, and mandible have to operate in a coordinated order. Recruitment of adequate muscle strength, accuracy, and coordination thus results in a safe swallow. Therapists often draw upon oral motor exercises as part of dysphagia treatment in an effort to modify the swallowing mechanism.

The purpose of using oral motor exercises is to increase awareness of the bolus, to control and direct its passage, and to maximize the driving and propulsive force of the bolus in transit to the oropharynx. The exercises can address the various features of motor function: muscle strength, range of movement, muscle tone, steadiness, and accuracy. But regaining muscle function in terms of strength, range, and tone will in itself not result in normal swallowing unless the coordination of the swallowing mechanism has been optimized as well.

During the oral phase of swallowing, labial awareness and control are essential to achieve adequate lip closure and prevent drooling. There are exercises for the tongue to improve bolus propulsion, which is created by posterior tongue thrust, and to diminish bolus pocketing or residue, as well as to reduce the risk of pre-swallow aspiration because of failure of bolus control (Robbins et al. 2007). Stretching exercises may improve the range of mandible movement in patients with reduced flexibility, and nasal regurgitation might be diminished by stimulating the soft palatal closure using velopharyngeal closure exercises. Increased submental muscle force generation by Expiratory Muscle Strength Training (EMST) has been associated with subsequent increased hyolaryngeal complex movements (Troche et al. 2010).

3.3 Sensory and Neurophysiologic Stimulation

A normal sensory awareness in the oral cavity and pharynx is crucial to secure bolus manipulation and transportation. Sensory and neurophysiologic stimulation activities may involve changing the taste of boluses or their temperature, applying pressure, or using neuromuscular electrical stimulation, such as chemical, physical, and/or electrical stimuli to increase sensory input. It has been theorized that providing a sensory stimulus before a swallow attempt may serve as an alert or trigger to the nervous system and thereby help prepare the swallow mechanism for the subsequent swallow.

Effects of the use of sour boluses have been described in the literature, suggesting that an alteration is induced in swallowing behavior—for instance, improved timing of the onset of swallowing (Logemann et al. 1995). Other examples of food sensory properties refer to the use of menthol, capsaicin, or carbonated boluses: stimulation aiming at reduced oral and pharyngeal transit times and both stronger and shorter submental muscle contraction (Loret 2015). Usually, tactile-thermal application procedures consist of cold, tactile stimuli which may be presented to the anterior faucial pillars by stroking the pillars with an ice stick (Rosenbek et al. 1998) or with a cold laryngeal mirror taken from a cup of ice. These procedures are thought to reduce the delay in the initiation of swallowing, primarily in the pharyngeal phase. Besides temperature stimulation, pressure may be used to improve sensory awareness. For example, a spoon can be used to apply light pressure to the blade of the tongue during swallowing exercises.

The use of electrical stimulation has been the subject of several studies (e.g., Blumenfeld et al. 2006; Bülow et al. 2008; Lee et al. 2014; Li et al. 2015; Ludlow et al. 2007; Power et al. 2006; Shaw et al. 2007). Surface electrical stimulation (NMES) activates muscles by stimulating the intact peripheral motor nerves. The main treatment goals are to strengthen weak muscles and to help in the recovery of motor control (Freed and

Wijting 2003). Stimulation at the motor level can be distinguished from stimulation at the sensory level. As defined by Ludlow et al. (2007), motor stimulation is the maximum tolerated stimulation level resulting in maximum muscle contraction without spasm. The level of sensory stimulation is set by gradually raising the intensity of the current until the patient reports the first sensation of stimulation, usually a tingling of the skin. Depending on the exact placement of skin electrodes in the neck and face, different groups of muscles are stimulated.

3.4 Postural Adjustments

Postural adjustment may involve head-positioning strategies such as head-turn or chin-tuck maneuvers or whole-body positioning strategies. In the literature, it has been shown that adjusting the head and/or body position can reduce or eliminate the risk of aspiration (Lewin et al. 2001; Logemann et al. 1994a; Rasley et al. 1993; Shanahan et al. 1993). Postural variations redirect and facilitate the bolus flow; they may improve oral and pharyngeal transit times; and they decrease the amount of residue after swallowing (Bogaert et al. 2003). These techniques are intended to change the dimensions of the oropharynx in order to accomplish a safer swallow by compensating for anatomic deficiencies, sensory loss, or a reduced propulsion or clearance of the bolus. Postural adjustments can be introduced as temporary techniques during the process of recovery of the swallow function. Alternatively, they may become a permanent compensatory technique after rehabilitation to facilitate the changed swallow motor pattern or mechanism.

3.4.1 General Postural Adjustments

General postural adjustments usually concern body postures like lying down or side-lying. Both of these postures reduce the effects of gravity during swallowing and the amount of post-swallow residue. Side-lying may be beneficial when there is a difference in pharyngeal function between the left and the right side. The patient must lie down on the stronger side, thereby using gravity to direct the bolus or residue towards the stronger and/or more sensitive hemipharynx (Drake et al. 1997). However, changing the posture may have a negative influence on the esophageal motor functions. Patients with suspected gastroesophageal reflux disease or poor esophageal motility may benefit from an upright position during and after feeding. In case of nocturnal reflux, head-of-bed elevation may be recommended during the night, thus reducing or prohibiting acid reflux from the esophagus.

3.4.2 Head Postural Adjustment

Head postural adjustment includes the following positions: head flexion, head extension, head rotation, and head tilt. Head flexion, also called chin tuck, narrows the oropharynx and shortens the distance between the hyoid and the larynx, thus narrowing the laryngeal entrance (Bülow et al. 2001). It facilitates airway protection and may be used in patients with difficulties in oral control or timing. However, head flexion may also result in a weaker pharyngeal contraction during swallowing, causing problems of bolus propulsion in patients with pharyngeal weakness.

Unlike flexion, the aim of head extension is to widen the oropharynx by raising the chin, resulting in a head-back position. An extended head adjustment uses gravity for bolus propulsion into the pharynx. It may be useful in patients showing deficiencies in oral control and bolus transport during the oral (preparatory) phase of swallowing. It should be noted that head extension can only be used in patients with an intact pharyngeal phase. Head extension may also have a negative impact on the pharyngoesophageal segment, increasing the intraluminal pressure and decreasing the duration of relaxation of the segment (Crary and Groher 2003). Furthermore, head extension reduces laryngeal closure. Thus, the swallowing outcome may deteriorate in patients with diminished laryngeal airway protection or deficits in pharyngoesophageal segment functioning.

The head rotation or head-turn maneuver is mainly used in patients with unilateral deficits (unilateral pharyngeal or vocal fold paralysis or paresis). By rotating the head towards the

weakened side before swallowing, the swallowing tract or pyriform sinus on this damaged side is narrowed or even closed off. This directs the bolus down the stronger side (Logemann et al. 1989). The cricoid cartilage is pulled away from the posterior pharyngeal wall, reducing the pressure in the cricopharyngeal sphincter and thereby increasing the sphincter opening. This, in turn, will reduce bolus residue after swallowing as well as the risk of aspiration.

If the patient has unilateral oral and pharyngeal weakness on the same side, the head-tilt adjustment can be applied. When the head is tilted to the stronger side prior to the swallow, the bolus is directed down to the stronger side by utilizing the effects of gravity, thus reducing the amount of bolus residue (Rasley et al. 1993).

3.5 Swallow Maneuvers

Apart from sensory and motor behavioral techniques or postural adjustments, behavioral swallowing therapy may combine a variety of swallow maneuvers. These allow the patients to gain improved and voluntary control of the swallowing process, including bolus propulsion and airway protection. Many of these maneuvers require active patient participation and intensive practice to induce the necessary physiological modification of the swallow mechanism.

3.5.1 Supraglottic Swallow

The supraglottic swallow maneuver may be suitable and advisable under certain conditions: in the event of restricted airway protection or risk of aspiration as a result of a delayed pharyngeal swallow, a reduced or late vocal fold closure, or laryngeal sensory deficits. The maneuver consists of several steps. Patients are first asked to inhale and hold their breath. Next, they place a bolus in the mouth and swallow while still holding their breath. Then, after swallowing and before inhaling, patients cough voluntarily. Finally, they swallow again. The aim of this maneuver is to close the vocal folds by holding one's breath and to clear any possible residue from the laryngeal vestibule that may have entered while swallowing (Logemann 1998). However, vocal fold closure may not always be achieved in patients when holding their breath.

3.5.2 Super Supraglottic Swallow

Patients who do not succeed in bringing about the required airway protective closure during the supraglottic swallow maneuver need to perform a forceful breath-hold or super supraglottic swallow maneuver. Adding force to the swallow maneuver increases the chances of establishing a complete vocal fold closure and may promote shorter swallowing transit times (Logemann 1998). Patient instruction is similar to that given during the supraglottic swallow maneuver, except for the request to bear down hard instead of just performing a swallow act. The rationale for applying either the supraglottic maneuver or the super supraglottic maneuver is similar. The difference lies in the amount of effort required. By bearing down, the arytenoids are tilted anteriorly, closing the false vocal folds as well as the entrance to the trachea.

3.5.3 Mendelsohn Maneuver

The aim of the Mendelsohn maneuver is to increase the extent and duration of laryngeal elevation and thereby enhance the duration and width of the cricopharyngeal opening (Logemann 1999). While the upper esophageal sphincter is open, bolus transfer may be facilitated, leaving less oropharyngeal residue. It is hypothesized that by prolonging the swallow at the peak of hyolaryngeal elevation and pharyngeal contraction, the frequency and the amount of aspiration will decline due to improved upper esophageal sphincter opening. The maneuver is designed for patients with a reduced range of laryngeal movement or a discoordinated swallow. Patients are instructed to press lightly on the thyroid cartilage with their fingers, keeping it in a raised position for several seconds directly after swallowing. Because the instruction to patients could be confusing and difficult to translate into practice, it may be advisable to offer adjunctive biofeedback such as surface electromyography during training. With electromyographic bio-

feedback, patients will have immediate visualization of their muscle activity while learning the Mendelsohn maneuver.

3.5.4 Effortful Swallow

The effortful swallow is also known as the hard swallow maneuver. The technique increases the posterior motion of the tongue base during the pharyngeal swallow, thereby improving bolus clearance from the valleculae (Logemann 1999). Thus, the effortful swallow may be recommended in case of reduced posterior movement of the tongue base or reduced oropharyngeal pressure. During training, the patient is instructed to squeeze with maximal effort while swallowing. This maneuver is considered to be easily taught and easily implemented. However, because it may be difficult to determine which muscles are being activated or recruited and to what degree, instrumental measurements or biofeedback (e.g., surface electromyography) may be useful during rehabilitation.

3.5.5 Masako Maneuver

During swallowing, the pharyngeal wall tends to bulge forward, contacting the tongue base. It is hypothesized that pushing the tongue out and holding the anterior tongue between the teeth while swallowing will increase tongue base pressure and duration of contact to the posterior pharyngeal wall. This technique is known as the Masako maneuver or tongue holding. In case of lingual weakness, for example after oral surgery, it might be considered a rehabilitative technique (Lazarus et al. 2002). By practicing the Masako maneuver, the pharyngeal wall may be trained to compensate for the lack of posterior tongue movement. The presumed result will be improved contact between the tongue base and the pharyngeal wall, thus creating a pressure source for bolus propulsion through the oropharynx. It is not advisable to combine this maneuver with swallowing food boluses because of the reduced duration of airway closure, the increased residue after swallowing, and the increased delay in pharyngeal swallow initiation (Crary and Groher 2003).

3.5.6 Shaker Exercise

The Shaker exercise, otherwise known as the isotonic/isometric exercise, serves as rehabilitative training of the suprahyoid muscles responsible for the opening of the upper esophageal sphincter. This maneuver may solve the problem of a reduced cricopharyngeal opening, thus decreasing the amount of postswallow residue. Patients are instructed to lie supine and raise their head without raising their shoulders. This position is maintained for about a minute, after which the patient will rest before repeating this head-raising maneuver. A suprahyoid muscle-strengthening exercise program has been found to be effective in patients with deglutitive failure due to an abnormal upper esophageal sphincter opening. The exercise stimulates the restoration of oral feeding, diminishes postdeglutitive residue, and resolves aspiration (Shaker et al. 2002).

3.6 Adjunctive Biofeedback

Most swallow maneuvers require complex learning or relearning of motor patterns by patients. The application of biofeedback as an adjunct to swallowing therapy may facilitate the learning processes and be valuable in enhancing the rate of motor learning. Several techniques can be used to reveal some of the internal physiological events, normal and abnormal, using visual or auditory signals. Patients will be able to manipulate these otherwise involuntary or unfelt events (Basmajian and Deluca 1985).

The literature describes positive effects of surface electromyographic feedback in dysphagia treatment (e.g., Bogaardt et al. 2009; Crary et al. 2004). For example, when surface electrodes are placed under the chin, between the front of the mandible and the hyoid, muscle activity in the submental muscles can be recorded. During therapeutic sessions, patients are asked to perform repeatedly the Mendelsohn maneuver while being provided with visual feedback of the electromyographic recordings that present muscle activity as a function of a time frame. Patients are able to judge for themselves the amount of success in prolonging the laryngeal excursion as

they watch the sEMG signal on a computer monitor receiving immediate feedback of their swallowing performance (Bogaardt et al. 2009). Surface electromyographic feedback may help teach muscle relaxation, straining, and strengthening, and the feedback may stimulate muscle coordination.

Other biofeedback techniques may be helpful in functional rehabilitation as well. The use of flexible videoendoscopic biofeedback in swallowing therapy, serving as pharyngeal image biofeedback, has been studied. It proved to shorten the period of functional rehabilitation (Denk and Kaider 1997). Endoscopic feedback may be helpful to teach breath-hold maneuvers such as the super supraglottic swallow or the supraglottic swallow. It can help by visualizing the degree of vocal fold closure or residue at the laryngeal vestibule. Instead of endoscopic recordings, videoradiographic recordings of swallowing may be used. Another technique, cervical auscultation, might be used to listen to swallow sounds as an adjunct to clinical swallowing assessment (Leslie et al. 2004). It has been speculated that swallow sounds provide audible cues that permit a reliable dichotomized classification of normal swallowing versus dysphagic swallowing with signs of penetration and/or aspiration.

4 Effects of Behavioral Treatment

It is not only treatments by physicians that have to be evaluated according to current standards of evidence-based medicine, so do interventions by allied health professionals. By extension, the therapy outcome of behavioral treatment of oropharyngeal dysphagia needs objective evaluation as well (Speyer et al. 2010). According to Logemann (1999), therapy procedures should not be implemented until data on their efficacy and positive outcomes has been published in peer-reviewed journals. Indeed, clinicians must be acquainted with the relevant literature in order to justify their choice of therapy strategies during the clinical decision-making process. Therapists are responsible for collecting clinical efficacy and outcome data on each of their patients. Only then can they objectify whether the goals set at the start of therapy have been adequately met at the end. Evidence-based practice is thereby the result of combining the current research, the clinician's expertise, and the patient's values and preferences (Wheeler-Hegland et al. 2009).

Meanwhile, several reviews have been published summarizing the literature on the behavioral treatment of oropharyngeal dysphagia. Some narrative reviews provide extensive information about treatment possibilities (e.g., Logemann 2006). Other studies describe the effects of swallowing therapy in general as applied by speech and language therapists. The latter reviews are based on a systematic literature search using diverse electronic databases (e.g., Speyer et al. 2010). Furthermore, a few systematic reviews have restricted the literature search to certain types of therapy. Some are focused on neuromuscular electrical stimulation (Carnaby-Mann and Crary 2007; Chen et al. 2016; Clark et al. 2009). Others are confined to well-defined patient populations: for example, patients suffering from neurological disorders (Ashford et al. 2009) or oncological problems in the head and neck area (McCabe et al. 2009). In 2016, a position document was published by the European Society for Swallowing Disorders (ESSD) on oropharyngeal dysphagia as a geriatric syndrome (Baijens et al. 2016).

Therapists can thus turn to the existing literature for short, systematic overviews that will help them select therapeutic interventions when treating patients with oropharyngeal dysphagia. However, as many questions remain unsolved, clinicians will have to rely on their professional and clinical insights as well. For example, the success of therapy in a given patient population cannot necessarily be generalized to another population. Furthermore, behavioral dysphagia treatment may combine many different interventions for the same patient. The question is then, will the final outcome of therapy be equal to the sum of each component? Or will redundancy or antagonistic factors complicate the task of determining the actual efficacy of an individual patient's treatment? The literature thus has its shortcomings,

but it still provides grounds for discerning trends in therapy success, even though methodological issues in outcome studies on oropharyngeal dysphagia remain to be addressed.

4.1 Trends in Treatment Effects

An overview of the literature on the behavioral treatment of oropharyngeal dysphagia shows statistically significant positive effects of therapy (Speyer et al. 2010). However, considering the major impact of dysphagia on a patient's quality of life (McHorney et al. 2003), the number of evidence-based studies is rather small. Only effect studies that meet certain quality criteria—notably, concerning study design, patient attrition, randomization plus allocation of subjects to intervention groups, and blinding of outcome assessors—may provide information that is sufficiently reliable for the study outcome to be translated into clinical practice (Frymark et al. 2009; Speyer et al. 2010). Besides these methodological issues, it should be noted that the behavioral treatment of dysphagia frequently combines different interventions (Speyer et al. 2010). Thus, even though a combination of techniques has proven to be effective in eliminating or diminishing the symptoms, it may be hazardous to make any firm statements about the effectiveness of each of the separate elements. Still, a number of well-designed effect studies have demonstrated a positive therapy outcome of behavioral approaches in swallowing therapy. Therefore, some general conclusions may be drawn and certain trends may be distinguished.

One very common therapy intervention is bolus modification. In a study of two groups of dysphagic patients who had experienced aspiration pneumonia prior to therapy, Groher (1987) demonstrated that viscosity modulation (soft mechanical diet with thickened liquids versus pureed diet with thin liquids) could reduce the number of episodes of aspiration pneumonia. In a later study by Groher and McKaig (1995), the changes in dietary level in a group of persons in residential care were described after a single evaluation by a speech and language pathologist. Based on their findings, the authors concluded that many nursing home residents may be inappropriately assigned or maintained on mechanically altered diets. Regular re-evaluation of the residents' dietary level was strongly advised. Several other studies have demonstrated the positive effects of increasing bolus viscosity in dysphagic patients. Clavé et al. (2006) found that changing the viscosity from liquid to nectar and pudding significantly improved the efficacy and safety of swallowing by reducing aspiration and penetration in patients with dysphagia. However, the timing of the swallow response and bolus kinetic energy was not affected, whereas increasing the bolus volume significantly impaired the efficacy and safety of swallowing. Similar effects were found in patients with unilateral vocal fold paralysis with aspiration and/or penetration (Bhattacharyya et al. 2003). In particular, paste bolus consistencies were found to be safer than thin liquids, as the paste led to much less penetration or aspiration despite a higher prevalence of pharyngeal residue. Increasing the bolus volume and viscosity in acute stroke patients (Bisch et al. 1994) led to decreased pharyngeal delay times. However, patients exhibited very few significant effects of temperature on swallowing disorders or swallow measures. Hamdy et al. (2003) concluded that combined thermal (cold) and chemical (citrus) modification of water consistently altered swallowing behavior after cerebral injury, resulting in slowed swallowing and reduced swallow capacity. On the other hand, Logemann et al. (1995) found an improved onset of the oral swallow in response to sour boluses compared to non-sour boluses in neurological patients. Increasing the bolus volume increased oral residue and the number of swallows but decreased the swallow times (oral transit time, pharyngeal delay time, and pharyngeal transit time).

Recently, the ESSD published a white paper as a first step towards the development of a clinical guideline on bolus modification for patients with oropharyngeal dysphagia (Newman et al. 2016). This paper confirms that there is evidence for increasing viscosity to reduce the risk of airway invasion, but also emphasizes that new thickening agents should be developed to

avoid the negative effects of increasing viscosity on residue palatability and treatment compliance. In conclusion, although bolus modification seems effective in therapy, further research will be needed.

Rehabilitation of the swallowing process may include an exercise program consisting of diverse oral motor exercises. Even though the rationale seems obvious, a few studies have objectified the effects of intensive oral motor training. For instance, by means of an isometric lingual exercise program, Robbins et al. (2007) demonstrated that lingual exercises enable acute and chronic dysphagic stroke patients to increase lingual strength, with associated improvements in swallowing pressure, airway protection, and lingual volume. Oral motor exercises like tongue pull-back, yawn, and gargle tasks have also been found helpful to improve the maximum range of posterior movement of the tongue base (Veis et al. 2000). Troche et al. (2010) demonstrated in a randomized sham-controlled EMST trial; that swallow safety improved in persons with Parkinson Disease after EMST intervention. In a study by Nagaya et al. (2000), the initiation time of the swallowing reflex in dysphagic patients with Parkinson's disease was reduced significantly after a single session of swallowing training. That training consisted of tongue motion and resistance exercises, exercises to increase the adduction of the vocal folds, the Mendelsohn maneuver, and motion exercises for the neck, shoulders, and trunk. The orofacial regulation therapy by Morales, combining motor and sensory stimulation, indicated long-lasting improvement in oropharyngeal dysphagia in stroke patients, as measured by quality-of-life questionnaires, videofluoroscopy, and clinical evaluation (Hägg and Larsson 2004). In fact, many effect studies use oral motor exercises in combination with a variety of other intervention techniques such as bolus modification, postural adjustments, or swallow maneuvers (e.g., Denk et al. 1997; Elmståhl et al. 1990; Huckabee and Cannito 1999; Kiger et al. 2006; Martens et al. 1990; Masiero et al. 2007; Neumann 1993). Overall, the effects of therapy are positive. But because techniques are used in combination, the outcome of swallowing therapy cannot be attributed to any single oral motor training (Speyer et al. 2010).

A heightened sensory input may be achieved in several ways: by changing the volume, taste, or temperature of the bolus; by applying pressure; or with neuromuscular electrical stimulation. Bolus modification and management have already been discussed. While no effect studies have been conducted on pressure application, considerable attention has been given to thermal application at the anterior faucial pillars, as studied by Rosenbek et al. (1991, 1996, 1998) in stroke patients. They were given intensive daily training using a chilled laryngeal mirror for repeated strokes on the pillars. Nonetheless, after 2 weeks of thermal application alternating with 2 weeks without it, there was no strong evidence that their dysphagia had improved (Rosenbek et al. 1991). A later study by Rosenbek et al. (1996) used a cross-over design to study the short-term effects of thermal application, comparing stroke patients' swallowing during 10 min in a treated and untreated condition. Swallowing durations were highly variable within an individual and across the patient group. Still, compared to no treatment, thermal stimulation reduced the duration of staged transition and total swallow duration. A third study (Rosenbek et al. 1998) investigated the effects of four intensities of tactile-thermal application combined with the effortful swallowing maneuver in acute stroke patients. Patients were randomly assigned to receive 150, 300, 450, or 600 trials of tactile-thermal application per week over a period of 2 weeks. No single treatment intensity emerged as superior. Overall, positive changes on an aspiration-penetration scale and decreased duration of stage transition did not reach clinical or statistical significance. Possibly, the observed changes might have been due to physiological recovery. These findings were confirmed by Lazarus et al. (2011) in a review of the literature on efficacy of oral sensory-motor treatment, as the limited number of studies provided insufficient evidence to draw further conclusions on the utility of these interventions.

The effect of neuromuscular electrical stimulation on swallowing has been summarized in

several systematic reviews (Carnaby-Mann and Crary 2007; Chen et al. 2016; Clark et al. 2009). All reviews indicate some small but significantly positive treatment effects. At the same time, they point out the need for additional research in this area. Some studies provide cumulative evidence of the effectiveness of this therapeutic intervention as an adjunctive modality for treatment of swallowing disorders (e.g. Carnaby-Mann and Crary 2008), whereas others remain conservative in their conclusions. Ludlow et al. (2007) suggested that low levels of sensory stimulation might be an additional tool for dysphagia therapy, though emphasizing the need for further systematic studies. Others found no significant differences between neuromuscular electrical stimulation compared to traditional swallowing therapy in a group of stroke patients (e.g., Bülow et al. 2008). A recent review of post-stroke dysphagia by Chen et al. (2016) confirmed that, even though swallow treatment with neuromuscular electrical stimulation seemed more effective than treatment without neuromuscular electrical stimulation, evidence was insufficient to indicate that neuromuscular electrical stimulation alone was superior to swallow therapy. Future research will provide more evidence on whether or not neuromuscular electrical stimulation would be useful for patients with swallowing problems.

Various outcome studies have described the effects of postural changes, mainly head postural adjustments, which may affect the direction and speed of the bolus transport through the oropharynx. Overall, evaluations of therapy outcome, mainly in single-session study designs, have noted significant improvement from postural changes. For example, the use of head flexion or chin tuck in a group of aspirating patients with esophagectomy (Lewin et al. 2001) and in a patient population with diverse neurological pathologies (Shanahan et al. 1993) significantly reduced the number of patients who were aspirating. In a group of patients with unilateral dysphagia, head rotation towards the paretic side increased the fraction of the bolus swallowed and the opening diameter of the upper esophageal sphincter (Logemann et al. 1989). However, studies on head tilt or general postural adjustments are rare and may be limited to single-case studies (e.g., Drake et al. 1997).

Behavioral swallow therapy may include diverse maneuvers, such as the supraglottic or super supraglottic swallow. However, to determine the isolated effect of a single maneuver, studies must restrict the intervention protocol to one specific swallow maneuver. This would entail providing outcome data before and after this intervention, without introducing other treatment techniques during the same therapy period. In general, the treatment outcomes reported in the literature have been positive.

Logemann et al. (1994b) described an improved oral intake in patients after supraglottic laryngectomy when using the supraglottic swallow. When the super supraglottic swallow was applied in a group of patients with head and neck cancer (Logemann et al. 1997), fewer motility disorders were observed. Furthermore, the maneuver eliminated or reduced aspiration in some of the patients. Using electromyographic biofeedback (sEMG) during the Mendelsohn maneuver in stroke patients and patients with head and neck cancer, the oral intake was improved and reflected a trend towards statistical significance (Crary et al. 2004). McCullough et al. (2012) demonstrated that use of the Mendelsohn maneuver as a rehabilitation exercise improved the duration of the hyoid maximum anterior and superior movement and the duration of the upper esophageal sphincter opening. Evidence for the benefit of the effortful swallow is limited. For example, in two case studies by Lazarus et al. (2002) describing two patients with dysphagia as a result of oncological problems, using the effortful swallow seemed to help them attain near-normal swallowing pressures and an improved oropharyngeal clearing efficiency. The literature also provides little evidence for the benefit of the Masako maneuver, although the rationale has been well described (e.g., Fujiu et al. 1995; Fujiu and Logemann 1996). The Shaker or head-raising exercise was studied in a randomized controlled trial by Shaker et al. (2002) in a group of dysphagic patients with diverse etiology and an abnormal upper esophageal sphincter opening. After a head-raising

exercise program, significant therapy effects were found. These included an improvement in the anteroposterior diameter of the sphincter opening and the anterior laryngeal excursion, a decrease in postdeglutitive residue, and the resolution of aspiration.

Several studies have been published on adjunctive biofeedback in dysphagia treatment with promising results. Denk and Kaider (1997) studied the use of videoendoscopic biofeedback in conventional therapy for patients with dysphagia associated with oncological disorders. Their main conclusion was that the functional rehabilitation period was shorter than in conventional therapy without adjunct biofeedback. In a study of tube-dependent stroke patients who had been previously treated by speech therapists without success, Bogaardt et al. (2009) demonstrated that using surface electromyography as biofeedback to standard exercises could result in a significantly positive change in oral intake. Some of these patients could have the percutaneous enteral gastrostomy tubes removed after therapy. In a study by Crary et al. (2004), the positive effects of electromyographic biofeedback on the functional oral intake in stroke patients and patients following treatment for head and neck cancer also showed a trend towards statistical significance. The findings of both studies are in line with the study outcome reported by Huckabee and Cannito (1999). In a population of chronic dysphagic patients with brain stem injury, they studied the effects of electromyography biofeedback and cervical auscultation biofeedback in combination with traditional swallowing therapy, including swallow maneuvers, oral motor exercises, and compensatory mechanisms. After therapy, significant improvements were observed in swallowing physiology as measured by severity ratings of videofluoroscopic swallowing studies, diet level, and pulmonary status.

Many more evidence-based studies have been published on issues related to outcomes in swallowing therapy using a combination of diverse intervention techniques (e.g., see review by Speyer et al. 2010). Actually, in daily practice, most clinicians or speech therapists will use a variety of treatment strategies instead of restricting therapy to a single technique. However, as stated before, it is hard to distinguish the particular contribution of each intervention in a behavioral therapy approach that is based on a combination of different techniques. Still, most of these studies show statistically significant, positive therapy effects (e.g., Carnaby et al. 2006; Kasprisin et al. 1989; Lin et al. 2003; Prosiegel et al. 2005). But when trying to determine whether swallowing therapy is effective or not, no blanket answer can be given. Many questions about the effects of therapy in oropharyngeal dysphagia as applied by speech and language therapists remain unanswered, while many methodological problems still need to be resolved.

4.2 Methodology in Outcome Studies

An overview of the literature on the effects of behavioral swallowing therapy in oropharyngeal dysphagia raises some questions about evidence-based practice in this field. The diverse methodological problems to which many of the outcome studies attest warrant further attention. First, it is striking that, despite the great impact on a patient's quality of life, relatively few studies have been published on this subject. Furthermore, among the research that has been done, there is great diversity in study design and treatment protocol.

To evaluate treatment outcome, most effect studies use a limited set of assessment instruments. They strongly favor videofluoroscopy, which seems to be the gold standard in effect studies, whereas very few studies use quality-of-life questionnaires (Speyer et al. 2010). Since correlations between therapy effects as measured by different assessment tools may vary greatly, it may be difficult to draw comparisons between therapy outcome from studies not using similar tools. But even if studies do use the same assessment instrument, for example, videofluoroscopic swallowing recording, the choice of outcome parameters, rating procedures, or protocols may differ considerably. Outcome parameters may be restricted to a single dichotomized variable such

as the presence or absence of aspiration, but they may also consist of multiple complex temporal and/or spatial variables measured in digitized videofluoroscopic recordings using specialized software packages (e.g., Clavé et al. 2006). There may be differences in the number of swallow trials performed, in the bolus consistencies and bolus volumes, or in the clinical cut-off points (e.g., wet voice, coughing, aspiration, or unsafe swallow as judged by the clinician during the videofluoroscopy). Many studies do not explain how the recordings have been assessed. A single expert or clinician can make the assessment during a patient's visit to an outpatient clinic for dysphagia, but it could also be performed afterwards by a panel of blinded expert raters. Using panel ratings, information can be gathered about the intra- and inter-rater reliability of scoring visuoperceptual variables in videofluoroscopic or fibreoptic endoscopic recordings of swallowing. The limited comparability may reflect the diversity of assessment protocols, in the absence of universal standardization.

Furthermore, the frequent use of unvalidated or unreliable instruments or questionnaires may generate data that can neither be interpreted adequately nor make any useful contribution to formal assessment. Some psychometric reviews in the field of dysphagia (e.g., Speyer et al. 2014, 2017; Timmerman et al. 2014) have addressed the need to determine all psychometric properties of assessments before use in clinical practice. These reviews referred to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN), which is a taxonomy of measurement properties and definitions for examining health-related patient-reported outcome measures (Mokkink et al. 2010a, b). In these reviews, many assessments showed incomplete data or lacked sufficient overall psychometric quality. As the use of a particular assessment can only be justified on its reliability and validity and its discriminative and evaluative purposes, these findings warrant further research and the development of new assessments with sufficient psychometric rigor (Speyer 2013).

Another issue is the enormous variation in the duration of therapies as found in the literature. Quite a few studies claim significant, usually short-term improvement after a single treatment session, such as when using postural adjustments or bolus modification. In contrast, other studies describe long series of therapy sessions. Very few trials have described any long-term treatment effects; for example, in a recent critique of the literature on swallowing and non-swallowing exercises, Langmore and Pisegna (2015) concluded that only a minority of exercises prescribed for patients with dysphagia showed sufficient evidence for long-term improvement in swallowing. The generalizability or comparability of effect data may be another problem. Treatment techniques that have been found effective in a specified patient population may not have the same positive therapy outcome when applied in a different group of dysphagic subjects with other etiological problems or patient characteristics, such as differences in age, severity of the dysphagic symptoms or underlying diseases, or motivation for therapy. Some studies use very small patient populations or restrict the number of therapists involved in treatment, thus introducing bias when no therapy effects may be found. The absence of significant therapy effects may be the result of a non-effective swallowing intervention. But in case too few subjects or therapists have been included, the absence of clear effects may also be due to an underpowered study design or a clinician lacking sufficient expertise. A further methodological issue concerns blinding of the assessors or raters to the pre- and posttreatment data; another concerns the random allocation of patients to different treatment groups. In the case of controlled trials, the intention-to-treat principle must be applied to all participating patients. Studies that present outcome data but lack baseline measurements cannot be considered useful for determining therapy effects. But also, studies intervening during a period of spontaneous recovery need to compensate for this positive tendency, for example by introducing a control group receiving no treatment (in the absence of any ethical objections) to enable group comparisons afterwards. Finally, the data or statistical analyses have to be well organized and documented.

The strength of the evidence supporting the key clinical recommendations for treatment is referred to as the level of evidence of a study (Siwek et al. 2002). The highest level of evidence can be achieved in randomized controlled trials. In the area of speech and language, however, many case studies have been published which are considered to be at the lower level of evidence. The literature abounds with examples of hierarchic schemes arranging study designs according to their presumed level of evidence. However, the methodological quality of an article is highly dependent on the degree to which the above-mentioned quality indicators have been taken into account, indicators such as the random allocation of subjects to an intervention or control group, the blinding of the outcome assessors, or patient attrition (Jüni et al. 2006; Khan et al. 2003; Lazarus et al. 2011). In light of the diverse methodological problems and the heterogeneity of study designs and therapies, statistical pooling of outcome data remains a hazardous challenge.

Conclusion

This chapter has given an overview of the most common behavioral intervention techniques in oropharyngeal dysphagia, pointing out new developments in the field. However, it has also emphasized the need for more evidence-based research and clinical trials. Progress in that direction is needed to objectify the effects of the intervention techniques, giving due attention to the reliability and validity of the measurement tools used.

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Rheological Aspects of Swallowing and Dysphagia: Shear and Elongational Flows

Edmundo Brito-de la Fuente, Mihaela Turcanu, Olle Ekberg, and Críspulo Gallegos

Contents

Abstract

The physiological process of swallowing is not only a simple transfer of liquids or food boluses from the oral cavity to stomach, but also a complex succession of voluntary and involuntary phases that involve complex deformations and require the entire functionality of the oropharyngeal apparatus. When this functionality is affected, people experience dysphagia, which is described as a combination of symptoms that impairs or reduces patient's ability to swallow.

On the other hand, food texture also plays an important role in swallowing. Each liquid viscosity or bolus consistency is processed differently in the mouth and it requires a specific amount of lubrication and effort in order to be easily and safely swallowed. The science of rheology deals specifically with the deformation and the flow of matter. Therefore, rheology helps to characterise food behaviour in complex deformations, such as those encountered during swallowing. The knowledge of the deformability and flow of the bolus is particularly important in understanding and managing dysphagia.

In this chapter, a short introduction on dysphagia is given. Section "Rheology Fundamentals" is dedicated to the science of rheology and provides a short description of the material functions relevant to this field. Dysphagia-designed products are used as examples. Section "Rheology, Swallowing and Dysphagia: State-of-the-Art" focuses

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on the rheological aspects of bolus oral processing and transport. A practical example on how shear rheology helps to tailor new dysphagia products is also included. Aspects about the role of extensional rheology in the swallowing are introduced. This section is followed by the rheological characterisation of different nutritional products in the presence of saliva. The role of human saliva in the management of dysphagia is as well discussed. The chapter ends with some concluding remarks.

1 Introduction

Eating and drinking are essential activities of human beings. Swallowing is a complex mechanism involving many muscles and nerves, aiming to transport the bolus into the stomach. As boluses may have several solid-like consistencies and drinks different viscous levels, rheology is involved. This science helps to better understand how a bolus is deformed or flows during the swallowing process. Knowledge of the deformability/flow of a bolus is important to better understand dysphagia or swallowing impairment.

The physiological process of swallowing is not only a simple transfer of liquids or food boluses from the oral cavity to stomach, but also a complex succession of voluntary and involuntary phases that involve complex deformations and require the entire functionality of the oropharyngeal apparatus. When this functionality is affected, people experience dysphagia, which is described as a combination of symptoms that impairs or reduces patient's ability to swallow.

On the other hand, food texture plays also an important role in swallowing. Each liquid viscosity or bolus consistency is processed differently in the mouth and requires a specific amount of lubrication and effort in order to be easily and safely swallowed. The science of rheology deals specifically with the deformation and the flow of matter. Therefore, rheology helps to characterise food behaviour in complex deformations/flows, such as those encountered during swallowing. The knowledge of the deformability and flow of the bolus is particularly important in understanding and managing dysphagia.

In this short introduction, the role of rheology in the framework of dysphagia is highlighted. Section 2 is dedicated to the science of rheology and provides a short description of the material functions relevant in this field. Dysphagia-designed products are used as examples. Section 3 focuses on the rheological aspects of bolus oral processing and transport. A practical example of how rheology helps to tailor new dysphagia products is included. The role of extensional rheology in bolus deformation and swallowing is also introduced. This section is followed by the rheological characterisation of different nutritional products in the presence of saliva. Therefore, the role of human saliva in the management of dysphagia is as well discussed. The chapter ends with some concluding remarks.

2 Rheology Fundamentals

2.1 Basic Concepts of Rheology

Rheology deals with the study of deformation and flow of continuous media, in particular of fluids. In April 1929, Prof. Eugene C. Bingham, from Lafayette College in Easton (PA, USA), proposed the term "rheology", inspired by Simplicius' aphorism "Panta Rhei" ("everything flows") in order to describe "the study of deformation and flow of matter" (Walters 2010).

It is well accepted that a given material can behave as a solid or a liquid depending on the timescale of the deformation process (Gallegos and Walters 2010). In other words, the mechanical properties of all materials are time dependent; that is, they vary with time in response to an applied load or deformation. This phenomenon is simply a consequence of the *Second Law of Thermodynamics*, according to which a portion of the imparted energy of deformation is always dissipated as heat by viscous forces even while the rest may be stored elastically. The dissipation is neither instantaneous nor infinitely slow and is therefore a rate process. It is this that renders the physical properties time dependent (Emri 2010).

The rheological behaviour of materials ranges from virtually purely elastic (no dissipation) to virtually purely viscous (instantaneous dissipation), showing both elastic and viscous properties in between. The behaviour of many materials, such as puddings for dysphagia nutritional support, typically falls between the extremes and they are defined as viscoelastic. The behaviour may be expressed suitably by the Deborah number, *De*; the ratio of the characteristic time of the material, λ on which molecular rearrangements take place; and the characteristic time of the deformation process, T (Reiner 1964):

$$De = \frac{\lambda}{T} \tag{1}$$

High Deborah numbers correspond to solid-like behaviour and low Deborah numbers correspond to liquid-like behaviour. A material can appear solid-like either because it has an infinite characteristic time or because the deformation process is very fast. One obvious consequence of this is that even mobile liquid systems with very low characteristic times can behave like elastic solids when exposed to a very fast deformation process (*viscoelastic liquids*). In contrast, solid-like materials will be able to flow for a time (*viscoelastic solids*).

Material viscoelasticity can be observed in many types of deformation, such as shear, compression, or extension. In the case of shear, small deformations are applied in order to establish parameters representative of the original microstructure of the material (linear viscoelastic behaviour), while high deformations are used to define material behaviour under flow (non-linear viscoelastic behaviour). In extensional flow, materials are also submitted to high deformations and the parameters extracted are, as well, relevant for the flow process (non-linear viscoelastic behaviour).

2.2 Linear Viscoelastic Behaviour

Viscoelastic materials possess both viscous and elastic properties in differing degrees. For a viscoelastic material, internal stresses depend not only on the instantaneous deformation, but also on the whole past history of deformation. When a material is deformed, thermodynamic forces immediately begin to operate to restore the minimum-energy state. Movement from the rest state represents storage of energy. If a material is submitted to deformations or stresses small enough so that its rheological functions do not depend on the value of the deformation or stress, the material response is said to be in the linear viscoelasticity range (Gallegos and Martínez-Boza 2010).

Consider the function $\gamma(t)$ as representative of some cause (shear strain) acting on a given material, and the shear stress, $\sigma(t)$, the effect resulting from this cause (Dealy and Wissbrun 1995). A variation in shear strain, occurring at time t_1, will produce a corresponding effect at some time later, t, which can be expressed as

$$\sigma(t) = G(t - t_1)\delta\gamma(t_1) \tag{2}$$

$G(t - t_1)$ is known as the relaxation function, or the relaxation modulus, which is a property of the material and relates cause and effect. It is a function of the time delay between cause and effect.

A series of N changes in the shear strain, each occurring at a different time, will contribute cumulatively to the stress at some later time (Boltzmann superposition principle). Thus,

$$\sigma(t) = \sum_{i=1}^{N} G(t - t_i)\delta\gamma(t_i) \tag{3}$$

If the change in strain occurs continuously, the sum may be replaced by an integral:

$$\sigma(t) = \int_{-\infty}^{t} G(t - t')d\gamma(t') \tag{4}$$

This linear constitutive equation is appropriate to describe the behaviour of materials subjected to shear deformations, which is one of the most relevant types of deformation concerning food swallowing process. However, this equation can be generalised for any type of deformation that can be applied to the material.

To gain information on the influencing function that relates cause and effect, a number of small strain experiments are used in rheology. Some of the most common techniques are stress relaxation, creep and sinusoidal oscillations (Ferry 1980; Macosko 1994; Dealy and Wissbrun 1995; Barnes 2000). Different experimental methods can be used as they might be more convenient for a particular material or because they provide data over a particular time range.

2.2.1 Stress Relaxation

Stress relaxation after a step strain is the fundamental way in which the relaxation modulus is defined. In this experiment, a sample is suddenly deformed at a given strain, γ_0, and the resulting stress is measured as a function of time. The relaxing stress data can be used to determine $G(t)$:

$$G(t) = \frac{\tau(t)}{\gamma_0} \tag{5}$$

The evolution of the linear relaxation modules for a selected enteral pudding formulation is presented in Fig. 1.

Knowledge of the evolution of the linear relaxation modulus with time is essential to model the non-linear viscoelastic behaviour of complex fluids, as it will be reviewed in Sect. 2.3.

2.2.2 Creep

Creep experiments are particularly useful for studying certain practical applications where long times are involved. In a creep experiment, a constant stress, σ_0, is instantaneously applied on a sample, and the resulting strain is recorded versus time. The strain values obtained as a function of time can be used to calculate the compliance, $J(t)$, as follows:

$$J(t) = \frac{\gamma(t)}{\tau_0} \tag{6}$$

A typical evolution of the creep compliance with time for a selected pudding formulation is shown in Fig. 2. This creep compliance function is independent of the shear stress applied in the linear viscoelasticity range.

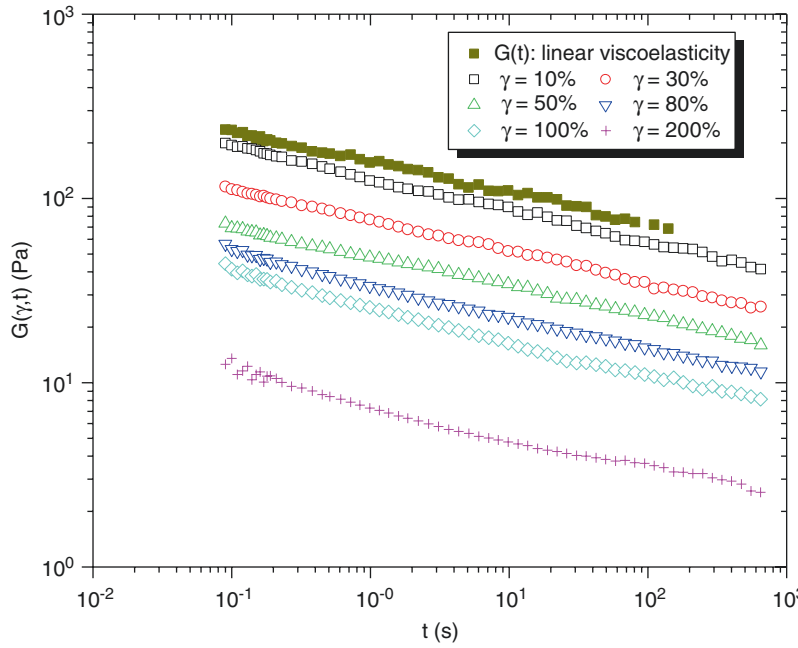

Fig. 1 Evolution with time of the linear and non-linear relaxation modulus for a selected enteral pudding formulation

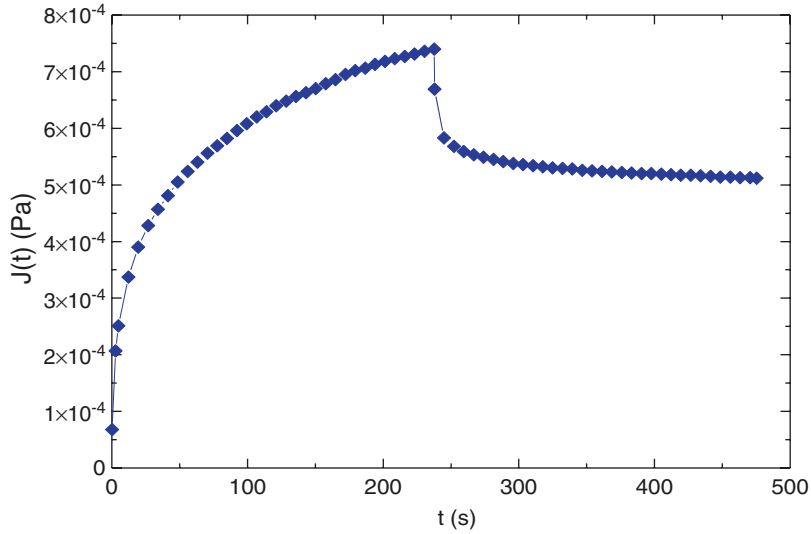

Fig. 2 Typical evolution of the creep compliance with the elapsed time, in the linear viscoelasticity region, for a selected pudding formulation

2.2.3 Small-Amplitude Oscillatory Shear

The most common type of test to characterise the linear viscoelastic behaviour of complex fluids is the small-amplitude oscillatory shear.

In a similar way to performing relaxation or creep tests over a range of time, oscillatory tests over a range of frequency can be conducted. It is obvious that short times correspond to high frequencies, and long times to low frequencies.

In this test, the material is subjected to a simple shearing deformation by applying a sine-wave-shaped input of stress or strain (Macosko 1994; Dealy and Wissbrun 1995; Barnes 2000). If a sinusoidal strain is applied, the shear strain as a function of time is given by

$$\gamma(t) = \gamma_0 \sin(\omega t), \tag{7}$$

where γ_0 is the strain amplitude and ω is the frequency.

By differentiating, the evolution of shear rate with time is obtained:

$$\dot{\gamma}(t) = \gamma_0 \omega \cos(\omega t) = \dot{\gamma}_0 \cos(wt), \tag{8}$$

where $\dot{\gamma}_0$ is the shear rate amplitude.

The resulting stress is measured as a function of time:

$$\sigma(t) = \sigma_0 \sin(\omega t + \delta), \tag{9}$$

where σ_0 is the stress amplitude and δ is a phase shift, also known as loss angle.

The stress data can be analysed by decomposing the stress wave into two waves of the same frequency, one in phase with the strain wave (sin ωt), and the other one 90° out of phase with this wave (cos ωt):

$$\sigma = \sigma' + \sigma'' = \sigma' \sin \omega t + \sigma'' \cos \omega t. \tag{10}$$

Two dynamic moduli can be then defined:

$$G' = \frac{\sigma_0'}{\gamma_0}, \tag{11}$$

elastic, storage or in-phase modulus, and

$$G'' = \frac{\sigma_0''}{\gamma_0}, \tag{12}$$

viscous, loss, or out-of-phase modulus.
The loss tangent is given by

$$\tan \delta = \frac{G''}{G'}, \tag{13}$$

In addition, a complex modulus, G^*, can be defined as

$$\sigma_0 = \left|G^*\right|\gamma_0, \tag{14}$$

G' and G'' being its real and imaginary parts, respectively:

$$G^*(\omega) = G'(\omega) + iG''(\omega). \tag{15}$$

For a purely elastic material, there is no viscous dissipation, and no phase shift, and the loss modulus is zero. In contrast, there is no energy storage for a purely viscous liquid, the storage modulus being zero and the loss angle being 90°.

Typical evolutions of the storage and loss moduli with frequency for enteral nutrition puddings, as a function of ageing, are shown in Fig. 3.

Another way to interpret the results obtained from small-amplitude oscillatory shear tests is in terms of a sinusoidal strain rate. Two new material functions are then defined:

$$\sigma(t) = \dot{\gamma}_0[\eta'(\omega)\cos(\omega t) + \eta''(\omega)\sin(\omega t)], \tag{16}$$

where

$$\eta' = \frac{\sigma_0''}{\dot{\gamma}_0} = \frac{\sigma_0}{\dot{\gamma}_0}\sin\delta = \frac{G''}{\omega}, \tag{17}$$

and

$$\eta'' = \frac{\sigma_0'}{\dot{\gamma}_0} = \frac{\sigma_0}{\dot{\gamma}_0}\cos\delta = \frac{G'}{\omega}. \tag{18}$$

The complex viscosity is

$$\eta^*(\omega) = \eta'(\omega) - i\eta''(\omega) \tag{19}$$

and its magnitude is

$$\left|\eta^*\right| = \frac{\sigma_0}{\dot{\gamma}_0}\sqrt{(\eta')^2 + (\eta'')^2}. \tag{20}$$

The reciprocal of the complex modulus is also defined as an additional oscillatory material function, the complex compliance, J^*:

$$J^*(\omega) = \frac{1}{G^*(\omega)} = J'(\omega) + iJ''(\omega), \tag{21}$$

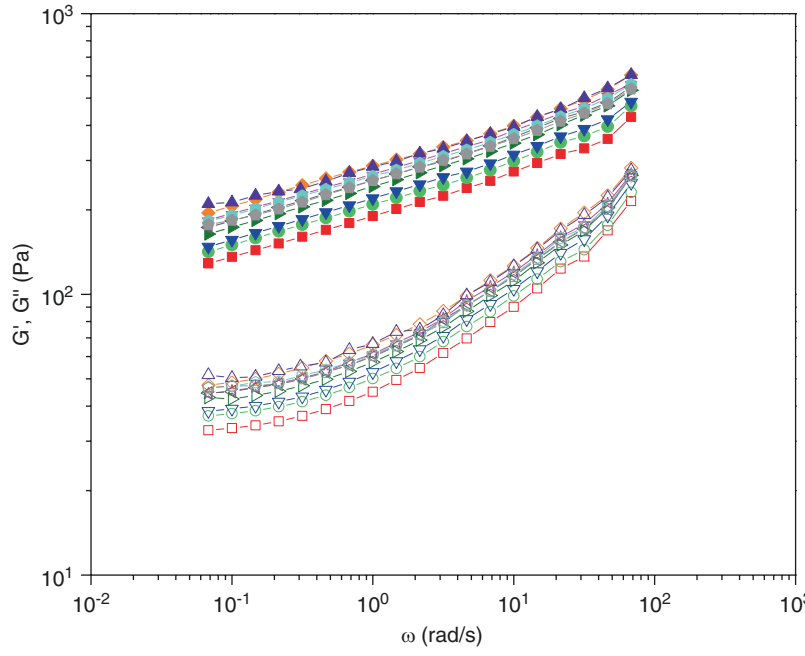

Fig. 3 Evolution of the storage and loss moduli with frequency for a selected enteral nutrition pudding, as a function of ageing

where the real and imaginary components of the complex compliance are related to those of the complex modulus by

$$J'(\omega) = \frac{G'(\omega)}{G'^2(\omega) + G''^2(\omega)}, \quad (22)$$

$$J''(\omega) = -\frac{G''(\omega)}{G'^2(\omega) + G''^2(\omega)}. \quad (23)$$

2.2.4 Linear Viscoelastic Behaviour Modelling

For dispersions with complex microstructure, their dynamic linear viscoelastic behaviour can be described by a generalised Maxwell model (Mackley et al. 1994; Madiedo and Gallegos 1997a, b):

$$G' = G_e + \sum_{i=1}^{N} G_i \frac{(\omega\lambda_i)^2}{1+(\omega\lambda_i)^2}, \quad (24)$$

$$G'' = \sum_{i=1}^{N} G_i \frac{\omega\lambda_i}{1+(\omega\lambda_i)^2}, \quad (25)$$

where G_e is the elastic modulus. This model considers a superposition of a series of N independent relaxation processes, each process having a relaxation time, λ_i, and a relaxation strength, G_i. The resulting distribution or spectrum of relaxation times can be used to compare the mechanical behaviour of complex fluids.

On the other hand, in the case of the linear relaxation modulus,

$$G(t) = \sum_{i=1}^{N} G_i \left[\exp(-t/\lambda_i)\right]. \quad (26)$$

However, Madiedo and Gallegos (1997a, b) have also used a continuous relaxation, or retardation spectrum, $H(\lambda)$, to represent the linear viscoelasticity data of food emulsions, which provides a continuous function of relaxation times, λ, rather than a discrete set. Thus, the linear relaxation modulus and the dynamic viscoelasticity functions are now defined as

$$G(t) = \int_{-\infty}^{\infty} H(\lambda)\left[\exp(-t/\lambda)\right] d(\ln\lambda), \quad (27)$$

$$G'(\omega) = G_e + \int_{-\infty}^{\infty} H(\lambda)\frac{\omega^2\lambda^2}{1+\omega^2\lambda^2} d(\ln\lambda), \quad (28)$$

and

$$G''(\omega) = \int_{-\infty}^{\infty} H(\lambda)\frac{\omega\lambda}{1+\omega^2\lambda^2} d(\ln\lambda). \quad (29)$$

As the spectra cannot be directly obtained from experimentation, the problem that generally arises is the calculation of these spectra from experimental data of a given linear viscoelasticity function. This, of course, implies inverting the corresponding integral equation relating the spectrum with the selected material function. However, it is well known that the resolution of these equations is an ill-posed problem, as small changes in the rheological functions give rise to strong oscillations in the spectra. For that reason, many approximation methods have been developed to perform such calculations (Madiedo and Gallegos 1997a, b).

2.3 Non-linear Viscoelastic Behaviour

At sufficiently large deformations, many products for dysphagia nutritional support show non-linear viscoelastic characteristics. This behaviour is clearly observed, for instance, by applying increasing deformation during relaxation tests or by characterising the viscous flow behaviour of these formulations in a wide range of shear rates.

2.3.1 Viscous Flow Behaviour

Thus, as a consequence of their complex microstructure, complex fluids (i.e. puddings for dysphagia nutritional support) show linear viscoelastic characteristics at sufficiently small deformations, and a non-Newtonian viscous response in a certain range of shear rates. The flow curve of a non-Newtonian fluid shows an apparent viscosity, shear stress divided by shear rate, which depends on flow conditions, i.e. shear rate, and, sometimes, even on the kinematic history of the fluid element under consideration (see Sect. 2.3.2).

Complex materials may show different types of non-Newtonian behaviour. However, the most common one found in dysphagia nutritional support product rheology is the shear-thinning behaviour. This viscous response is characterised by a continuous decrease in apparent viscosity as shear rate increases (Partal and Franco 2010).

However, most shear-thinning fluids with a complex microstructure also exhibit Newtonian regions at low and high shear rates. The resulting constant viscosity values at very low and high shear rates are known as the zero-shear-rate-limiting viscosity, η_o, and the high-shear-rate-limiting viscosity, η_∞. Thus, the apparent viscosity of a shear-thinning fluid decreases from η_o to η_∞, with increasing shear rate. These fluids are known as "structured fluids", because shear rate affects material microstructure and their viscous behaviour changes according to the evolution of its microstructure. Data in a sufficiently wide range of shear rates may illustrate this complete viscous behaviour (see Fig. 4).

Several equations have been proposed to model the non-Newtonian flow behaviour of food dispersions. Some of them have a theoretical basis, whereas others are curve fittings which provide empirical relationships for the shear stress (or apparent viscosity) versus shear rate curves (Bird et al. 1987; Carreau et al. 1997; Chhabra and Richardson 1999). The more widely used viscosity models that may represent the "structured" fluid response of these binders are described next.

Ostwald-de Waele's or Power-Law Model

The relationship between shear stress and shear rate (plotted on log-log scale) for a shear-thinning fluid can often be approximated by a straight line over a wide shear rate range (or stress):

$$\sigma = k\dot{\gamma}^n \tag{30}$$

where k is the consistency index and n is the flow index. Thus, the apparent viscosity for the so-called power-law (or Ostwald-de Waele) fluid is given by

$$\eta = k\dot{\gamma}^{n-1}, \tag{31}$$

For $n = 1$, the fluid shows Newtonian behaviour. For a shear-thinning fluid, the index n ranges from 0 to 1, so that the smaller the value of n, the greater is the degree of shear-thinning. The value of k can be viewed as the value of apparent viscosity at the shear rate of unity.

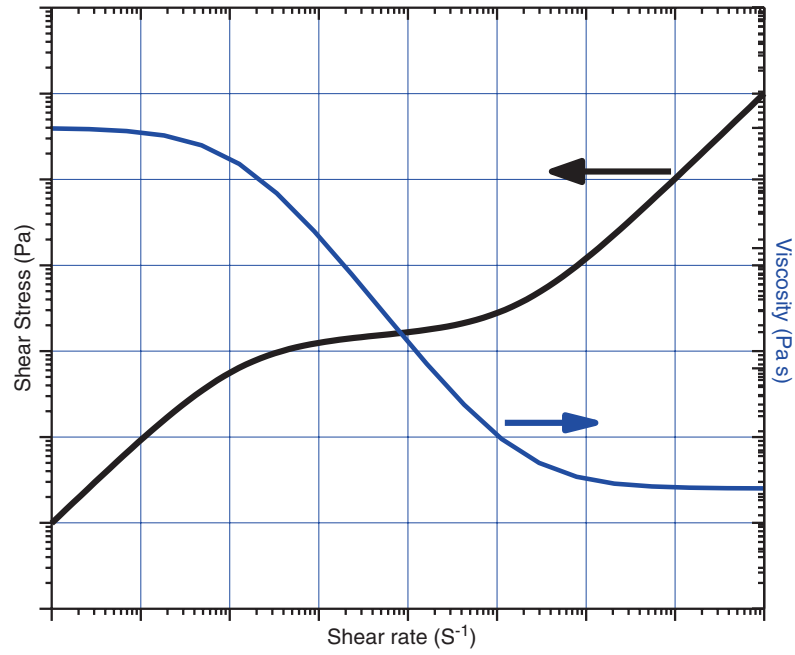

Fig. 4 Log-log plot of the viscous flow behaviour of a standard "structured" fluid

Sisko's Model

This three-parameter model predicts a shear-thinning region at intermediate shear rates and a Newtonian viscosity, η_∞, at high shear rates:

$$\eta = \eta_\infty + k\dot{\gamma}^{n-1}, \tag{32}$$

where η_∞ is a high-shear-rate-limiting viscosity and k and n are parameters related to the consistency and flow indexes. With the use of the third parameter, this model provides a somewhat better fit to some experimental data, being particularly recommended to describe the material flow behaviour in the high shear rate region.

Carreau's Model

Based on molecular network considerations, Carreau (1972) proposed the following viscosity model, which incorporates both low and high shear-rate-limiting viscosities, η_o and η_∞:

$$\frac{\eta - \eta_\infty}{\eta_o - \eta_\infty} = \frac{1}{\left[1 + (\lambda\dot{\gamma})^2\right]^s} \tag{33}$$

Parameter $\lambda = 1/\dot{\gamma}_c$, where $\dot{\gamma}_c$ is a critical shear rate for the onset of the shear-thinning region. On the other hand, s is a parameter related to the slope of the power-law region. This model can describe the so-called structural behaviour over a very wide range of shear rate.

2.3.2 Transient Flow Behaviour

Shear viscosities of complex fluids for dysphagia nutritional support viscosity, in many cases, are not only a function of the applied shear stress or shear rate, but also on the length of time that the shear rate or stress is applied on the sample. A suitable way of measuring time-dependent effects during viscous flow is to follow the evolution of viscosity with time, after applying a constant shear rate (see Fig. 5). As can be deduced from this figure, viscosity decreases with time down to a steady-state value.

This behaviour is known as thixotropy. All fluids that develop a certain level of complex microstructure can show this behaviour. Thixotropy is a reversible phenomenon; that is, it reflects the finite time taken by the fluid to change its microstructure, which is fully recovered after cessation of the perturbation. The occurrence of thixotropy implies that the flow history of the fluid has to be taken into account when making predictions of its flow behaviour.

Different models can be found in the literature that adequately describes the thixotropic response of complex fluids (Partal and Franco 2010). In this sense, Figoni's model has successfully been used to fit the transient flow behaviour of enteral puddings for dysphagia nutritional support. Figoni's model is a stress decay model with two kinetic functions:

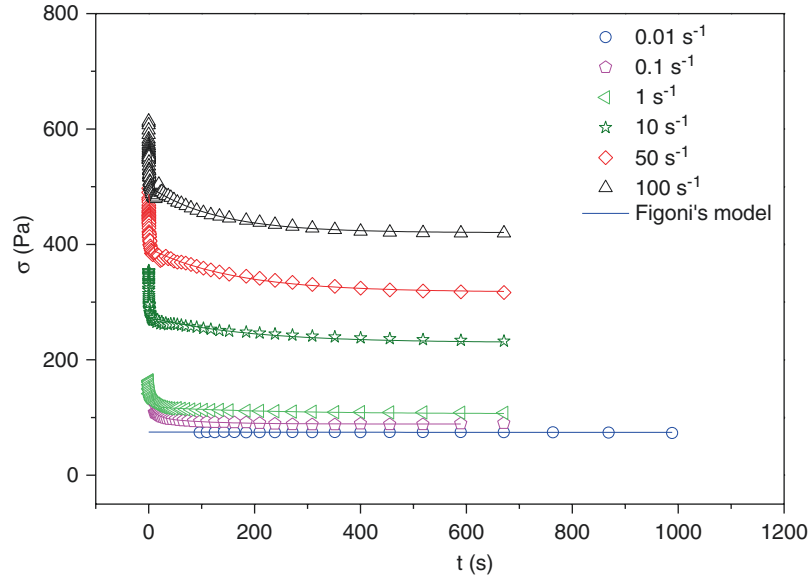

Fig. 5 Transient shear flow tests, at different constant shear rates, for a selected pudding-like formulation

$$\sigma - \sigma_e = (\sigma_{01} - \sigma_{e1})\exp(-k_1 t) + (\sigma_{02} - \sigma_{e2})\exp(-k_2 t), \quad (34)$$

where k_1 and k_2 are kinetic constants at short and long times, respectively. Subindexes 0 and e refer to initial and equilibrium stresses, respectively.

2.3.3 Non-linear Viscoelasticity Modelling

One approach to describing non-linear behaviour (transient and steady state) of rheologically complex materials is based on continuum mechanics principles, aiming to establish a rheological constitutive equation to replace the Boltzmann principle (Eq. 4).

Wagner (1979) proposed the introduction of a non-linear memory function in the constitutive equation for non-linear viscoelasticity. Taking into account that the relaxation of stress following a large step strain (non-linear relaxation modulus) can often be separated into time-dependent and strain-dependent factors (see Fig. 1, parallel lines in a log-log plot for different strains), Wagner proposed the use of a memory function, defined as the product of the linear memory function and the *damping function* (reflecting strain influence), an empirical function whose parameters are determined by fitting experimental data.

$m(t - t')$ is the memory function, related to the linear relaxation modulus by differentiation:

$$m(t - t') = \frac{dG(t - t')}{dt'}, \quad (35)$$

where t is the time at which stress is evaluated and t' a time prior to the time t at which the stress is evaluated.

If the time-strain separability for the non-linear relaxation modulus is possible, and considering only the simple shear component, the Wagner model can be expressed as

$$\sigma\left(t, \dot{\gamma}\right) = -\int_{-\infty}^{t} \frac{dG(t - t')}{dt'} h(\gamma)\gamma(t, t')dt', \quad (36)$$

where $\tau(t, \dot{\gamma})$ is the transient shear stress and $h(\gamma)$ is the damping function, which can be easily calculated from the ratio between the non-linear relaxation modulus, $G(\gamma, t - t')$, and the linear relaxation modulus, $G(t - t')$ (Rolón-Garrido and Wagner 2009):

$$h(\gamma) = \frac{G(\gamma, t - t')}{G(t - t')}. \quad (37)$$

Different types of damping functions have been proposed. For instance, according to Wagner (1979)

$$h(\gamma) = \exp(-k\gamma), \quad (38)$$

and assuming that the evolution of the linear relaxation modulus with time can be described by a generalised Maxwell model:

$$G(t) = \sum_{i=1}^{n} g_i e^{-(t - t')/\lambda_i}. \quad (39)$$

The steady-state viscosity is then

$$\eta(\dot{\gamma}) = \sum_{i=1}^{n} \frac{g_i \lambda_i}{(1 + k\lambda_i \dot{\gamma})^2}. \quad (40)$$

Nevertheless, Quinchia et al. (2011) have also used a damping function described by the Soskey-Winter model, which fits fairly well the experimental results obtained with different types of emulsions, and more specifically with puddings for dysphagia nutritional support:

$$h(\gamma) = \frac{1}{1 + a\gamma^b}. \quad (41)$$

Figure 6 shows the experimental and calculated values of $R(t)$, the ratio between the shear stress after instantaneous imposition of a constant shear rate, $\sigma(t)$, and the steady-state stress, $\sigma(\infty)$, for a transient flow test carried out on a selected pudding. As it can be observed, the Wagner model fits fairly well the experimental results obtained.

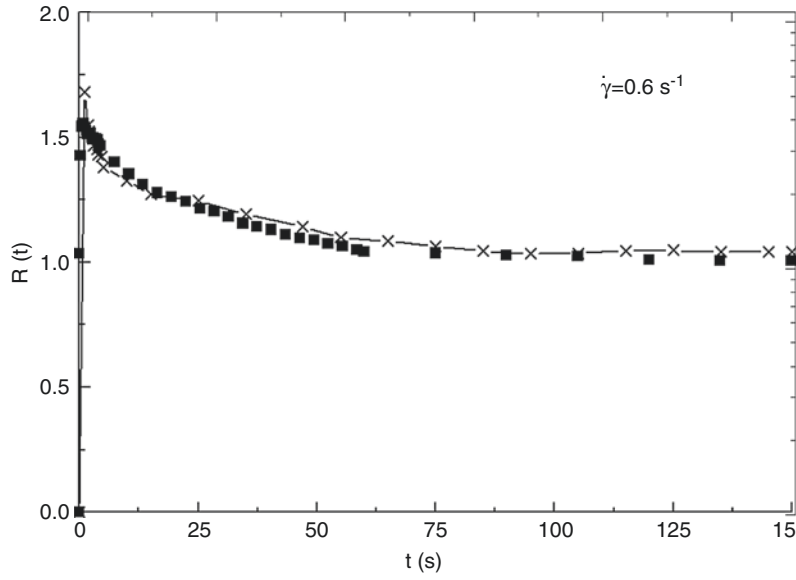

Fig. 6 Relationship between transient and steady-state stress values, and Wagner's model fitting, as a function of shear time for a selected pudding sample (*squares:* model predictions, *crosses*: calculation from experimental values)

2.4 Extensional Behaviour

Viscoelastic materials, such as puddings for dysphagia nutritional support, behave differently in shear and extensional flows. In shear, the velocity profile triggers rotation and gradual alignment of molecules in the flow direction, while in extensional flow the molecules are aligned, oriented and stretched. Streamlines are parallel in shear flows; therefore large strains can be achieved by going to long residence times (Macosko 1994). In extensional flows, the streamlines diverge (or converge), which elongates the material in one direction and contracts it in the other flow directions. The process of stretching induces high tension (and large strains) in the material structure and requires more energy than the simple rotation or shear processes (Petrie 2006a). Therefore, compared to shear, extensional flows are more sensitive to material structure.

Extensional flow is less discussed in the framework of dysphagia, even though it might play a key role in the interpretation of bolus swallowing (Waqas et al. 2017; Gallegos et al. 2017). For viscoelastic materials, the resistance to flow in extension can exceed by several orders of magnitude the resistance to shear flow (Clasen et al. 2006; Chhabra and Richardson 2008). A way to quantify material resistance to flow in extension is through the determination of extensional viscosity.

The main extensional flows are illustrated in Fig. 7. According to the type of extensional deformation imposed (uniaxial, biaxial, planar), it is possible to define different extensional viscosities, such as uniaxial, biaxial or planar extensional viscosity.

Uniaxial elongational flow is the easiest to reproduce experimentally, since it implies a simple stretching of a fluid volume, initially considered undeformed (Fig. 7b). When a material undergoes uniaxial elongation, it will stretch in one direction and contract in the other two directions, with a half of the imposed deformation. In this type of flow, the entire volume is involved in the deformation, and the velocity gradient has components in all the flowing directions.

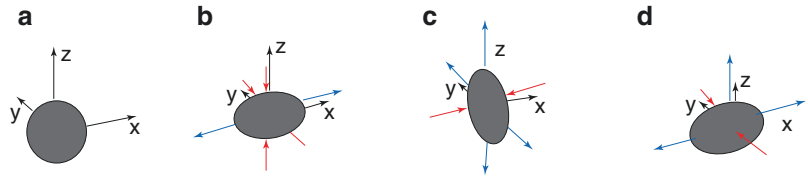

Fig. 7 Elongational flows: undeformed volume (**a**), uniaxial deformation (**b**), biaxial deformation (**c**) and planar deformation (**d**). In *blue*, deformation directions; in *red*, contraction directions (image rebuilt after Sajjadi et al. 2013)

Shear viscosity implies the existence of a shear stress, while extensional viscosity requires a difference of normal stresses (James and Walters 1993):

$$\eta_e(\dot{\varepsilon}) = \frac{\tau_{zz} - \tau_{rr}}{\dot{\varepsilon}}, \tag{42}$$

where the deformation rate is

$$\dot{\varepsilon} = -\frac{1}{L}\frac{dL}{dt} \tag{43}$$

and L is the material length during deformation.

Extensional viscosity of a Newtonian fluid, the so-called coefficient of viscous traction, was firstly determined by Trouton, as being three times its shear viscosity (Trouton 1906). Trouton ratio was therefore introduced as the ratio between extensional and shear viscosity of a material (Sridhar et al. 1991):

$$\eta_e(\dot{\varepsilon}) = \frac{\eta_e(\dot{\varepsilon})}{\eta_e(\dot{\gamma})}\bigg|_{\dot{\gamma}=\sqrt{3}\dot{\varepsilon}}. \tag{44}$$

The magnitude of Trouton ratio is conditioned by the internal structure of the material. For viscoelastic materials, for instance, at very small extension rates, the extensional viscosity obeys Trouton's rule, while at high deformation rates, Trouton ratio can be very high (Phan-Thien 2002).

Apart from extensional viscosity, another way to monitor the viscoelasticity of a material during elongation is through its relaxation time. This parameter represents the time needed for a material to return to its equilibrium state after being deformed for a certain period of time. In shear, the Zimm theory offers a theoretical framework to calculate relaxation times of semi-dilute solutions, based on zero shear viscosity data (Tirtaatmadja et al. 2006), while for semi-dilute and concentrated solutions, the relaxation time can also be determined by using either small-amplitude oscillatory shear measurements or primary normal stress growth in large shear deformation (Mackay and Boger 1987). The relaxation time in extensional flow can be obtained from filament stretching experiments (Miller et al. 2009). In general, the relaxation time obtained from extensional flow data is often higher than that obtained from shear flow data (Liang and Mackley 1994; Clasen et al. 2006; Tirtaatmadja et al. 2006).

Several methods have been proposed to generate purely extensional flows in viscoelastic fluids. Fibre spinning, bubble collapse, stagnation flows, contraction flows, entrance flows and capillary breakup extensional flows are some of the most successful (Macosko 1994, Sachsenheimer 2014).

Filament stretching (Tirtaatmadja and Sridhar 1993; Papageorgiou 1995; McKinley et al. 1999) and filament break-up rheometry (Entov and Hinch 1997; Anna et al. 2001) are the most commonly used extensional techniques nowadays. Other devices designed to characterise material behaviour in extensional flow include the opposed-jet apparatus (Fuller et al. 1987), spine-line rheometers and drop pinch-off set-ups (Tirtaatmadja et al. 2006). More recently, contraction flow devices have been used to characterise dysphagia-designed fluids (Nyström 2015; Nyström et al. 2015; Rodd et al. 2005; Waqas et al. 2017).

The filament break-up technique has previously been used to characterise polysaccharide solutions, such as chemically modified guar (Duxenneuner et al. 2008; Torres et al. 2014), casein-starch mixtures (Chan et al. 2007), modified hydroxyethyl cellulose (Patruyo et al. 2002) and Mamaku gum (Jaishankar et al. 2015). A considerable number of studies, however, concern synthetic polymers (Anna et al. 2001; Clasen et al. 2006; Clasen 2010, Sridhar et al. 1991).

In this method, a fluid sample is held between two parallel plates, the lower plate is fixed, while the upper plate movement is controlled by a computer. A step-stretch deformation is applied. This triggers a self-driven uniaxial elongation flow, in which surface tension is counterbalanced by the extensional stresses in order to produce the capillary thinning of the filament and eventually its break-up. An optical laser system is used to measure the filament diameter evolution at the middle distance between the upper and the lower geometry plates (Entov and Hinch 1997). This evolution is then used to measure the apparent extensional viscosity of the test fluid.

Whereas during capillary thinning the midfilament diameter decays linearly with time for purely Newtonian fluids (Papageorgiou 1995; Anna et al. 2001), the decay is exponential for elastic fluids, leading to a longer break-up time compared to inelastic solutions (Anna et al. 2001). The relaxation time of the fluid can be calculated from the rate of midfilament decay (Liang and Mackley 1994; Entov and Hinch 1997):

$$\dot{\varepsilon} = -\frac{1}{D_{\text{mid}}(t)}\frac{dD_{\text{mid}}(t)}{dt} = \frac{2}{3\lambda_e}. \qquad (45)$$

Several issues have been reported regarding the use of filament stretching to extract relaxation times in extension, the main problem being the lack of controllability of the stretching process (Petrie 2006a). The operator does not control the strain applied to the sample and must rely on a balance of viscous, elastic and capillary forces to maintain the sample in a near-cylindrical shape. This is particularly difficult in the case of dysphagia-designed fluids.

Food oral processing and swallowing may include strong extensional components in addition to shear, which could influence both the mouthfeel perception and the swallowing pattern of dysphagia fluids.

Yet, uniaxial extensional characterisation of puddings for dysphagia support has not sufficiently been studied. This is mainly due to the difficulty in achieving homogenous or pure extensional flows with such complex fluids, as well as reaching steady state before non-uniform deformation or material rupture (Petrie 2006a; Macosko 1994; Mackley et al. 2013; Turcanu 2017).

When complex fluids, such as dysphagia-designed fluids, are stretched, a transition from exponential to linear decrease of the diameter with time is observed at long times (i.e. at high strain). This is interpreted as a quasi-Newtonian state, for which the polymer coils are aligned and

stretched at a maximum extend, prior to break-up. The apparent steady-state extensional viscosity can be calculated from the filament thinning using the equation proposed by McKinley and Tripathi (2000):

$$\eta_e = -(2x-1)\frac{\sigma}{\frac{dD_{\text{mid}}(t)}{dt}}. \tag{46}$$

where σ is the material surface tension and x is a geometry coefficient that takes into account how the filament shape deviates from a uniform cylindrical thread due to inertia and gravity. The value $x = 1$ is considered for ideally elastic fluids, while $x = 0.7127$ for highly viscous fluids (McKinley and Tripathi 2000).

To calculate the apparent extensional viscosity, the diameter measurements can be fitted with a spline and then differentiated numerically or, in the case of well-defined fluids, such as polymer solutions, the diameter can be fitted with an appropriate function and then differentiated with respect to time (Fig. 8). The second option should be applied only when excellent qualitative fitting can be obtained; otherwise it could mask the real diameter decay and therefore the right interpretation of the thinning process.

In order to obtain the apparent extensional viscosity, the surface tension of the fluid is required. It should be mentioned that dysphagia puddings are highly concentrated fluids, and the measurement of their surface tension is not always straightforward. In many cases, extrapolation or mathematical fittings are used to extract such surface tension values.

On the other hand, many other factors, such as surface tension, material homogeneity as well as inertial and geometrical forces, may affect the filament thinning and break-up time of complex fluids, such as those used in dysphagia treatment.

Due to their high molecular complexity, dysphagia-designed fluids show very different behaviour during stretching. Their extensional properties can be directly quantified through the capacity to form filaments. Cylindrical filaments and longer filament lifetimes are elasticity markers, while necking during elongation, apparition of droplets during break-up and short filament lifetimes are correlated to low elastic fluid properties. In Fig. 9, the apparent extensional viscosities of three different dysphagia puddings for nutritional support are illustrated.

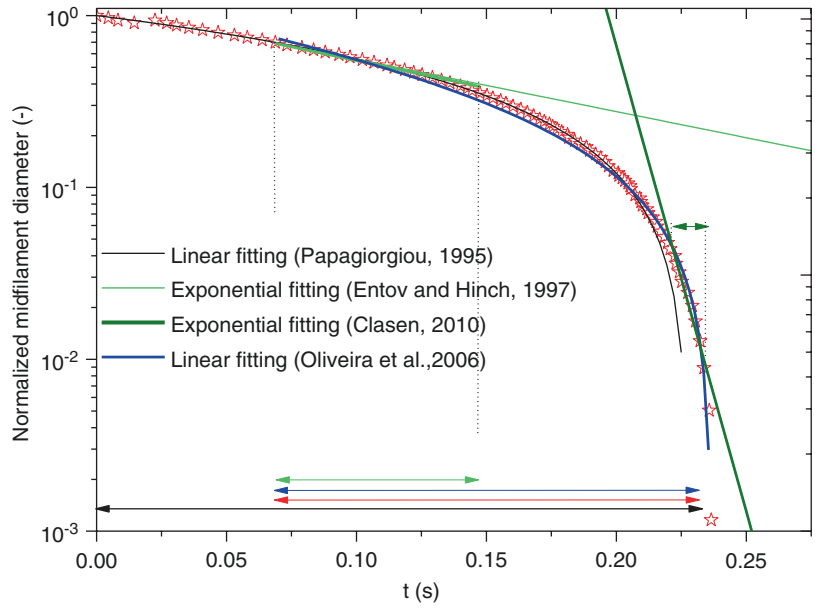

Fig. 8 Normalised midfilament evolution of a dysphagia-designed fluid for oral nutritional support

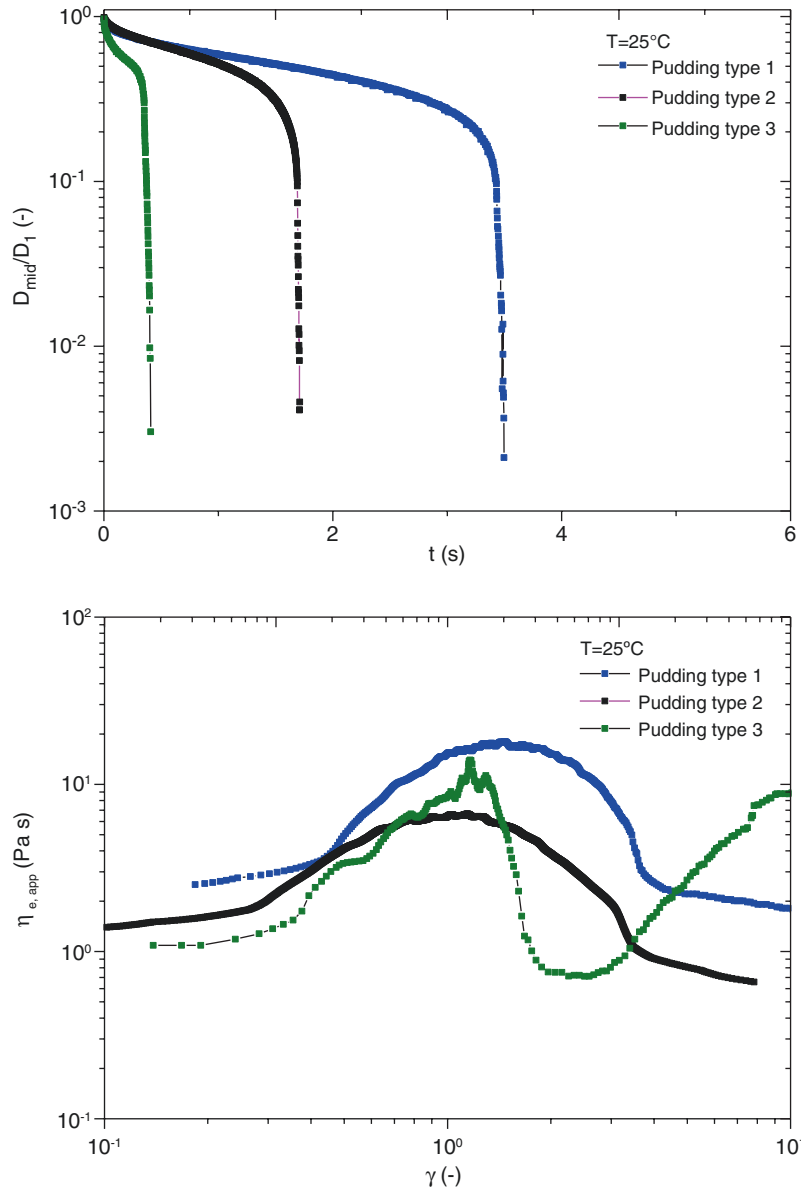

Fig. 9 Extensional behaviour of different dysphagia-designed puddings for nutritional support

3 Rheology, Swallowing and Dysphagia: State of the Art

3.1 Shear Rheology in the Swallowing Process

There are several angles from which dysphagia may be analysed. The medical side is perhaps the one that has attracted most scientists and researchers in this field and includes several disciplines, such as neurology, radiology and gastroenterology, as well as speech and language pathologists and therapists. Nowadays, it is well accepted that dysphagia management process begins with an interdisciplinary assessment from which a treatment plan is designed and developed with the goal of minimizing the risk of aspiration, pneumonia, malnutrition and dehydration.

However, knowing that dysphagia is a combination of symptoms affecting patient's ability to swallow, one may analyse dysphagia from another angle, which is from the fluid kinematics/dynamics point of view. This may be considered as the *dysphagia engineering point of view*.

Fluid kinematics deals with describing the motion of fluids without necessarily considering the forces and moments that cause the motion. Fluid kinematics describes velocity, acceleration and visualisation of flow motion. On the other hand, fluid dynamics deals with the analysis of the specific forces necessary to produce the motion.

A kinematic/dynamic analysis of dysphagia aims to gain insights into the mechanisms of bolus and liquid flow during swallowing. Because rheology is the study of the deformation and flow of matter, the connection between dysphagia and rheological properties of food bolus is clear.

Viscosity is a key parameter in rheology and describes fluid resistance to flow. Since shear deformations are assumed to dominate the swallowing process, shear viscosity is the main fluid property considered both for diagnosis and management of dysphagia. Viscosity is a function of temperature, pressure and, for non-Newtonian fluids, flow rate. In the swallowing process, no pressure or temperature fluctuations are assumed, while flow rate is considered to vary during the different stages of the swallowing process.

The velocity spectrum of bolus flow in the pharynx and oesophagus has been determined using different techniques. So far, the "gold standard" videofluoroscopy has been the most frequently used. Other non-radiological techniques like high-resolution manometry (Takasaki et al. 2008; Bredenoord and Smout 2008; Bardan et al. 2006), intraluminal impedance (Omari et al. 2006) and ultrasonic pulse Doppler method (Hasegawa et al. 2005) have also been used to generate bolus transit velocity data and then conduct a swallowing kinematic analysis. Instrumental models mimicking the physiological swallowing were also proposed (Lee et al. 2013). Regardless of the technique used for kinematic analysis of dysphagia, it is clear that bolus transit time and thus velocity are highly dependent on both patient's medical conditions and bolus rheology.

A nonexhaustive literature review on kinematic analysis of dysphagia has been gathered in Table 1. The purpose is to show how the bolus transit velocity changes depending on the swallowing phase and the rheological properties of the bolus. The results from Table 1 clearly suggest that the bolus transit velocity is considerably higher for the pharyngeal phase than for the oesophageal phase. On the other hand, as bolus viscosity increases, the bolus transit velocity decreases, as expected.

By using some of the information given in Table 1, and under the assumption that bolus deformation only occurs under shear, an estimation of the shear rates that may be associated with the swallowing was performed, and the results are shown in Table 2. As the results clearly suggest, bolus deformation (i.e., shear rate) during the swallowing process is greater for the pharyngeal phase than for the oesophageal phase. In general, the shear rate spectrum for the whole swallowing process goes from 1 to 1000 s^{-1}. This is in line with previous estimations (Steele et al. 2003). Experimental values in vivo are not available owing to the complex and irregular oral geometry and the lack of reliable techniques. However, several authors have tried to estimate shear rates associated with the swallowing process. Nicosia and Robbins (2001), using a rheological approach based upon parallel plates to simulate the squeezing effect of food bolus from the oral cavity into the pharynx, predicted a shear rate of 180,000 and 3000 s^{-1} for bolus viscosities of 10^{-3} Pa s and 1 Pa s, respectively. These values are very unlikely in reality. On the other hand, Meng et al. (2005) estimated a shear rate of around 400 s^{-1} for water, which seems to be more reasonable.

Recently, some fundamental concepts about the kinematics of a food bolus during swallowing were introduced (Burbidge et al. 2016). Even with the simplification of a Newtonian bolus, the difference between slow flows (laminar flows—viscosity controlled) and fast flows (turbulent flows—inertia controlled), as well as the difference between a pressure-driven and a force-driven

Table 1 Kinematic analysis of dysphagia

Reference	Bolus transit velocity (cm/s)	Comments
Pharyngeal phase		
Nguyen et al. (1997)	37.1 ± 1.1	Bolus head traversing the pharyngeal region. Data from Multiple Intraluminal Impedance (MII)
	28.3 ± 2.1	Bolus head velocity decreases as viscosity increases
	9.6 ± 1.0	Mean pharyngeal propulsion velocity of bolus body
Williams et al. (2001)	42	Bolus head entering into the UES. Data from high-resolution manometry
Omari et al. (2006)	8.13[a]	Bolus tail estimated from MII and videofluoroscopy
Hasegawa et al. (2005)	50	Transit time of 1 s
Bardan et al. (2006)	37.6 ± 8.1	Bolus head traversing the pharyngeal region. Data from videofluoroscopy
	10.3 ± 3.0	Bolus tail average velocity as it traversed the pharynx and passed through the UES
Esophageal phase		
Li et al. (1994)	1–4	Peristaltic waves velocities from videofluoroscopy—Kahrilas et al. (1988)
Nguyen et al. (1997)	9.6 ± 1.4	Head liquid bolus (low viscosity); subjects in supine position. Data from MII
	14.2 ± 2.2	Head liquid bolus (low viscosity); subjects in upright position
	6.3 ± 0.8	Head high viscosity bolus (yogurt); subjects in supine position
	5.0 ± 0.4	Body liquid bolus (low viscosity); subjects in supine position
	5.2 ± 0.8	Body liquid bolus (low viscosity); subjects in upright position
	4.0 ± 0.2	Body high viscosity bolus (yogurt); subjects in supine position
	4.1 ± 0.1	Tail liquid bolus (low viscosity); subjects in supine position
	4.7 ± 0.2	Tail liquid bolus (low viscosity); subjects in upright position
	4.1 ± 0.2	Tail high viscosity bolus (yogurt); subjects in supine position
Srinivasan et al. (2001)	2.9[b]	Estimation from bolus transfer times values for applesauce. Data from MII
Mizunuma et al. (2009)	8[c]	Head liquid bolus—Estimations based on BTT from CFD for a jelly

MII multiple intraluminal impedance, *UES* upper oesophageal sphincter, *BTT* bolus transfer time, *CFD* computational fluid dynamics
[a]BTT (tail) = 0.664 s; h = 5.4 cm
[b]BTT (average) = 6.24 s; h = 18 cm; v = 1–4 mL apple sauce
[c]BTT (head) = 0.5 s; h = 4 cm up to the epiglottis

Table 2 Estimated swallowing shear rates from bolus transit velocities

Swallowing phase	Liquid bolus kinematics velocity, V^c (cm/s)	Estimated shear rate, γ^d (1/s)
Pharyngeal		
Bolus head (maximum)[a]	35.5	931.7
Bolus tail (average)[a]	10	262
Oesophageal		
From BTT (BTT = 6.12 s)[b]	2.94	4.7

[a]Anatomy—data from Battagel et al. (2002)
[b]Data based on MII from Srinivasan et al. (2001)
[c]Kinematics—data from Bardan et al. (2006)
[d]From capillary and peristaltic flow equations

bolus movement, has important implications in the bolus deformation and in the accurate estimation of the swallowing quality. When the complex non-Newtonian behaviour of the food bolus is considered, the estimations become even more complicated.

The reader should note that, in reality, not only shear but also elongational flows are involved in the deformation of food bolus, as clearly seen from the videofluoroscopy and the real-time magnetic resonance imaging (Imam et al. 2005; Buettner et al. 2001). The shape of the deformed bolus is typical of the ones produced under elongational stretching. This is in line with the fact that many boluses exhibit extensional properties (Ekberg et al. 2009; Chen 2009). Unfortunately, little attention has been given to the role of elongational flows and dysphagia. So far, shear viscosity is the only property considered in the dysphagia guidelines and still with too many limitations.

Several studies acknowledge the beneficial effect of high shear viscosity in increasing patient's safety during swallowing. It is assumed that high-viscous boluses are transported slower through the pharynx, allowing more time to the oropharyngeal mechanism to properly secure the airways and to lead the bolus to the oesophagus.

In relation to dysphagia management, the viscosity category boundaries are consensus based (Frazier et al. 2016). For instance, the National Dysphagia Diet Task Force (2002) of the American Dietetic Association proposed terms for liquids and other viscoelastic fluids using shear viscosity measurements at 25 °C and a single shear rate of 50 s^{-1}. No scientific evidence or rationale was given by the National Dysphagia Diet Task Force for the temperature and shear rate chosen for this scale. In fact, on the basis of sensorial analysis from lingual perception viscosity, a wide range of shear rates ranging from 5 to 1000 s^{-1} have been proposed, but the value of 50 s^{-1} being the most frequently cited, perhaps because this value was adopted by the National Dysphagia Diet Task Force. These conditions have been challenged by our research group and others (Brito-de la Fuente et al. 2010; Quinchia et al. 2011; O'Leary et al. 2010; Steele et al. 2003). As previously shown, from bolus transit velocities, shear rates may vary from 1 up to 1000 s^{-1}, depending on the swallowing phase (see Table 2).

Moreover, in the UK, the British Dietetic Association (2009) in its *National Descriptors for Texture Modification in Adults* is using subjective descriptors from sensorial analysis. Quantitative measurement of viscosity is acknowledged to be currently impractical according to the British Dietetic Association and thus it is not performed by healthcare professionals or others. This practice remains at all levels, in hospitals and nursing home care settings, in spite of all the scientific evidence regarding the complex rheological properties (i.e. non-Newtonian behaviour and thus shear-dependent viscosity) of different boluses found during swallowing (Quinchia et al. 2011; Ekberg et al. 2009; Steele and Cichero 2008; Germain et al. 2006; Clavé et al. 2006; Bülow et al. 2003) and the clinical evidence suggesting that the pharyngeal swallowing phase occurs at different bolus transit velocities and thus shear rates, as previously discussed.

To date, there is no available information regarding a specific shear viscosity value that has been demonstrated to result in clear, measurable positive impact on swallowing pattern (Frazier et al. 2016; Steele et al. 2015).

Rheology and swallowing are also connected at the diagnosis level. The "gold standard" technique is a videofluoroscopic swallowing study (VFSS). The swallowing process can be visualised by means of videoradiography, by either using ready-to-use commercial contrast medium or by mixing food with barium sulphate ($BaSO_4$), making it radiopaque. Unfortunately, there is no standardisation for how to perform VFSS. For instance, in the USA, it is common to use commercial ready-to-use contrast media but this is not the case in Europe. This lack of standardisation leads to variability in practice and results and encourages individual speech pathologist, dieticians and dysphagia-designed food manufacturers to determine their own dietary consistencies.

However, what it is more important to mention here is the fact and recognition that the

rheological properties of the radiopaque bolus prepared by mixing contrast medium (e.g. barium sulphate, $BaSO_4$) with normal food are quite different from the normal food used as vehicle for the VFSS. If the results from VFSS are extrapolated to dietary recommendations using foods without added barium, there may be a severe problem.

Ekberg et al. (2009) found significant differences in the rheological properties of a model food versus the same food but mixed with $BaSO_4$. In addition, the sensory texture dimensions of this model food were significantly affected by the added barium. Ould-Eleya and Gunasekaran (2007) reported significant differences in the rheological properties of both pre-thickened and videofluoroscopy fluids, currently used for diagnosis and treatment of dysphagia. Sopade et al. (2007) studied the rheological properties of typical food powder thickeners and proposed equations to match VFSS fluid viscous behaviour and obtain an objective classification of the thickened fluids. Brito et al. (2010, 2012) proposed a rheological similarity approach with VFFS fluids, for the design of oral nutritional supplements having complex formulations.

Popa Nita et al. (2013) applied the same method to match the viscosity of commercial thickening powders dispersed in water with those of thickeners dispersed in videofluoroscopy contrast fluids. However, it might seem that such an approach could affect the properties of contrast solutions relevant in diagnosis, such as the range of viscosity on which the product is intended for, the visibility of the radioscopic image and the degree of coating of the fluid on the pharyngeal mucosa (Steele et al. 2013). More recently, Reyes-Ocampo et al. (2017) used a further elaborated rheological similarity approach to successfully match both shear and elongational viscosities of milk-thickened fluids for dysphagia management with those of a barium sulphate contrast fluid.

Regardless of the progress achieved from rheological sciences applied to bolus properties and experimental in vivo kinematic studies, health professionals in charge of the dietary management of dysphagia have hardly integrated this information in their guidelines for diet modification. As an example, the only association using a viscosity dimension is in the USA—American Dietetic Association (National Dysphagia Diet Task Force) which proposed different bolus viscosity categories on the basis of viscosity values estimated at only one shear rate of 50 s^{-1}. More details are given in the next section.

3.2 Shear Rheology in Nutritional Support-Product Design

Malnutrition and dehydration are quite often a consequence of dysphagia. Neurogenic dysphagia impairs swallowing and thus reduces oral feeding, leading to malnutrition and/or dehydration (Ickenstein 2011; Cabre et al. 2010). However, dysphagia remains mainly a transport problem that has to be solved first, before thinking of nutrition, in particular if the swallowing function should be stimulated. Ideally, if the two problems can be solved at once by transferring under safer conditions high-quality nutrient boluses, then the quality of life of dysphagic patients may significantly increase (Brito-de la Fuente et al. 2010).

It is already acknowledged that low-viscosity boluses are more difficult to be swallowed safely than high-viscosity boluses (Zargaraan et al. 2013; Nyström et al. 2015). The nutritional management of patients with dysphagia is fundamentally based upon the so-called diet modification of texture or consistency, more likely by increasing liquid viscosities to a certain range, considered safe for swallowing. The rationale behind altering or modifying the consistency of foods and/or drinks is to change/reduce their rate of transport through the pharynx and thus to decrease the risk of food aspiration due to their weakened swallowing reflex. A recent white paper (Newman et al. 2016) reviewed the relevant literature regarding the effect of bolus modification on the safety of swallowing in adults with oropharyngeal dysphagia. The results suggested that, apart from the increase in safety during swallowing, the increase in bolus viscosity may lead to a series of side effects, such as

increase in residues, reduction of palatability, increased risk of dehydration and reduced treatment compliance. Therefore, thickness should be chosen according to patient's medical condition, since too thick fluids or boluses might be as detrimental as very thin liquids. Studies showed that very thick boluses were poorly accepted by patients with dysphagia (Steele et al. 2013). Therefore, dysphagia-designed fluids need to be described more carefully from a rheological point of view, not only through indicators such as thin or thick. Casanovas et al. (2011) considered viscoelastic parameters, such as loss and storage moduli, as well as thixotropic factors in the characterisation of dysphagia-designed fluids. Using 34 commercially available products, 11 rheological parameters were introduced for an exhaustive characterisation of dysphagia-designed fluids.

However, the assessment of consistency, through viscosity control, remains rather subjective in the dysphagia world. The preparation, as well as the rheological evaluation and administration of thickened fluids to patients, is universally subjective. Unfortunately, healthcare professionals, responsible for prescribing patient's modified diet, have shown poor or little knowledge about this field and thus the wide range of viscous properties for the same dysphagia level or recommendation (Steele and Cichero 2008; Steele et al. 2003).

Ideally, the most appropriate modification of food consistencies should follow from a clear assessment of the swallowing problem, as reviewed by Penman and Thomson (1998). However, this is not possible in all cases and quite often healthcare professionals rely on national guidelines for the dietary management of dysphagia.

The subjective manner and the various labels and descriptors used for describing fluids for dysphagia management, according to different national guidelines, make difficult their classification worldwide and discourage the possibility of finding key properties with clinical evidence for supporting the safe swallowing. Currently, many efforts are done for raising awareness on the need of an international terminology for texture-controlled fluids used in dysphagia management (Cichero et al. 2013; Hanson 2016; Cichero et al. 2017).

Nevertheless, the major challenge in dietary management of dysphagia continues to be the achievement of the right rheological characterisation of the product consistency. This leads to the still fundamental question: Is it possible to design better products for the dietary management of dysphagia under safe conditions? One answer to this question may be the design of nutritional products that are ready to swallow by following a rheological similarity approach: this means by matching the rheological properties of the fluids used for the diagnosis (e.g. swallow barium test feeds used in videofluoroscopy examination) with those of the bolus.

Brito-de la Fuente et al. (2012) have proposed a dynamic triad strategy for closing the gap between the rheological properties of the swallow barium tests feeds and the ready-to-use product under design (see Fig. 10). This strategy has been applied quite successfully in the design and commercial production of complex-structure oral nutritional supplements rich in proteins, with a pudding consistency (e.g. Fresubin® Crème). The benchmark used for this design was the "gold standard" barium-based product, E-Z-EM Varibar® Pudding. The main rheological results of this exercise are described next.

Regarding viscous properties, Fresubin® Crème showed shear-thinning behaviour, i.e. a viscosity-decreasing function of shear rate,

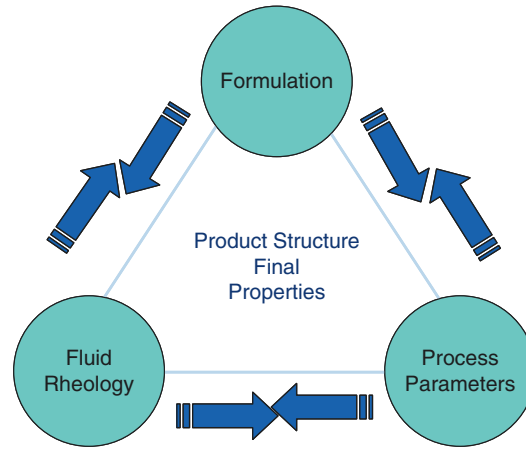

Fig. 10 Dynamic triad strategy for the design of oral nutritional supplements with rheological similarity to swallow barium test feeds

matching the results of Varibar® Pudding, as seen in Fig. 11. Regarding viscoelastic properties, G' values clearly confirm the gel-like behaviour of both products, which means that they are structured systems. For both products, the linear viscoelastic properties can be considered essentially similar, as seen in Fig. 12.

These results suggest that it is possible to design oral nutritional supplements that exhibit similar rheological properties to those of barium sulphate suspensions used for diagnosis of dysphagia. A complete rheological characterisation of the final oral nutritional supplement was published elsewhere (Quinchia et al. 2011).

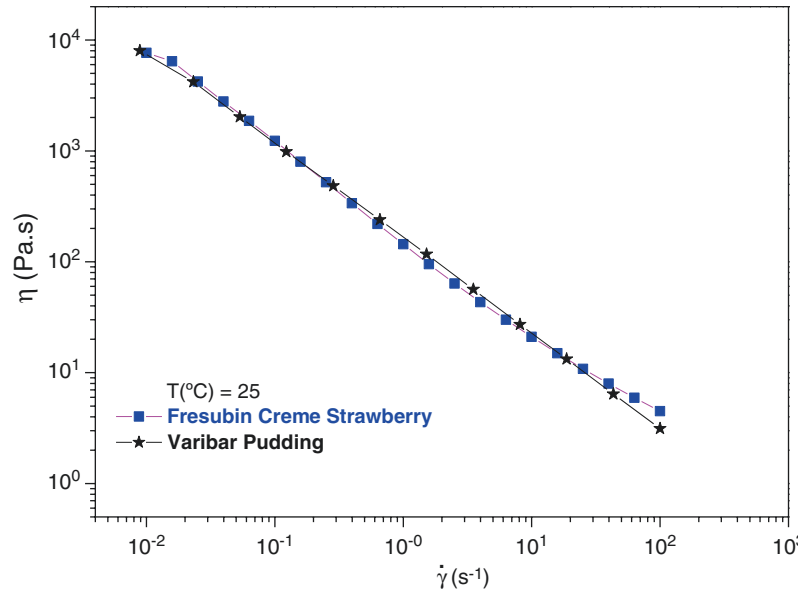

Fig. 11 Steady-shear viscosity curves for Varibar® Pudding and Fresubin® Crème

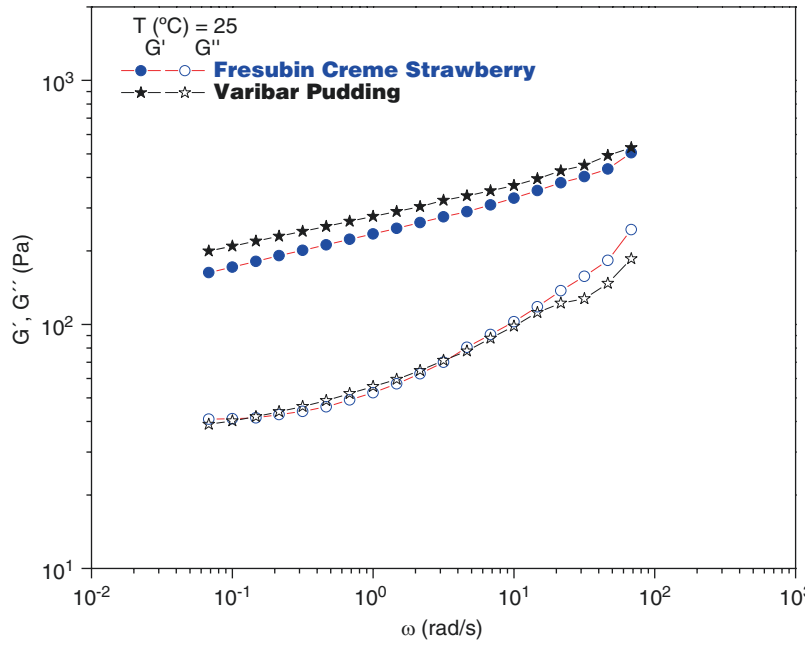

Fig. 12 Viscoelastic properties for Varibar® Pudding and Fresubin® Crème under dynamic linear oscillatory conditions

Brito-de la Fuente et al. (2010, 2012) described an in-depth rheological characterisation of prethickened foods and videofluoroscopy diagnostic fluids, showing the important role that rheology plays in diagnosis and dietary management of dysphagia.

3.3 Extensional Rheology and the Swallowing Process

As mentioned before, shear viscosity has been considered by the medical community sufficient for estimating if a certain fluid is safe or unsafe for being swallowed by patients with dysphagia.

Such naïve classification omits two important aspects when it comes to dysphagia. Firstly, the deformation rates are broad and even more difficult to estimate in patients with dysphagia, while dysphagia-designed fluids show significant shear rate dependence, and, secondly, not only shear deformations occur during swallowing. In the mouth, the food bolus is squeezed between the palate and the tongue, which leads to a primary extensional flow, followed by more pronounced extensional flows during the oropharyngeal phase of the swallowing (Burbridge et al. 2016). The simplicity of this commonly accepted rheological control proposed by National Dysphagia Diet Task Force, both in relation to the deformation complexity during the swallowing process and in relation to the rheological complexity of fluids used in the treatment, has been highlighted in several occasions (Cichero et al. 2013; Gallegos et al. 2012; Quinchia et al. 2011; Zargaraan et al. 2013).

However, several studies showed that the increase in shear viscosity reduces the risk of aspiration and penetration of food associated to dysfunctional swallowing (Leonard et al. 2014; Newman et al. 2016). Apart from shear viscosity, the knowledge of how other rheological properties, such as elasticity, thixotropy or yield stress, affect swallowing is still limited (Gallegos et al. 2012; Newman et al. 2016; Nyström et al. 2015).

Recent studies on texture-modified foods showed that both bolus elasticity and its cohesivity could have beneficial roles in swallowing. Nyström et al. (2015) studied the perceived ease of swallowing in three different classes of edible fluids (a Newtonian, a Boger and a viscoelastic fluid) and conclude that fluids that show higher elasticity might be easier to swallow than inelastic fluids with the same shear viscosity.

Fluid elasticity is better highlighted during extensional flow, as already discussed in the previous section. Extensional viscosity is often considered a manifestation of fluid elasticity. In oral processing of food, bolus elasticity is usually correlated to its degree of cohesiveness, since cohesive boluses are less prone to disintegration during swallowing. In the context of dysphagia, cohesive boluses might reduce the risk of food aspiration during the pharyngeal stage of the swallowing.

Despite some data in the literature, a clear investigation of the extensional properties of dysphagia products is still lacking (Chen 2009; Choi et al. 2014; Mackley et al. 2013; Gallegos et al. 2017, Turcanu et al. 2015b). This is mainly due to some limitations: the technical difficulty to achieve steady state in extensional flows (Petrie 2006a, b) and the non-homogenous molecular structure of dysphagia-designed products that makes difficult their characterisation during elongation (Mackley et al. 2013). Nevertheless, techniques such as multiple extrusion cell, compression flows, hyperbolic contraction flows and capillary break-up extensional rheometry started to be used for the investigation of elongational properties of such complex fluids (Engelen et al. 2005; Foo et al. 2011; Haward et al. 2011, Ekberg et al. 2009; Waqas et al. 2017; Turcanu et al. 2015a, b; Turcanu 2017).

3.4 The Role of Saliva in the Swallowing Process and Dysphagia Management

Safe swallowing is directly correlated to bolus formation and its safe passage through the pharynx. A model that simultaneously incorporates two requirements of food swallowing (food mechanical processing and lubrication) was proposed in the late 1990s by Prinz and Lucas (1997). According to its theory, swallowing should take

place when the bolus reaches the maximum cohesive force. The model predicts that the smaller the food particles or the closer the distance between food particles, the higher the cohesive forces and therefore the more beneficial and easier is the swallowing. In contrast, extended chewing and contact with saliva can lead to an increased distance between food particles and a much decreased cohesive force, which would make swallow unsafe, by increasing the risks of aspiration (Chen 2009). The principles behind the model proposed by Prinz and Lucas appear to be similar, but rather simplified over those of the model proposed by Hutchings and Lillford (1988). The model is a dynamical approach that describes food perception through three different aspects: the rheological behaviour of food (degree of structure), the oral experience or saliva participation (the degree of lubrication) and the sequence of the oral processing (the timescale). This model seems to be closer to reality, since it integrates both oral experience and time, making food bolus rheological appreciation a dynamic process. Despite its interesting complexity, the importance of this model has been overseen and research in this direction has not sufficiently been followed on. Chen (2009) suggested that, most probably, this is due to the limited knowledge of the food breakdown throughout the eating process and he suggests that the saliva-food interaction should be incorporated, if possible, into instrumental measurements. Still, the actual methods for investigating the oral perception of not only dysphagia-designed fluids but also food products, in general, are mainly oversimplified, due to the overlook of the role of saliva.

It is well known that human salivary alpha-amylase is responsible for the in vivo enzymatic breakdown of starches and other carbohydrate sources present in food and beverages. Traditional dysphagia-oriented products and powder thickeners were based on starch. In the last years, hydrocolloids, such as xanthan gum and guar gum, tend to substitute starches in dysphagia products, since they were found to be more stable during oral processing (Hanson et al. 2012a; Morell Esteve et al. 2014).

Many studies have been dedicated to shear rheology of food products and to their interaction with saliva, since the enzymatic effect of alpha-amylase could alter food behaviour during swallowing (Engelen et al. 2005; Hanson et al. 2012b; Newman et al. 2016; Stading et al. 2008; Steele 2005).

A pioneering study regarding the effect of saliva on the capillary break-up elongational properties of xanthan-based thickened fluids (Choi et al. 2014), followed by the study of the elongational behaviour of a starch-based food product in the presence of saliva (Turcanu et al. 2015b), started to highlight the need for a systematic extensional characterisation of dysphagia-designed fluid-saliva interaction for a better understanding of the swallowing process and, thus, for management of dysphagia.

Turcanu (2017) used the filament break-up time and axial forces developed during uniaxial elongation to quantify the elastic properties of dysphagia-designed fluids. This strategy has been applied quite successfully in the characterisation of different commercially available products. A clear differentiation between starch-based and gum-based products, as well as between ready-to-use and powder-thickened fluids, in terms of elongational pattern and filament break-up time was possible.

In the next example, the elongational properties of a ready-to-use dysphagia-designed fluid (Fresubin® Crème Strawberry) are compared to those of a commercially available product (Babyvita Pumpkin) that is not intended for dysphagia treatment. The effect of saliva on the elasticity of the two products is as well analysed.

Both nutritional products show shear-thinning behaviour and high viscosity, when compared to the Newtonian behaviour of water. According to National Dysphagia Diet standard, these fluids have almost the same shear viscosity, at a shear rate of 50 s^{-1}, equivalent to pudding-like consistency (Fig. 13). Therefore, only by taking into account this single value of shear viscosity, it can be assumed that both products fulfil the requirements that render them suitable for dysphagia management, in patients with stage three of dysphagia (the most critical).

Despite their similar shear-thinning behaviour, these products differ significantly in structure. The commercial pudding is intended for

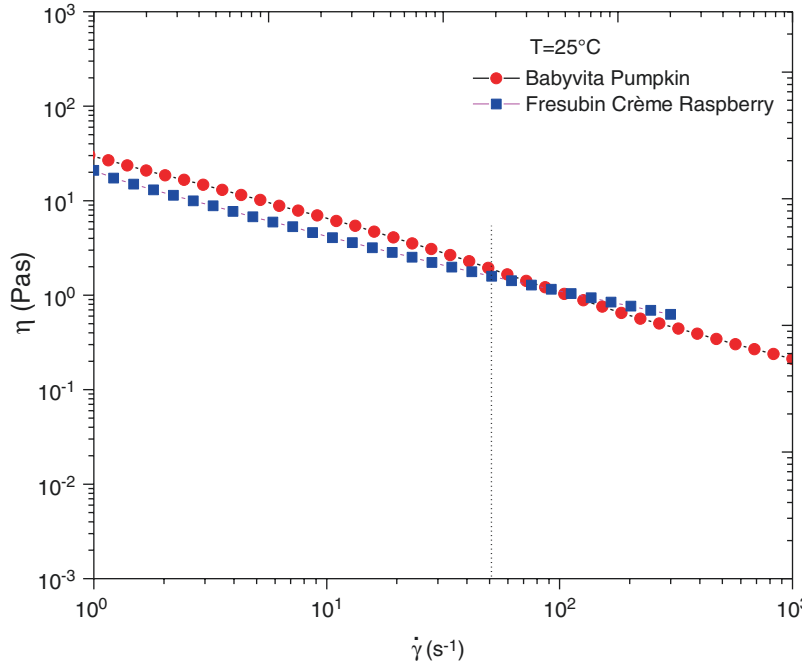

Fig. 13 Flow curves of two commercial nutritional products

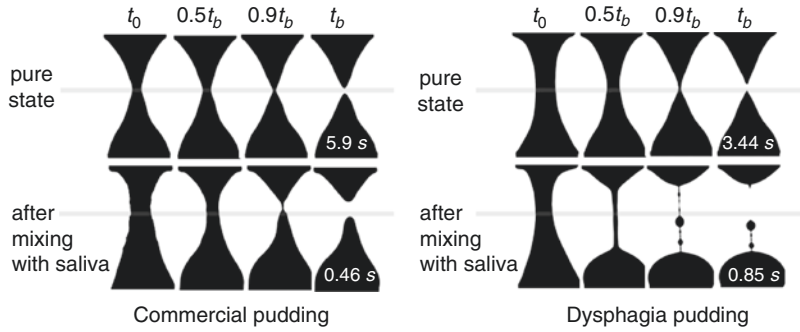

Fig. 14 Filament shape and evolution of the selected pudding samples, before and after contact with human saliva

infant nutrition and contains pure pumpkin purée, while the commercial Fresubin Crème Raspberry is a mixture of maltodextrin, resistant starches, proteins and fibres.

Figure 14 illustrates the filament shapes during capillary thinning of the two puddings, in pure state and after in vivo mixing with human saliva. The average filament break-up times are shown in Fig. 15. In pure state, both puddings show non-cylindrical, emulsion-like filaments that neck and break in the centre. In terms of break-up time, both pure products show filament lifetime of order of seconds. Babyvita Pumpkin purée filament lifetime is almost twice the filament lifetime of the dysphagia-designed fluid, while a water filament barely lasts for 10 ms in the same imposed elongational conditions (data not shown).

When mixed with human saliva, Babyvita Pumpkin purée filament did not change significantly its emulsion-like shape during uniaxial elongation, even though the filament break-up time drops drastically when saliva is mixed with the pure fluid. In contrast, dysphagia-designed pudding changes its filament evolution after the contact with human saliva, by forming a cylindrical thread during elongation. The apparition of beads-on-a-string

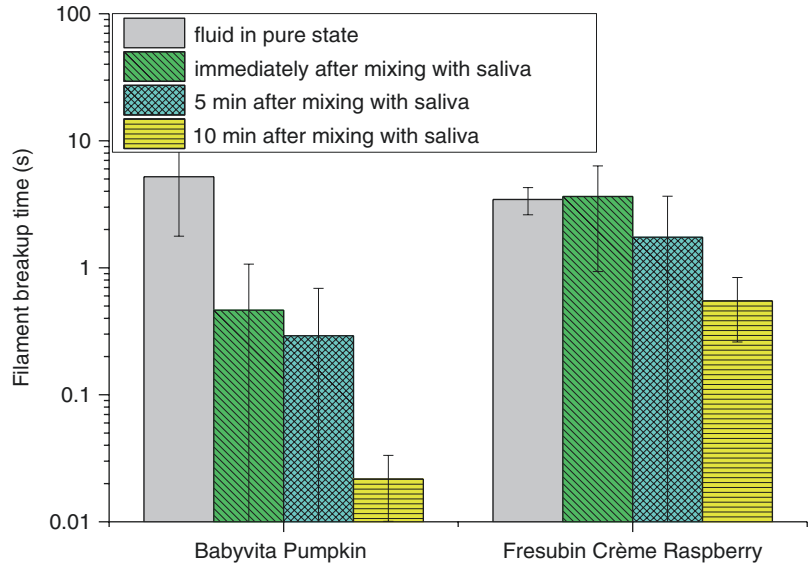

Fig. 15 Filament break-up time for the two selected nutritional food products, before and after in vivo interaction with human saliva. The interaction with saliva was measured right after mixing, 5 min after mixing and 10 min after mixing

elastic instability before the break-up of Fresubin Crème filament is an objective manifestation of the elasticity of the mixture product-saliva. This increase in saliva elasticity in the case of the strawberry pudding can be explained by the natural production of saliva rich in mucins during the oral processing of slightly acidic food products. Similar elastic response was obtained when saliva production was stimulated acidically with lemon juice (Turcanu et al. 2015a).

When the filament break-up time of the food bolus is monitored over the first 10 min after mixing with human saliva, it becomes clear that the dysphagia-designed pudding (Fresubin Crème) shows more stable elongational properties than Babyvita Pumpkin purée in the presence of saliva. In pure state, the pumpkin pudding showed slightly higher elongational functions than Fresubin Crème. Saliva was found to dramatically reduce its elastic properties in the first 10 min after being mixed with human saliva. The more stable filament lifetime over the first 10 min, observed for the dysphagia product in contact with human saliva, may be explained by the presence of some food ingredients in the composition of Fresubin Crème, such as gums, that are not sensitive to the enzymatic effect of alpha-amylase and help maintaining the fluid structure even after the mixing with human saliva.

The complex rheology of the two nutritional puddings studied is clear. Even though both products showed similar shear behaviour, the elongational results displayed significant differences in filament shape (Fig. 14) and filament break-up time (Fig. 15) after in vivo mixing with human saliva. The same behaviour was confirmed by small-amplitude oscillatory shear tests (Fig. 16). It was shown that, compared to a dysphagia product, a commercial pudding product with the same shear profile might be less safe for a dysphagia patient, since it could be more strongly affected by the enzymatic effect of alpha-amylase present in saliva.

Compared to shear rheology, filament break-up experiments are simpler and faster in analysing the effect of saliva on different nutritional fluids, highlighting important elongational aspects of food-saliva interaction, aspects often neglected in dysphagia product design and characterisation. These results highlight the importance of considering, additionally to shear, elongational properties and saliva effect when optimising the therapeutic efficacy and safety of fluids during swallowing.

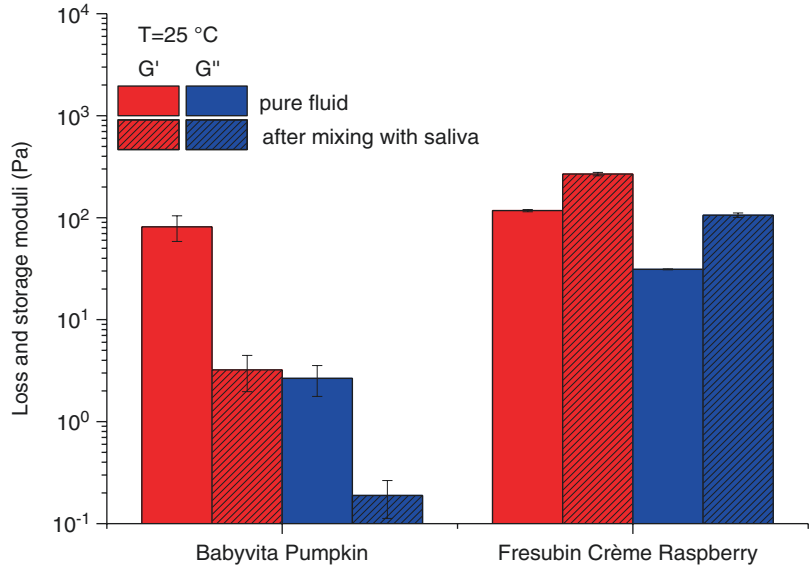

Fig. 16 Loss and storage moduli of the two nutritional puddings measured in the linear viscoelastic range of SAOS. Measurements were performed in a cone-plate geometry at constant frequency (ω=1 rad/s) and constant strain (γ=0.1) for 10 min

4 Concluding Remarks

Dysphagia and rheology are closely interconnected. Regardless of the experimental technique used for the assessment of dysphagia, bolus flow properties play an important role to guarantee higher levels of safety swallowing.

Kinematic analysis of more dysphagic patients is needed to better understand how boluses with different rheological properties are transferred under different neurological or medical conditions. New techniques like computation fluid dynamics applied to complex swallowing situations may be of high value for pre- and post-diagnosis as well as an educational tool to increase patient's compliance under diet modification programs.

The creation or design of novel foods for dietary management of dysphagic patients or the improvement of existing ones depends on a better understanding of the complex interrelationship between food structure and performance. More sophisticated experimental techniques coming from material sciences, like rheology, play an important role in the design and development of new products for dysphagia. On the other hand, a better understanding of the flow properties of the fluids used for the videofluoroscopic assessment of dysphagia and later on the recommendation of specific diets should be of high priority in the dysphagia world. Even though this knowledge is now being used to rationally design safer dysphagia products, this approach should be extended to different consistencies and nutritional profiles.

On the other hand, it has been shown that, in order to guarantee a safe swallowing of dysphagia patients, food products and drinks should most preferably keep both their shear and elongational behaviour during swallowing.

Finally, the incorporation of more knowledge on the role rheology plays during swallowing is crucial to proper management of dysphagia.

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The Dietitian's Role in Diagnosis and Treatment of Dysphagia

M. Macleod and S. O'Shea

Contents

Abstract

This chapter aims to provide an overview of the registered dietitian's role and the commonplace feeding dilemmas present at the practical level when applying the modified textured prescription for food and fluids in adults with dysphagia. The dietitian is one of a range of professionals involved in service provision, and there is an increased emphasis on an interdisciplinary and transdisciplinary team approach to care for people with dysphagia at both the acute and the community levels. The role of the dietitian can be wide ranging, from traditional nutritional management to a whole-systems approach encompassing screening, assessment, diagnosis and organisation of the modified textures within a dynamic nutritional framework. A person-centred approach is essential to provide nutrition in a mode which not only sustains nutrition and hydration integrity but also serves to enhance the individual's quality of life.

1 Introduction

The ideal approach to the management of dysphagia involves a multidisciplinary team (MDT) (Giammario et al. 2012; Rudakiewicz 2015). The registered dietitian is an integral member of this

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team and fundamental to service provision in both the acute and the community settings (Heiss et al. 2010; Dietitians of Canada 2015). The role of the registered dietitian within dysphagia includes:

- Assessing an individual's nutritional status and advising on nutritional requirements to minimise nutritional deterioration, including dehydration and different administration modalities such as oral, enteral and parenteral
- Applying evidence-based knowledge, skills and expertise to interpret height, weight and anthropometric measurements when assessing nutritional status and formulating a nutritional diagnosis
- Working within a professionally recognised nutrition and dietetic care process ensuring provision of evidence-based care and effective outcome monitoring and evaluation
- Working collaboratively within the dysphagia team
- Using a holistic approach to assess, problem-solve and ensure that health and well-being needs as expressed by the individual are met
- Using appropriate health facilitation skills within the therapeutic framework
- Contributing to the application of a legal and ethical framework
- Identifying, referring and working in partnership with health and social care colleagues, agencies and organisations
- Addressing inequalities in health and social care
- Advocating both formally and informally
- Supporting individuals[1] and carers in decision-making
- Providing counselling and education for individuals, carers and other members of the dysphagia team
- Using augmented/alternative communication for those with acquired and non-acquired cognitive impairments
- Working in dynamic environments with individuals who may display unpredictable behaviours that present a challenge
- Ensuring continuity and consistency of quality care across professional and organisational boundaries

Membership of a typical MDT is shown in Fig. 1, with the individual with dysphagia being pivotal in assessment and all management decisions. A brief summary of roles is shown in Table 1.

Although the terms 'multidisciplinary' and 'interdisciplinary' are often used interchangeably, there is an important difference in function. The interdisciplinary team model expands the MDT process where collaboration (rather than just sharing information on uni-professional interventions) in setting team goals and team action plans results in more effective management (Dyer 2003). As so many disciplines are involved in the assessment and treatment of dysphagia, collaborative working within the MDT is essential to provide coordinated evidence-based and safe person-centred care (National Patient Safety Agency 2007; Nazarko 2009; Ptomey and Wittenbrook 2015).

In some areas, as a matter of necessity, such as a lack of skilled dysphagia therapists, pressure of response times within clinical pathways or professional development within extended roles of practice, the management of dysphagia is moving from the role-specific professions within an MDT framework to a transdisciplinary approach in practice where disciplines undertake similar and complementary roles (Butt and Lam 2005). Members of a team based on a transdisciplinary model share knowledge, skills and responsibilities, thus blurring traditional boundaries between the professions and enabling the delivery of effective and timely person-centred care.

[1]As dysphagia is managed in both the acute and the community health (and social) care settings, the term 'individual' is used within the text to represent patient, client and service user.

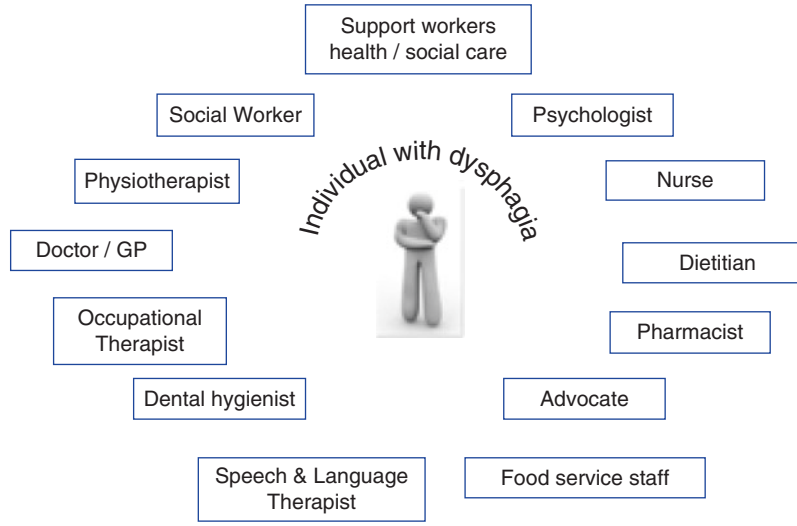

Fig. 1 Members of the multidisciplinary team (MDT) for dysphagia (Burton et al. In Diagnostic Imaging Ekberg 2012)

Table 1 Roles of each member of the dysphagia multidisciplinary team (MDT)

Member	Role
Individual with dysphagia and their carers	Participate in assessment, treatment and management decision-making where possible
	Inform MDT of any problems adhering to guidelines
	Inform MDT of any changes in clinical presentation
Advocate	Represents the individual's views, interests and rights
	Participates fully in decisions made about the individual's life
Clinical psychologist	Assessment, treatment and management of socio-emotional, behavioural and psychological aspects of dysphagia
Catering staff/carers in community settings	Adheres to eating and drinking guidelines
	Provision of attractive, nutritious and suitably fortified foods
	Provision of food and fluids of suitable consistency
	Provision of adequate amounts of food and fluid as required
Dietitian	Initial screening, assessment and diagnosis (*where trained*)
	Close liaison with speech and language therapist
	Assessment, treatment and management of nutrition and hydration
	Assessment of need for supplements and monitoring efficacy
	Assisted eating and drinking training
	Independent/supplementary prescribing (*where trained)*
	Together with speech and language therapist supports decision-making in relation to artificial feeding
Physician/GP	Referral to relevant other professionals if dysphagia is suspected
	Medical investigation into the cause of dysphagia and treatments if required
	Prescribes medication in suitable presentations

(continued)

Table 1 (continued)

Member	Role
Nurse	Initial screening (*where trained*)
	Implementation of dysphagia/feeding advice
	Monitors food and fluid intake as appropriate
	Liaison with dietitian and speech and language therapist
	Administers medication in the correct format
Occupational therapist	Assessment and management of the impact of physical and environmental factors
	Advice regarding adaptive equipment, technical skills and positioning at mealtimes
	Assisted eating and drinking training
Pharmacist	Advice on availability of medication in suitable presentations
	Checks side effects of medications in relation to dysphagic properties
	Advice on drug–nutrient interactions
Physiotherapist	Assessment, treatment and management of the respiratory system
	Advice on positioning when eating and drinking, including head control management
	Assisted eating and drinking training
Social worker	Assesses, advises and coordinates a suitable care package for home in liaison with other professionals
Speech and language therapist	Assessment, diagnosis and monitoring of swallowing problems
	Advice on compensatory strategies
	Close liaison with dietitian
	Assisted eating and drinking training
	Together with dietitian supports decision-making in relation to artificial feeding
Support workers in health/social care	Assistance with choosing appropriate foods and fluids
	Follow feeding guidelines in place such as correct environment, suitable posture and assisted eating

These roles are not exhaustive. All may be involved in risk assessment; MDT training and best interest decision-making

2 Role in Diagnosis

2.1 Screening

The aim of screening is to inform and guide the safest management (Antonios et al. 2010; Arens et al. 2015). During a routine nutritional assessment, the dietitian is in an ideal situation to observe potential signs and symptoms of dysphagia, especially in people who do not present with an overt neurological condition such as cerebrovascular accident, cerebral palsy, or motor neuron disease or a mechanical cause such as oesophageal stricture, injury or carcinoma. Insidious onset with symptoms such as unexpected weight loss, taking longer to eat and drink and becoming increasingly selective with food choices can be missed or not seen as important by carers or indeed the person himself/herself. Indices of malnutrition such as reduced serum levels of transferrin and albumin have been found to be present in people with severe dysphagia, although a statistically significant relationship has not been found (Brody et al. 2000). Biochemical and haematological data, however, could be additional triggers for a detailed assessment to be undertaken following an initial screen. Thus, for individuals exhibiting signs of dysphagia, assessment and treatment can be conducted in a timely manner to avoid inappropriate feeding or long periods of starvation which could lead to malnutrition and/or refeeding syndrome (Mehanna et al. 2009).

2.2 Assessment

Traditionally, it was the unique province of the speech and language therapist (SLT) to assess swallow and that of the dietitian to advise on how to meet nutritional needs within the textures allowed. Within the UK, dietitians undertake dysphagia assessments in some stroke units, and according to the outcomes of the 2008 International Confederation of Dietetic Associations education and work survey (ICDA 2008), dietitians practising in other countries also fulfil this role, which includes the prescribing of modified foods and fluids. Countries such as the USA and Canada have documented evidence which indicates that with appropriate training to enhance existing knowledge and skills, dietitians are becoming as proficient as SLTs at conducting swallowing assessments and making recommendations on suitable textures (College of Dietitians of Ontario 2016). Close working with the SLT trained in dysphagia is essential, especially in more complex cases where instrumental assessment is required, such as the gold standard modified barium swallow or videofluoroscopy.

3 Role in Nutritional Management

This is the long-established role of the dietitian, who is lead professional in the assessment and treatment of malnutrition and dehydration. Individuals with dypshagia must be frequently monitored as their needs may constantly change. At all stages in the progression of dysphagia the dietitian should be consulted to ensure that nutritional requirements are tailored to meet the individual's needs. Factors which need to be considered before making the initial and subsequent nutritional recommendations are highlighted as follows:

3.1 Nutrition

Not only is dysphagia an independent risk factor for malnutrition (Carrion et al. 2015), but it has also been shown that hospitalised and institutionalised individuals on texture-modification regimens have suboptimal fluid, energy and protein intakes (Wright et al. 2005). In addition, clinical practice reveals deficits in a range of macronutrients and micronutrients, requiring supplementation in both acute and community care. Nutritional intake has been shown to improve with targeted feeding assistance (Wright et al. 2008), although there are many other factors which have an effect on achieving adequate nutrition. These include the quality of food preparation and presentation and more person-specific influences such as the psychological burden of being unable to swallow without coughing, being unable to clear foods and fluids from the mouth and an inability to manage salivation. All these need to be taken into account when devising an individualised eating and drinking programme (Nazarko 2007), as well as the need to sensitively manage the transition from normal to modified textures (Ullrich and Crichton 2015).

Food that is not eaten is not nutritious whatever the merits of its nutritive constituents. Nutrition is much more than calculating an individual's requirements for nutrients and meeting recommendations. The art and skill of the dietitian lie in translating scientific evidence into practical solutions which must be fit for purpose, using a holistic and person-centred approach.

If consumption does not provide the nutrition required to match individual requirements, then either food enrichment which will increase nutrient density without increasing volume or prescription of oral nutritional supplements may be needed, and the adequacy of such measures will need close monitoring (National Institute for Health and Clinical Excellence 2017). The dietitian will recommend and monitor the usage of any specific oral nutritional supplements needed by the individual which will address their nutritional needs, taking into account taste and preparation preferences. Nutritional management and treatment of dysphagia are further complicated by cognitive decline and end-of-life pathway where any decision to commence enteral tube feeding should be carefully balanced against the individual's known wishes and impact on his/her quality of life.

It must be remembered that nasogastric or gastrostomy feeding does not significantly reduce aspiration risk even though such means of artificial nutrition can rectify any nutritional and hydration deficits. There are both positive and negative aspects to enteral tube feeding. Gastrostomy feeding may reduce the stress associated with mealtimes but results in a reduced quality of life by missed opportunities for social eating, disruptive sleep patterns and stoma site infections.

There is also a risk of rapid and undesired weight gain as standard energy predictive equations such as the Schofield and the Harris–Benedict equations overestimate energy requirements for some groups, such as people with profound and multiple physical and learning disabilities (Dickerson et al. 1999; Fairclough et al. 2008) and those with low resting energy expenditure due to hypothermia (Gervasio et al. 1997; Dickerson et al. 2003). The British Association of Parenteral and Enteral Nutrition recommends using the Henry Equation in the UK (BAPEN 2016) within the Nutrition and Dietetic Care Process (British Dietetic Association 2012). Whichever formula is used by clinicians, such equations and stress factors act primarily as an objective starting point for estimating energy and protein requirements.

3.2 Hydration

Healthy adults manage hydration through thirst. Individuals who have dysphagia may lack the ability to recognise thirst or may experience problems with swallowing normal fluids. Adequate hydration is essential for life, and as there is no easy non-invasive method of monitoring hydration, the dietitian will always consider fluid requirements when advising on dysphagia diets. Many of these individuals may have significant fluid loss due to poor oral control, ineffective management of salivation (ptyalism, sialorrhoea, 'drooling') or aspirating (Bavikatte et al. 2012). It has been estimated that 1.5 L of parotid saliva is produced per day, with electrolyte losses of 169 mmol sodium and 28.5 mmol potassium (Lee 1974).

There is no scientific method to calculate fluid loss from drooling as each individual will produce different amounts of saliva and have different volumes of loss, depending on the ability to achieve mouth closure. One novel way of estimating these losses would be to weigh the towels or absorbent cloths (often used by individuals and carers to protect their clothing from getting wet), and then reweigh them but keeping wet towels in a plastic bag to reduce evaporation. Fluid losses need to be replaced as part of day-to-day fluid requirements.

Traditionally, fluid requirements for adults are based on age and weight, so for an adult under 65 years the fluid requirement is 35 mL/kg; for adults over 65 years this is reduced to 30 mL/kg in a temperate climate (Todorovic and Micklewright 2011). Again, as there is no scientific method to calculate fluid loss from poor mouth seal, the 'towel method' as detailed above could be utilised. The individual could be given a known volume of fluid without food. On completion of the drink, the towel/cloth is reweighed, providing the practitioner with an estimate of fluid lost. This can be repeated on several occasions and at different times of the day. In clinical experience, the fluid lost could be as great as 50% of the fluid offered. This volume would also have some saliva present, but can give some observational information to inform judgement on fluid requirements or the ability to meet needs orally.

Though the use of modified or thickened fluids has long been recommended by dietitians and SLTs (Khlemeier et al. 2001; Bhattacharyya et al. 2003; Butt and Lam 2005; Garcia et al. 2005: Clave et al. 2006; Logemann 2008; Robbins et al. 2008), their use in the management of dysphagia is complex. The impact of liquid consistency on swallowing behavior, medication bioavailability, effect of saliva on thickened drinks and different properties of an increasing range of commercial thickeners also need to be factored in (Steele et al. 2015;Vallons et al. 2015; Garcia et al. 2010; Cichero 2013).

Normal swallow requires well-coordinated timing of sensory and motor mechanisms to safely transport boluses of food. In individuals who have dysphagia, these processes may no

longer work effectively and the need for texture modification is indicated to assist safety in moving foods (and liquids) from the oral cavity.

3.3 Considerations when Using Thickeners

Achieving appropriate consistency using subjective measures is not reliable, as commercial thickeners have different properties depending whether they are primarily starch based or gum based (Garcia and Chambers 2010; Garcia et al. 2010).

Amylase-resistant thickeners based on guar gum/guar gum starch combinations have been put forward as being beneficial for individuals who hypersalivate, although recent research questions this evidence (Hanson et al. 2012). From a pragmatic point of view, the best thickener to use will be that preferred by the person who has to ingest it day after day, as any scientific rationale proved or disputed should not override individual preference for taste, and achieving that elusive characteristic—consistent consistency. The dietitian will be able to advise a change in prescription as necessary, especially if an individual reports changes in gut function after the introduction of thickeners. Sensory characteristics of drinks (and foods) may be enhanced with thickeners (Longton et al. 2003; Matta et al. 2006; Pelletier 1997), which may contribute to non-compliance (Table 2).

Table 2 Properties of thickeners

Starch-based thickeners	Gum-based thickeners
Particles expand like a balloon capturing the fluid, which means they often tend to keep on absorbing fluid and getting thicker. Affected by refrigeration. May continue to thicken over time	Interact with liquid by forming 'nets' that trap liquid. Require careful preparation and must be vigorously shaken or blended with base fluid, otherwise mixed consistency may result. If mixed correctly, they will maintain relatively stable viscosity over time
Can be added to hot or cold drinks	Hot liquids may need to be cooled then reheated
Less effective water binding than gum	Excellent water-binding properties
More prone to chemical reactions with base fluids, e.g. pulp, thickness, acid content	More stable, less likely to react to base fluid, although some drinks such as adult nutritional beverages contain ingredients that may interact and form clumps
Sensory perceptions: Tendency to impart a starch grainy texture to fluids, enhanced flavour	Sensory perceptions: Tendency to impart a slick flavour or texture, enhanced flavour
Metabolism and water absorption in the small intestine	Metabolism and water absorption in the large intestine

Garcia et al. (2010) found that most healthcare providers were unable to consistently prepare modified liquids. Seventy-five per cent could not prepare a honey texture and 31% could not replicate a syrup consistency despite following the manufacturers' instructions. These typical descriptors (thin, nectar and honey), however, have proved to be too subjective in practice and have led to wide variations in interpretation and resultant consistency of the modified fluid (Hanson 2016).

The addition of thickener in fluids may lead to an increase in energy intake, resulting in weight gain, which may or may not be advantageous. The dietitian should consider the implications of the additional energy component, impact on weight and which thickener to use as the energy content of thickeners may differ. The dietitian should consider carefully the complex factors on a case-by-case basis to ensure that the individual receives hydration. It is essential that the dietitian calculates the volume of fluid and also the quantity of thickener required to inform and generate accurate medical prescriptions.

Just because thickened fluids reduce the risk of aspiration, this does not always result in adequate hydration (Murray et al. 2014; Cichero 2013). Variables such as temperature, rate of mixing, method of mixing and base properties of the drink to be thickened all have an impact on the resultant texture. Timing is also a key consideration, especially for individuals who are slow to drink, with the product continuing to thicken in the cup (Garcia et al. 2008). Where an individual has capacity and is unwilling to comply

with thickened fluids, free water may be the safest acceptable oral option. Aspiration of saliva contaminated with pathogens can lead to pulmonary infection and so adherence to aggressive oral and dental care is essential especially where individuals are unable to clean their own teeth and gums (Panther 2005).

There is evidence to demonstrate that 'free' water (Frazier free water protocol) is increasingly becoming an acceptable treatment option for individuals who have been assessed as requiring modified fluids (Karagiannis and Karagiannis 2014). The Frazier free water protocol was developed by a unit in Canada, and allows individuals who have been identified at risk from thin liquids to drink plain water between meals. The authors theorise that if plain water is aspirated, then it is less likely to create pneumonia as the lungs have high moisture content and therefore have an ability to handle fluid.

The safety of allowing patients to consume 'free' water is constantly an area of great debate. Another area has been the variations in the descriptors for modified fluids (and foods) within the professions and the need for a 'common language' to enhance patient safety and improve professional communication. The plethora of nomenclature regarding food and fluid descriptions worldwide has also made it difficult to compare treatment options and research articles. In 2013 Cichero et al. identified that there was a need for international classification and through a systematic review, stakeholder involvement and identifying practical issues (Cichero et al. 2013). The subsequent development of the International Dysphagia Diet Standardisation Initiative (IDDSI) Framework with a mandate for implementation on a global level was published a few years later (Cichero et al. 2016). See Fig. 2.

Additionally recommendations were made so patients, carers and professionals could test foods and fluids, thereby helping them identify the required texture/consistency.

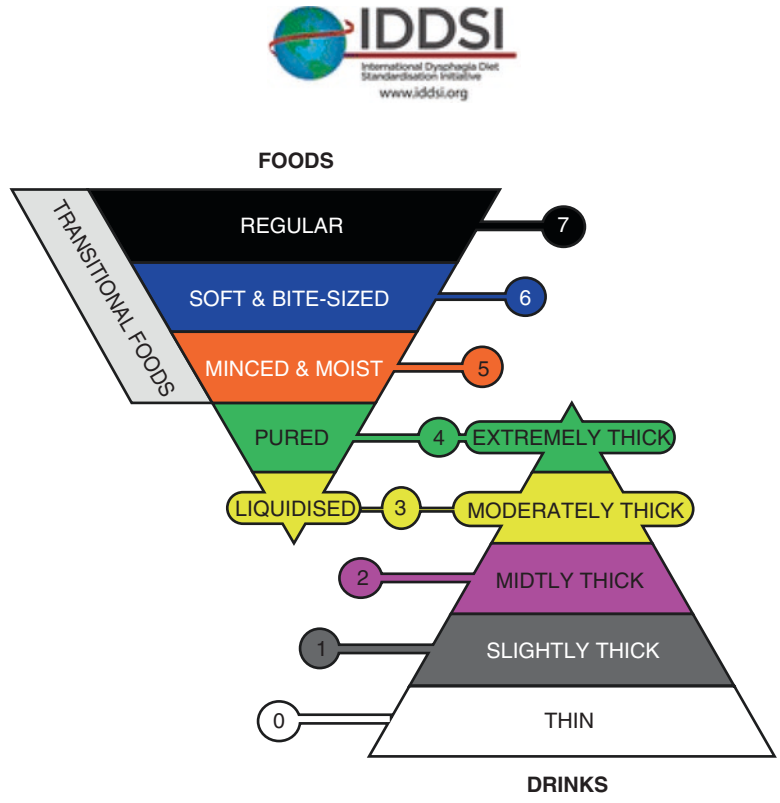

Fig. 2 Texture descriptors of foods and fluids—IDDSI. ©The International Dysphagia Diet Standardisation Initiative 2016. @http://iddsi.org/framework/Attribution is NOT PERMITTED for derivative works. Incorporating any alterations to the IDDSI Framework that extend beyond language translation

Fluids: The recommendation is to use a 10-mL syringe to ascertain the flow propety of a fluid. To ensure accuracy the authors have provided syringe specifications and instructions.

Foods: These are much more challenging as there are several properties to consider such as mechanics, size and shape, food hardness, cohesiveness and adhesiveness. The recommendations here relate to particle size for minced/moist and hard foods. In adition tests are recommended to ascertain the hardness, cohesiveness and adhesiveness properties.

The development and agreement of the IDDSI Framework is a huge step forward in achieving a globalised consistent approach and improving patient safety.

As far as possible, nutrition and hydration are provided orally. When careful feeding, hydration and adherence to recommendations do not result in a safe swallow and prevention of recurrent aspiration and malnutrition, then alternative and more aggressive routes of administration need to be explored with the individual and his/her carers. Even if the individual has been assessed as having an unsafe swallow, a risk management approach, especially if care is palliative, may offer the best quality of life for that person (Royal College of Physicians and British Society of Gastroenterology 2010).

3.4 Medication

Medications need to be administered in a format suited to the individual's safe swallowing capacity, especially if the route of administration is via an enteral feeding tube (White and Bradnam 2015). Prescribers are recommended to check not only the format of the preparation but also any contraindications which will apply for swallowing disorders. The knowledge and skills of the pharmacist within the MDT are crucial to safe management of medicines especially if they are mixed with thickening agents which may alter the desired therapeutic effect (Cichero 2013). During assessment and treatment, medication reviews are essential to identify any impact on the swallow as a result of medication. The following are examples of medication effects on swallowing, taken from the online resource DMR Health Standard 07–1 (2011).

- *Dysphagia as a side effect of medication*, e.g. medications that affect the smooth and striated muscles of the oesophagus involved in swallowing may cause dysphagia, such as preparations with anticholinergic and antimuscarinic effects.
- *Medications that cause xerostomia*, e.g. angiotensin-converting enzyme inhibitors, antihistamines and selective serotonin reuptake inhibitors, may interfere with swallowing by impairing the person's ability to move food.
- *Medications that cause movement disorders*, e.g. antipsychotic/neuroleptic medications which impact on the muscles of the face and tongue.
- *Dysphagia as a complication of the therapeutic action of the medication*, e.g. antiepileptics, narcotics and other medications that depress the central nervous system, can decrease awareness and voluntary muscle control that may affect swallowing.
- *Medications that can cause oesophageal injury and increase risk*, e.g. non-steroidal anti-inflammatory agents: These can cause dysphagia because of injury to the oesophagus as a consequence of local irritation.

Interactions between enteral tube feed formulations and medications can be clinically significant. As a general rule, if the absorption of a drug is affected by food or antacids, it is also likely to be affected by the feed, and a time lag between feeding and drug administration is necessary (BAPEN 2003). The dietitian will need to be aware of the prescribed medications and make the necessary adjustments to the timing of enteral tube feeding to minimise risk.

3.5 Quality-of-Life Issues

Any intervention should consider the four principles of medical ethics—respect for autonomy, beneficence, non-maleficence and justice (Beauchamp and Childress 2013) as well as the issue of consent, which always needs to be obtained for dietetic

interventions. When dealing with the general population, one customarily obtains consent verbally. In clients with cognitive impairment, however, the issue about capacity to consent needs to be explored fully. When capacity to consent is being determined, it is essential to involve both the individual and the carers in the assessment and treatment process and to communicate openly (Burton et al. 2011).

Nutritional assessments can be conducted without considering whether the individual has the ability to give consent to treatment, but in order to treat the individual, that individual's capacity must be determined. Determining capacity to consent must always be time and decision specific. It is important to remember that an individual should not be treated as unable to make a decision unless all practicable steps to help him/her have been taken without success. This includes the use of alternative forms of communication, for example:

- Short, concise, non-complex language
- Body language
- Eye pointing
- Symbolised information
- Photographs
- Signing
- Audio-visual

In the UK, legislation exists to provide a legal framework for decision-making on behalf of adults who lack the capacity to make specific decisions for themselves. It also provides the means for adults, with the capacity to do so, to plan ahead in the event of future incapacity.

Readers are recommended to refer to the relevant legislation pertaining to their geographical work base as legislation may differ between countries. In the UK, for example, there are three different acts dealing with this issue, namely:

- Scotland—The Adults with Incapacity Act (Scottish Parliament 2000).
- England and Wales—The Mental Capacity Act (MCA) (Department of Health 2005).
- Northern Ireland—Seeking Consent [DHSSPS (2003)].

In clinical practice, individuals who maintain the oral route seem to have fewer reflux problems than those who are nil by mouth. Nutrition and hydration therefore need to be supported for as long as possible by establishing a safe and effective eating environment, using texture modification and judicious addition of supplements. In severe dysphagia and/or severe malnutrition, the dietitian and the SLT work together to support the individual and carers in the decision-making process, where the transition from an inadequate and unsafe oral route to the enteral feeding route is clinically recommended. Where the individual is unable to participate in the decision-making process and consent to treatment, best interest decisions should be made by the whole MDT.

4 Education and Training Role

Carers and individuals with dysphagia may struggle with the day-to-day practical management of food and fluids. Interactive and practical training sessions underpinned with theory and delivered in partnership with the SLT are an invaluable method of training, thus enabling people to experiment with using thickeners in a range of food and fluid preparations.

Key components of training for individuals with dysphagia and carers include:

Understanding the rationale for thickening and the risks of non-compliance.
Understanding the rationale for texture modification of foods and items which are prone to leaching.
Understanding the sensory properties of thickeners.
Understanding foods unsuitable for texture modification, e.g. pureed lettuce.
Menu planning to reduce repetition of using same foods, avoiding taste fatigue.
Correct preparation of textured foods to preserve nutritional content.
Correct preparation of thickened fluids depending on the type of thickener used.

Presentation to enhance compliance.
Food fortification using prescribed and non-prescribed products.
Correct usage of prescribed supplementary drinks and puddings.

Key components of training for health and social care professionals include:

Understanding the role and responsibilities of the dietitian.
Understanding the consequences of malnutrition in relation to dysphagia.
Understanding the rationale of nutritional consequences of texture modification.
Correct usage of any prescribed supplements, including type and amount of thickeners.

It has been shown that when implementing a diet for dysphagia, training enhances patient safety and increases energy intake (Garcia et al. 2010; Garcia and Chambers 2010). Dietitians along with the SLT are integral in training medical and nursing staff, healthcare assistants and carers at all levels on the recognition and consequences of dysphagia. Management options must also be included, so that all aspects of the swallowing mechanism and consequences of undernutrition can be highlighted and discussed.

5 Summary

The registered dietitian is one of a range of professionals involved in dysphagia management, and the role can be wide ranging, from traditional nutritional management through to a whole-systems approach encompassing screening, assessment, diagnosis and organisation of the modified textures within a dynamic nutritional framework. A person-centred approach is essential to provide nutrition in a manner which not only sustains nutrition and hydration integrity but also serves to enhance the individual's quality of life. The dietitian's expertise lies in using the available clinical evidence, applying this to the individual's wider health and well-being needs, devising and delivering targeted training to the individual, carers and other key health and social care professionals, so ensuring that the resultant recommendations are wholly person centred.

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Direct and Indirect Therapy: Neurostimulation for the Treatment of Dysphagia After Stroke

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Abstract

Swallowing problems (dysphagia) are common after brain injury and can affect as many as 50% of patients in the period immediately after stroke. In some cases this can lead to serious morbidity, in particular malnutrition and pulmonary aspiration. Despite this, swallowing therapies remain controversial, with limited evidence base and few objective outcome measures that would provide scientific support for the observed changes. Moreover, swallowing can recover in some patients to a safe level within weeks, introducing stroke as an interesting model for understanding brain recovery and compensation. A better understanding of these adaptive processes, seen during the spontaneous recovery phase, may help in developing therapeutic interventions capable of driving brain changes and encouraging the recovery process and is therefore a key goal for clinical neuroscience research warranting systematic investigation. In this chapter, we will review current knowledge and discuss some of the pioneering work conducted by researchers in the field of human

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swallowing neuromodulation over the last decade. The chapter will provide insights as to how the cerebral control of swallowing can be studied non-invasively in the human brain using neuroimaging tools and neurostimulation techniques. In addition, it will describe how both using these neurostimulation techniques to manipulate the brain's natural capacity to re-organise (cortical plasticity) after injury or in response to new stimuli and studying brain capacity to re-organise help in the development of novel therapies for the treatment of dysphagia and other motor disorders in humans.

1 Introduction

Deglutition (swallowing) is a usually effortless everyday sensorimotor task providing nutrition and hydration. During deglutition, the safe transport of the food through the oropharynx towards the stomach for digestion without compromise of the integrity of the airway, a multi-dimensional dynamic network involving 26 pairs of muscle, 5 cranial nerves and different levels of the central nervous system (CNS) have to operate in a timely manner. Deglutition is an integral component of feeding, learned during gestation, organised at birth (Hooker 1954), and essential for the continuation of life.

Dysphagia or swallowing difficulties are common following different disorders and structural or neurogenic impairments (Table 1). The consequences of dysphagia can become extremely debilitating in specific cases, with the major complications being malnutrition, dehydration and aspiration pneumonia. Patients who experience dysphagia as a result of cerebral injuries such as stroke (Singh and Hamdy 2006) may experience these life-threatening complications. In particular, aspiration pneumonia is a common consequence of dysphagia (Johnson et al. 1993; Mann et al. 1999; DePippo et al. 1994; Kidd et al. 1995; Katzan et al. 2003; Cabre et al. 2010; Martino et al. 2005) and carries a significantly increased risk of morbidity and mortality (Katzan et al. 2003; Smithard et al. 1996). Moreover, neurogenic causes of dysphagia often lead to patients requiring enteral nutrition (Foley et al. 2009; Ha and Hauge 2003) and increase the need for institutionalised care (Smithard et al. 2007).

Table 1 Common causes of dysphagia

Structural causes of dysphagia	Causes of neurogenic dysphagia
• Amyloidosis • Cervical spine osteophytes • Congenital anatomic abnormalities, e.g. cleft palate • Iron and B12 deficiency • Oral malignancies of the tongue and palate • Pharyngeal malignancy of the epiglottis, tongue base or larynx • Salivary gland disease • Skull base tumours • Thyroid disease • Thyroid tumours • Zenker's diverticulum	• Cerebral palsy • Guillain-Barre and other polyneuropathies • Head trauma[a] • Huntington's disease • Infectious disorders, e.g. Meningitis, Syphilis, Diphtheria, Botulism, and Encephalitis • Medication side effects • Motor neurone disease (MND)[a] • Multiple Sclerosis (MS)[a] • Myasthenia Gravis • Myopathy, e.g. Polymyositis, Dermatomyositis, Sarcoidosis • Neoplasms, e.g. brain tumour • Parkinson's disease and other movement and neurodegenerative disorders • Post-polio syndrome • Progressive supranuclear palsy • Stroke[a] • Torticollis • Tardive dyskinesia • Wilson's disease

[a]Indicates conditions which specifically cause pyramidal disease. In the UK stroke is the most common cause of neurogenic dysphagia

2 Neurophysiological Substrates of Swallowing and Dysphagia Post-stroke

2.1 Neurophysiology of Swallowing: Summary

Historically, the central neural control of swallowing was believed to be almost entirely dependent on brainstem reflexive mechanisms (Miller 2008).

However, in recent years, the role of the cerebral cortex in swallowing has received increased recognition and has been the subject of much research (Michou and Hamdy 2009). Its role in the control of human swallowing was first reported over a century ago by Bastian (Bastian 1898), who described a patient suffering from dysphagia following a hemispheric stroke.

Safe deglutition requires the timely coordination of several muscle groups from the upper aero-digestive system and is controlled by a topographically diverse brain network. In brief, cortical and subcortical areas communicate with motor nuclei in the brainstem for the execution of the swallow. Swallowing patterned response is a result of polysynaptic connections with several neurotransmitters transferring information across and within brain areas, such as the sensorimotor cortex, the supplementary motor areas (SMA), the premotor cortex, basal ganglia, brainstem and cerebellum. This communication between the areas of CNS is important for the sensorimotor integration and subsequent motor execution, the formulation of the motor plan and the initial drive and, lastly, the modulatory executive function for the motor output of the swallow. The oral preparatory phase is under voluntary control, while the pharyngeal stage is a more automatic, involuntary sequence of neuromuscular events following the elicitation of the swallowing response. It is important to understand that sufficient cortical and subcortical drive can also override this sequence.

Unsurprisingly, much of our understanding of the neural control of swallowing has come from invasive neurophysiological observations in animals such as the seminal studies conducted by Miller and Sherrington (Miller 1920; Miller and Sherrington 1916). Replication studies by other authors (Hamdy et al. 2001; Issa 1994; Weerasuriya et al. 1979; Goldberg et al. 1982; Huang et al. 1988, 1989; Yao et al. 2002; Sumi 1969; ten Hallers et al. 2004; Amarasena et al. 2003; Martin et al. 1997, 1999; Narita et al. 1999; McFarland and Lund 1993; Grelot et al. 1992; Jean 2001) have shown that artificially stimulating cortical swallowing areas using invasive electrical micro-stimulation of either cortical hemisphere in anaesthetised animals is capable of inducing full swallow responses visible to the investigator, providing evidence that swallowing musculature is represented bilaterally. In humans, neural cartographer Wilder Penfield and colleagues, using the same techniques (invasive electrical micro-stimulation) in anaesthetised patients undergoing neurosurgery, demonstrated that stimulation to certain parts of the cerebral cortex could also induce swallowing (Penfield 1937). One of the first non-invasive studies of swallowing conducted in canines showed that with the use of transcranial magnetic stimulation (TMS) devices, stimulation of the cerebral cortex from the scalp surface could still elicit full swallowing response (Valdez et al. 1993).

Nowadays, a number of TMS techniques are used for routine diagnostic application in neurophysiological settings (Kobayashi and Pascual-Leone 2003; Rossi et al. 2009). Transcranial magnetic stimulation is a safe and non-invasive technique which uses a high current pulse generator discharging currents of several thousand amperes that flow through a coil of wire. The result is the generation of a brief magnetic pulse with field strengths up to several Tesla. When the coil is placed over the subject's head, the magnetic field undergoes little attenuation by extracerebral tissues (scalp, cranial bone, meninges, and cerebrospinal fluid layer) and induces an electrical field sufficient to depolarize superficial axons and to activate cortical neural networks. Several physical and biological parameters play a role in the outcome of the stimulation, such as the type and orientation of coil, the distance between the coil and the brain, the magnetic pulse waveform and the intensity, frequency and pattern of stimulation (Lefaucheur et al. 2014). Perpendicular currents of sufficient strength are generated to depolarize neuronal elements and evoke electromyographic responses on the targeted musculature, called motor evoked potentials (MEPs).

With TMS, the midline structures involved in swallowing, mylohyoid, pharyngeal and oesophageal musculature were mapped in healthy volunteers

by Hamdy and colleagues (Hamdy et al. 1996). In health, human swallowing musculature in the cerebral cortex was shown to be discretely and somatotopically represented bilaterally (motor and premotor cortices) with a marked display of interhemispheric asymmetry, independent of handedness; thereby inferring the presence of 'dominant' and 'non-dominant' hemisphere for the task of swallowing.

In the recent years, neuroimaging and neurostimulation studies have provided insights into the activation patterns of the swallowing sequence and muscle activities (for reviews (Michou and Hamdy 2009; Martin 2009)) and verified earlier results. An activation likelihood estimation meta-analysis of imaging studies on swallowing (Soros et al. 2009) showed that the most consistent areas that are activated in these neuroimaging studies include the primary sensorimotor cortex (M1/S1), sensorimotor integration areas, the insula and frontal operculum, the anterior cingulate cortex and supplementary motor areas (SMAs). Recently, Mihai et al. (2014) using dynamic causal modelling examined the potential effective connectivity of areas such as SMA, M1/S1 and insula during swallowing and showed that there is high probability of bidirectional connections of the areas such as the SMA and M1/S1 during swallowing. In addition the cerebellum, important in planning and executing complex motor tasks, has been strongly implicated in the neurophysiological control of swallowing, both through animal studies (Colombel et al. 2002) and human functional brain imaging (Hamdy et al. 1999a; Mosier et al. 1999; Zald and Pardo 1999; Mosier and Bereznaya 2001; Suzuki et al. 2003; Malandraki et al. 2009; Mihai et al. 2013) as well as TMS studies as it will be described later.

2.2 Neurophysiology of Dysphagia in Stroke: Summary

In summary, dysphagia in stroke is experienced following disruption of or damage within swallowing neural network. This disruption or damage could evolve either at the level of the descending corticobulbar tracts disrupting the communication between the diverse swallowing network, or the lesion may disrupt the cortical swallowing network or/and could be localised at the level of the central pattern generator. Paciaroni and colleagues (2004) presented data based on the clinical assessment of stroke patients that oropharyngeal dysphagia is more frequent in large middle cerebral artery (MCA) infarction and that size of the lesion is more important than the location for the presentation of swallowing impairments post-stroke. The latter has been validated by others showing that the size of the lesion as an indicator for higher risk of dysphagia (Gonzalez-Fernandez et al. 2008; Falsetti et al. 2009; Suntrup et al. 2015a).

The changes that patients with stroke experience in their swallowing function could be summarised as changes in coordination of the swallowing events or impairment of muscle control (changes of tone, strength), leading to a reduction of swallowing safety. Common changes in swallowing physiology include the following:

- Reduced lingual control
- Delayed/absent swallowing reflex
- Reduced pharyngeal peristalsis
- Reduced laryngeal adduction
- Upper oesophageal sphincter (cricopharyngeal) dysfunction
- Longer pharyngeal transit duration times
- Laryngeal penetration and aspiration before/after swallow and others

Several attempts have been made to associate specific changes in swallowing with topographical neural changes following stroke. In the past, pure subcortical stroke has been associated with impairments in oral transfer (Cola et al. 2010), while others have observed that supratentorial lesions may produce buccofacial apraxia (Steinhagen et al. 2009), while impairments of lingual control have been observed in more frontal lesions compared to parietotemporal (Daniels and Foundas 1999). Posterior territory lesions have been associated with pharyngeal dysfunction on formal imaging assessments (Terre and Mearin 2006). Increased residue in the valleculae or pyriform sinuses has been associated with strokes of subcortical and posterior circulation

(Kim et al. 2014). Upper oesophageal sphincter dysfunction has been primarily associated with brainstem lesions and lateral medullary infraction (Steinhagen et al. 2009; Kwon et al. 2005).

3 Mechanisms of Recovery of Swallowing After Cerebral Cortex Damage

Given sufficient time, a large proportion of dysphagic stroke patients eventually recover the ability to swallow again (Mann et al. 1999; Barer 1989). The mechanism for this recovery, seen in many of the initially dysphagic stroke patients, has, however, remained controversial. As a first step towards understanding the mechanisms, midline structures involved in swallowing such as the pharyngeal, oesophageal and mylohyoid musculature were mapped in healthy volunteers (Hamdy et al. 1996). As aforementioned, the findings of this study demonstrated that in health, human swallowing musculature in the cerebral cortex was discretely and somatotopically represented in both hemispheres in the motor and premotor cortices, with interhemispheric asymmetry, independent of handedness. In a seminal study of swallowing in stroke using TMS, both dysphagic and non-dysphagic patients had the cortical topography of their pharyngeal musculature serially mapped over several months (Hamdy et al. 1996) (Fig. 1). Results from an earlier study by the same authors (Hamdy et al. 1996) taken together with a follow-up study (Hamdy et al. 1998a) showed that the cortical map representation of the pha-

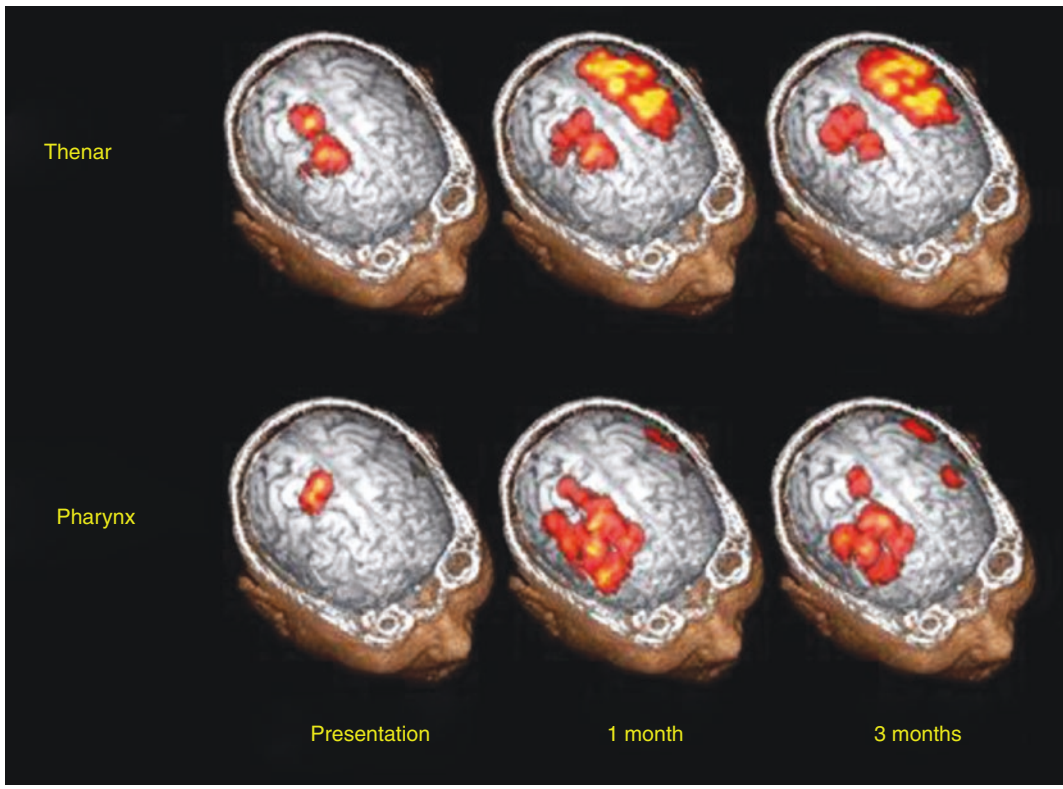


Fig. 1 Transcranial magnetic stimulation and magnetic resonance imaging co-registered representational map data from pharynx and thenar in a left hemisphere stroke patient. This patient, who was dysphagic at presentation, recovered swallowing function by one month, which was sustained at three months. Recovery of swallowing appears correlated to compensatory reorganisation of the unaffected hemisphere, whereas hand recovery appears to occur in the damaged hemisphere. *Reprinted from Hamdy et al. (1998a)

ryngeal musculature in the undamaged hemisphere markedly increased in size in dysphagic patients who recovered swallowing, whilst there was no change in patients who had persistent dysphagia or in patients who were non-dysphagic throughout. Furthermore, changes seen in the damaged hemisphere in any of the groups of patients were not significant. These observations imply that over a period of weeks or months, the recovery of swallowing after stroke may be reliant on compensatory strategies of cortical reorganisation, through neuroplastic changes, mainly observed in the undamaged hemisphere.

The validity of early observations on the usefulness of TMS in the study of swallowing musculature organisation and reorganisation (Hamdy et al. 1996, 1998a) has been supported by evidence via TMS studies in oesophageal musculature by Khedr et al. (2008) and in mylohyoid musculature by Gallas et al. (2010), both of which illustrate the potential therapeutic role of neuroplastic changes in the unaffected hemisphere of dysphagic patients. This situation appears to differ from the recovery pattern observed for the limb muscles, where magnetic stimulation and functional magnetic resonance imaging studies, including the study by Hamdy et al. (where limb function was used as a control for recovery pattern (Hamdy et al. 1996; Pascual-Leone et al. 2005; Calautti et al. 2001; Marshall et al. 2000)), have indicated that limb recovery after hemiparesis is more likely to result from an increase in the activity of the remaining viable cortex in the damaged hemisphere. In such cases, scope for expansion of a normal connection from the undamaged part of the brain may be a limiting factor in recovery. However, cortical reorganisation for limb function accompanied with functional changes has also been observed to occur within the contralesional hemisphere (Cramer et al. 1997; Ward et al. 2003).

A study with functional MRI (Li et al. 2009) in a small number of stroke patients in the acute stage has shown that in the acute stage unilateral stroke can result in dysphagia with no specific laterality dependency and that effective recovery is associated with compensation or recruitment of areas in the intact hemisphere, validating previously observed studies with TMS. Recently, a study compared the recovery stroke patients whose swallowing ability recovered post-stroke with age-matched healthy participants (Mihai et al. 2016). The results showed that patients exhibited decreased fMRI-activation in the entire swallowing network apart from an increase of activation in the contralesional primary somatosensory cortex and the ipsilesional anterior cerebellum, validating further the importance of contralesional cortical reorganisation post-stroke as the important factor for dysphagia.

4 Current Clinical Management of Dysphagia in Stroke

Current clinical guidelines for the management of dysphagic patients mainly constitutes assisting patients to use compensatory strategies to prevent complications of penetration or aspiration of the boluses, or change in the method of nutritional and hydration intake to allow stabilisation of the nutrition status, whilst any natural recovery takes place (Speyer et al. 2010). Delivered by speech and language therapists, compensatory manoeuvers and exercises promote a form of dysphagia rehabilitation, and these include a variety of head and neck exercises (chin tuck, head-turn or Mendelsohn manoeuver), but with limited evidence to support their efficacy (Geeganage et al. 2012). However methodological studies conducted with different modalities such as fMRI (Peck et al. 2010; Arima et al. 2011) are starting to appear in the literature. In addition, certain behavioural techniques, described earlier by Shaker and colleagues, have been shown to reduce pharyngeal residue after swallowing by promoting opening of the upper oesophageal sphincter by reinforcing the actions of the suprahyoid muscles (Shaker et al. 2002). Nonetheless, patients often become increasingly dependent during their lengthy hospital stays and are generally placed upon a modified consistency diet or made nil by mouth if their symptoms are

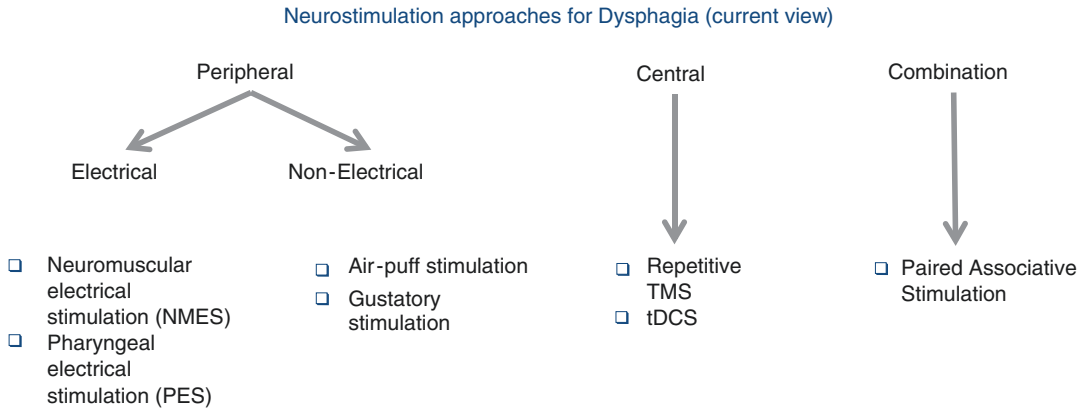


Fig. 2 The current list of direct and indirect neurostimulation approaches for dysphagia rehabilitation covered in this review is shown

severe. Artificial feeding either via nasogastric tube or percutaneous endoscopic gastrostomy is frequently resorted to but has been shown to have no benefit in reducing the risk of pneumonia or aspiration or in improving patient outcomes (Norton et al. 1996; Dennis et al. 2005a, b). According to the recent Cochrane review (Geeganage et al. 2012), there remains insufficient data on the effect of swallowing therapy, feeding, and nutritional and fluid supplementation on functional outcome and death in dysphagic patients with acute or subacute stroke.

In summary, it is well established that significant reorganisational change, observed as either beneficial or maladaptive, can occur in the adult cortex throughout life and after stroke lesions (Murphy and Corbett 2009). Furthermore, unmasking of existing connections, shifting of synaptic weighting, even sprouting of new dendritic connections and formation of new synapses are possible (Sanes and Donoghue 2000; Kaas 1997) and are part of the neuroplastic changes to promote recovery post-stroke. Treatment for dysphagia post-stroke should be timely and should take place early enough following stroke to avoid the deliberating consequences of aspiration pneumonia and malnutrition. This is the notion behind the emerging use of neurorehabilitation strategies with neurostimulation interventions: to accelerate the natural process of recovery. Neurorehabilitation strategies have been applied to dysphagic stroke patients and have shown favourable outcomes although their effectiveness has yet to be confirmed.

There is some uncertainty that neurostimulation techniques can and will be viewed as powerful tools in the hand of a rehabilitation clinician in the future. However, currently the field of neurorehabilitation science in dysphagia is diverse in nature and methodological differences across research studies are accentuating the need for further investigations. Below we review the different direct and indirect approaches to dysphagia rehabilitation in stroke. In Fig. 2, we present the different approaches discussed in this chapter.

5 Modulation of Brain Plasticity by Neurostimulation

There are a number of different neurostimulation techniques that have been applied to the study of human cerebral control of swallowing and to experimentally manipulate cortical reorganisational mechanisms for therapeutic benefit. These studies show promising data; however clinical trials have proven challenging, with sample sizes being small and as a result none of these modalities are currently recommended for clinical use (Cheeran et al. 2009).

Most of the research in the dysphagia neurostimulation field has been built upon the results

provided from the following studies mainly: (a) stimulation of the pericentral cortex or the frontal cortex can evoke swallowing in primates (Lamkadem et al. 1999; Doty 1951), (b) electrical stimulation of the pharyngeal branch of glossopharyngeal nerve can elicit the swallowing reflex (Kitagawa et al. 2002), (c) bulbar-cortical-bulbar feedback loops participate in the pharyngeal phase of swallowing (Narita et al. 1999; Sumi 1972), (d) swallow-related neurons in the medulla are influenced by spatial summation of afferent stimuli (Ootani et al. 1995; Sessle and Kenny 1973) and lastly (e) the repetitive electrical stimulation of SLN can evoke swallowing reflex in a number of animal species (Doty 1951).

5.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

5.1.1 Cortical rTMS

Repetitive TMS uses regularly repeated stimulation to a specific site over the cortex and is known as fast or high-frequency rTMS when used at rates above 1 Hz. In general, rates of stimulation of 1 Hz or below have inhibitory effects whilst those above 3 Hz have excitatory effects on the cortex (Bailey et al. 2001; Ridding and Rothwell 2007). A number of randomised placebo-controlled studies have been conducted for the use of rTMS in a variety of pathological conditions and diseases such as stroke, depression, tinnitus, obsessive–compulsive disorders, pain syndromes, migraines, refractory epilepsy, dystonia, tremors, and spasticity (for reviews, see (Lefaucheur et al. 2014; Chervyakov et al. 2015)). In an extensive evidence-based synthesis of established and potential therapeutic applications of rTMS, Lefaucher and colleagues (2014) concluded that Level A recommendation has been achieved so far for the beneficial effect of high-frequency rTMS on neuropathic pain (target: M1 contralateral to pain side) and major depression, but highlighted the fact that more controlled studies should take place to verify the utility while controlling for factors as time of introduction of the treatment and concurrent pharmacological interventions. The changes following the application of the rTMS are thought to be relative to synaptic, and/or molecular genetic mechanisms (changes in gene expression, enzyme activity, and neuromediator production) levels. One of the most important mechanisms underlying the changes following rTMS is thought to be changes in neurotransmitter concentrations following rTMS, such as endogenous dopamine (Strafella et al. 2001; Ko et al. 2008).

Similar to all brain neurostimulation techniques, several parameters play a role for the effective application of rTMS application, including coil orientation, coil type, target selection, distance to target (from the maximum output of magnetic field to the brain area target for stimulation) and specific parameters such as intra-train interval, pulse width, frequency of the pulses, duration of the stimulation protocol and intensity used to deliver the stimulation. Worth mentioning is that the repetition of application within a protocol (treatment regimen) as well as factors such as time of the day (circadian rhythms) and brain activation state prior to treatment can play a role in the outcome (Siebner and Rothwell 2003).

The risks of the application of single pulse TMS over swallowing motor cortex are very low and no significant side effects have been shown to be produced in healthy individuals (Gow et al. 2004). However, much longer trains of stimulation are used in rTMS, and have the potential to induce seizures, especially when given at high intensities or frequencies and can also induce a spread of cortical excitation (Kandler 1990). Thus, guidelines were drawn up to limit rTMS applications in humans based on the frequency and intensity of the stimulation applied (Wassermann 1998) (updated by Rossi et al. (2009)). There are a number of contraindications to the use of TMS because of the magnetic field produced; these include studying people with cardiac pacemakers, electronic

implants and certain metal foreign bodies within the head as the coil may induce movement or heating. Patients with significant heart disease or raised intracranial pressure are at increased risk of complications following seizures and should be excluded, as should those on medications that are CNS active or lower the seizure threshold. Other contraindications include a history of epilepsy and pregnancy (Rossi et al. 2009; Wassermann 1998).

The pharyngeal motor cortex appears to be specifically responsive to stimulation at 5 Hz. When 100 pulses of rTMS are given over the cortex at 80% of pharyngeal threshold (capped at 120% of thenar threshold to comply with safety guidelines), there is increased excitability of the corticobulbar projection to the pharynx, which lasts for over 1 h (Gow et al. 2004). Jefferson et al. (2009a) applied differing trains of 5 Hz rTMS to pharyngeal motor cortex, ranging from 100 to 1000 pulses. This work found that 250 pulses at low threshold intensities were as effective as longer or stronger 5Hz rTMS trains at inducing plasticity in the swallowing motor system. Conversely, Mistry et al. (2007) have shown that using an inhibitory 1 Hz rTMS paradigm for 10 min (600 magnetic stimulation pulses) at the 120% of pharyngeal threshold, it is possible to generate a unilateral virtual lesion in the pharyngeal motor cortex that affects swallowing neurophysiology for up to 45 min and can also interfere with swallowing behaviour, as measured using reaction time swallowing tasks. Verin et al. (2012) have used videofluoroscopy to examine the effects of 1 Hz rTMS on oropharyngeal motor cortex and observed a transient change in swallowing behaviour in a way reminiscent to that seen in stroke patients with hemispheric lesions.

Since the publication of the aforementioned seminal work with the neurostimulation paradigms in health, rTMS has been studied vastly over the last few years as means to either augment or as a treat-alone avenue for dysphagia rehabilitation. The effects of rTMS have been studied mostly in stroke patients in studies where various outcome measures were employed. There are now two published systematic reviews and meta-analyses for brain stimulation in dysphagia, where studies with rTMS on stroke patients with dysphagia were included (Pisegna et al. 2016; Yang et al. 2015).

Table 2 presents all the studies where rTMS was performed to dysphagic patients.

Even though only the effects of single sessions of rTMS have been investigated only in health, several studies have used either excitatory (Khedr et al. 2009; Khedr and Abo-Elfetoh 2010; Park et al. 2013, 2017; Momosaki et al. 2014; Cheng et al. 2017; Du et al. 2016; Lee et al. 2015) or inhibitory (Verin and Leroi 2009; Kim et al. 2011; Lim et al. 2014; Ghelichi et al. 2016; Du et al. 2016) rTMS treatment regimen in stroke patients with dysphagia repeatedly over a different number of days with few exceptions (Michou et al. 2014). Additionally, an interesting fact to mention is that there are differences in the rationale behind the target selection (lesioned vs. unlesioned cortical representation) to apply the stimulation. Figure 3 shows the different protocols together with the underlying rationale. In addition, different cortical musculature representations, i.e. representations of upper oesophageal sphincter (Khedr et al. 2009), mylohyoid (Verin and Leroi 2009; Kim et al. 2011) and pharyngeal (Park et al. 2013; Michou et al. 2014), have been targeted with varying parameters or intensities.

A recent meta-analysis (Pisegna et al. 2016) showed that there is greater benefit in swallowing outcomes in stroke patients with dysphagia following the application of rTMS (compared to transcranial direct current stimulation (see below)); however, some of the aforementioned differences in the studies' parameters have not been taken into account. Another systematic review and meta-analysis (Momosaki et al. 2016a) showed that there is only low-quality evidence for the effectiveness of the rTMS on outcome measures, such as penetration-aspiration scores, and there is a

Table 2 The different parameters of the studies using rTMS are shown in this table

Study	Demographics		Study design	Parameters						Results/comments
	Total participants	Characteristics		Stimulation	Design	Hemisphere	Location (motor cortex)	Coil size	Schedule	
Khedr et al. (2009)	26 (10 male) 57.3 ± 12 yoa	Acute hemispheric stroke	RCT (rTMS vs. Sham)	3 Hz rTMS (120% rMT)	10 blocks of 30 pulses	Affected	Oesophageal	90 mm figure-of-8	5 days, 10 min/day	Real rTMS increased MEP amplitude bilaterally, decrease dysphagia Severity Degree (self-rated)
Verin and Leroi (2009)	7 (4 male) 65 ± 10 yoa	Hemispheric or sub-hemispheric	Uncontrolled case series	1 Hz rTMS (120 % rMT)	1 block	Unaffected	Mylohyoid	70 mm figure-of-8	20 min, once a day, 5 days	Real rTMS reduced Swallowing Reaction time on VFS (liquids and paste boluses), the AP scores with liquids, and the residue score with paste
Khedr and Abo-Elfetoh (2010)	22 (16 male) LMI group: 56 ± 15 yoa BI: 58 ± 10 yoa	LMI = 11, BI = 11	Controlled design	3 Hz rTMS (130% rMT unaffected)	10 blocks of 30 pulses	Bilateral	Oesophageal	90 mm figure-of-8	5 days, 10 min/day	Both groups reduced Dysphagia Severity Degree (self-rated). Results maintained over 2 months
Kim et al. (2011)	30 (17 male) 68.2 ± 1 yoa	Infarct (n = 15), Haemorrhage (n = 13), TB I (n = 2)	RCT (2 rTMS arms vs. Control)	5 Hz rTMS (100% rMT) 1 Hz rTMS (100% rMT)	20 blocks of 50 pulses 1 block of 1200 pulses	Affected Unaffected	Mylohyoid 'hot spot'	90 mm figure-of-8	10 days, 20 min/day	1 Hz rTMS improved Functional Dysphagia Scale and AP scores
Park et al. (2013)	18 (10 male) 71 ± 7 yoa	3 haemorrhage, 15 infarction	RCT (treatment vs. Control)	5 Hz rTMS (90% rMT)	10 blocks of 50 pulses	Unaffected	Pharyngeal	70 mm figure-of-8	10 days, 10 min/day	Real rTMS reduced AP scores and residue
Michou et al. (2014)	18 (15 male) 66 ± 3 yoa	Hemispheric and sub-hemispheric	RCT (3 arms) T1: rTMS T2: PES T3: PAS	5 Hz rTMS (90% rMT)	5 blocks of 50 pulses	Unaffected	Pharyngeal	70 mm figure-of-8	Single	No significant difference between real and sham for cortical excitability and no difference in cumulative AP scores

Momosaki et al. (2014)	4 (2 male) 56–80 yoa	Bilateral stroke	Uncontrolled case series	3 Hz rTMS (130% rMT)	Twice × 300 LH and 300 RH, total 1200 pulses/day	Bilateral	Pharyngeal	70 mm figure-of-8	6 day	Reduced AP score in ¾ patients
Lim et al. (2014)	Total: 47 rTMS arm, *n* = 14 (6 males) 59.8 ± 11 yoa	Unilateral hemispheric stroke	Controlled Trial (3 arms) T1: rTMS T2:NMES T3: Traditional therapy	1 Hz rTMS (100% rMT)	1200 pulses (20 min)	Unaffected	Pharyngeal	figure-of-8	5 days/week, 2 weeks	Decrease in Functional Dysphagia Severity and decrease of AP after rTMS
Cheng et al. (2015)	4 (2 male) 71 yoa	Hemispheric and sub-hemispheric stroke	Case series	5 Hz rTMS (90 % rMT)	3000 pulses/ session	Site with minimum intensity to elicit MEP	'Tongue' hotspot	70 mm figure-of-8	5 days/week, 2 weeks	Improvement in videofluoroscopy measurements and quality of life after real rTMS.
Cheng et al. (2017)	15 (4 male) 63.3 yoa	Chronic stroke patients, first ever dysphagia	RCT (11 real rTMS vs. 4 Sham)	5 Hz rTMS	3000 pulses/ session	Affected	Tongue (intraoral EMG)	70 mm figure-of-8	5 days/week, 2 weeks	No significant different or treatment effects
Ghelichi et al. (2016)	4 male Age range: 59–72	Acute stroke	Observational	1 Hz plus traditional therapy (TT)	1200 pulses (20 min)	Unaffected	Tongue (Submental EMG)	70 mm figure-of-8	5 days/week (3 days TT, 6 weeks	Improved clinical score after 10th session
Du et al. (2016)	40 (26 male) 58.3 ± 2 yoa	Acute stroke	RCT (High frequency vs. low frequency vs. sham)	3 Hz vs. 1 Hz vs. Sham	1200 pulses	3 Hz: affected, 1 Hz unaffected	'Tongue' hotspot Submental	90 mm figure-of-8	5 daily sessions	Both high and low frequency improved swallowing. 3 Hz increased excitability only ipsilaterally but 1 Hz bilaterally
Lee et al. (2015)	24 (17 male) 63.5 ± 11.3 yoa	Stroke patients (age matched)	Case control (submental vs. APB	10 Hz rTMS (110% rMT)	1000 over 10 min	Affected	'Tongue' hotspot vs. APB	70 mm figure-of-8	5 days/week, 2 weeks	Swallowing improved only for those with rTMS to submental
Park et al. (2017)	33 (23 male) 65.9 ± 12.4 yoa	Unilateral stroke subacute stage	RCT (Bilateral vs. Unilateral vs. Sham)	10 Hz rTMS (90% rMT)	500 pulses	Bilateral vs. unilateral (affected)	'Tongue' hotspot Submental	70 mm figure-of-8	5 days/week, 2 weeks plus therapy post-stimulation	Bilateral stimulation showed cumulative effects compared to unila\teral

Key: *yoa* years of age, *TT* traditional treatment, *RCT* randomised controlled trial, *rMT* resting motor threshold, *MEP* motor evoked potential, *VFS* videofluoroscopy, *AP* aspiration-penetration, *PES* pharyngeal electrical stimulation, *PAS* paired associative stimulation, *LH* left hemisphere, *RH* right hemisphere, *NMES* neuromuscular electrical stimulation

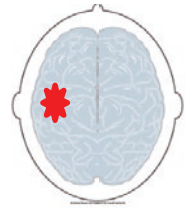
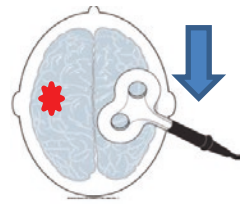
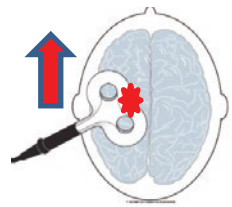
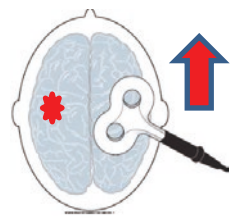
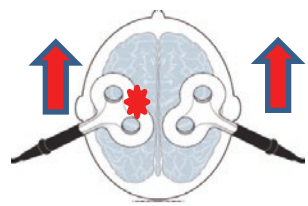
Research Studies	Lesion 	Rationale
Verin and Leroi (2009), Kim et al. (2011), Lim et al. (2014), Ghelichi et al. (2016), Du et al. (2016) and Park et al. (2017)	Inhibitory Stimulation over the contra-lesioned (healthy) M1. 	Decrease in the transcallosal inhibition to the affected hemisphere and an increase in the excitability of healthy hemisphere.
Khedr et al. (2009), Cheng et al. (2017), Du et al. (2016), Lee et al. (2015) and Park et al. (2017)	Excitatory Stimulation over the lesioned M1 	Increase in cortical excitability of the lesioned hemisphere
Park et al. (2013) and Michou et al. (2014)	Excitatory Stimulation over the conta-lesioned M1 	Undamaged hemisphere will promote recovery.
Khedr and Abo-Elfetoh (2010), Momosaki et al. (2014) and Park et al. (2017)	Bilateral excitatory stimulation 	Clinical identification of the dominant hemisphere is frequently difficult. Bilateral stimulation method may generalize the effects.

Fig. 3 Studies with repetitive TMS applied on the cortical level on dysphagic stroke patients. The rationale for using either excitatory (*red upwards arrow*) or inhibitory (*blue downwards arrow*) over the lesioned or unlesioned (lesion marked with a start) is shown in the third column. Reprinted from Michou et al. (2016)

need for further well-designed studies with larger samples. Nevertheless, it seems that the selection of the target hemisphere (lesion vs. non-lesion hemisphere) and the nature of the stimulation (excitatory vs. inhibitory) are the most significant differences between the studies (Michou et al. 2016).

Lastly, our group has presented further evidence with regard to the variability in the responses following the single application of the excitatory and inhibitory neurostimulation (1 and 5 Hz). In a study with 41 healthy subjects, neurophysiological responses of the participants showed large variability following both 5 and 1 Hz rTMS (Raginis-Zborowska et al. 2016a). Interestingly, it was shown that within the sample, the corticobulbar excitability of a small proportion of participants changed bidirectionally following the application of both techniques, more so following 1 Hz stimulation. This variability in the responses was further investigated with regard to endogenous factors, such as genetic factors. The group investigated whether the variability observed previously could be a result of putative selected single nucleotide polymorphisms (SNPs) (Raginis-Zborowska et al. 2016b). Two SNPs from COMT and DRD2 genes appear to play a role in pharyngeal cortex excitability depending on the stimulation applied (1 and 5 Hz). This is the first convincing evidence that the direction and extent of the effects of central stimulation with rTMS (in the swallowing motor system) might be influenced by genetic associations.

5.1.2 Cerebellum and Neurostimulation

In addition to confirming the importance of multiple cortical sites in the control of swallowing, Positron Emission Tomography (PET) and Functional Magnetic Resonance (fMRI) studies have consistently shown bilateral activation in the cerebellum during swallowing, with stronger activation reported in the left cerebellar hemisphere (Zald and Pardo 1999; Mosier and Bereznaya 2001; Suzuki et al. 2003; Malandraki et al. 2009; Hamdy et al. 1999b). Recent studies have increased our understanding of the contribution of the cerebellum in the control of swallowing. There is also some evidence from animal literature which suggests that the cerebellum may be implicated in swallowing. For instance, in cats, throat contractions and overt swallowing are observed following cerebellar stimulation (Mussen 1930). High intensity cerebellar stimulation using neurosurgically implanted cerebellar electrodes has also been shown to facilitate chewing, swallowing and predatory attack of prey in cats (Reis et al. 1973). A more recent study by Zhu et al. (2006) involving cerebellar stimulation in rats has also reported altered feeding regulation.

In humans, further evidence for cerebellar involvement in swallowing comes from a recent neurophysiological study using non-invasive magnetic cerebellar stimulation. In this study, Jayasekeran and colleagues (2011a) demonstrate that distinct motor responses can be induced in the pharyngeal musculature using single pulses of TMS. Together with findings from a paired-pulse experiment, they also indicate that cerebellar stimulation has the potential to excite the pharyngeal motor cortex (Jayasekeran et al. 2011a).

Recently, Vasant and colleagues (2015) examined the effects of differing frequencies of cerebellar rTMS on pharyngeal cortical and cerebellar excitability. High-frequency cerebellar rTMS (10 Hz) can robustly produce physiologically relevant effects on the excitability of frequency specific of corticobulbar projections to the pharynx. Of interest and as before, these effects were frequency specific. In Fig. 4, one can observe the use of neuronavigation, allowing the research team to confirm the optimal posterior fossa sites where stimulation can be applied to modulate pharyngeal corticobulbar excitability and swallowing responses. Further research will inform whether there is any potential benefit following the application on rTMS to the cerebellum for rehabilitation of dysphagia post-stroke.

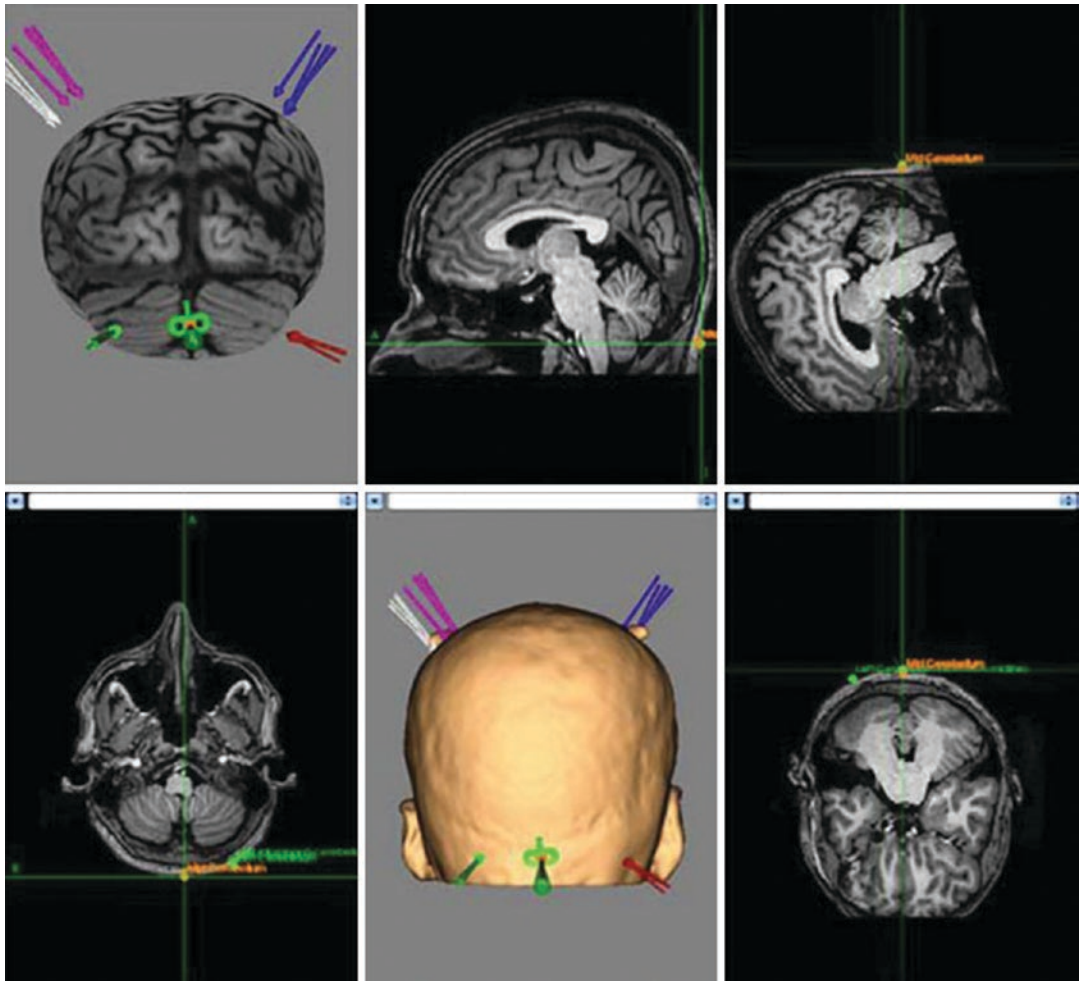


Fig. 4 Neuronavigated-TMS mapping data from one subject co-registered with the subject's own MRI brain scan. This figure shows TMS 'hot-spot' reproducibility (each *arrow* at each site showing the area stimulated each session, five in total). In this figure the coil is being targeted over the cerebellar midline. Reprinted from Vasant et al. (2015)

5.2 Peripheral Stimulation

5.2.1 Air-Puff Stimulation, Gustatory Stimulation and Neuromuscular Electrical Stimulation

In contrast to direct (or transcranial) stimulation of the brain, it is also possible to modulate cortical plasticity by stimulation of peripheral nerves. There are a number of postulated mechanisms by which changes in swallowing occur following peripheral stimulation such as the notion that by increasing sensitivity of the mucosa may allow more effective triggering and modulation of the swallow in response to a bolus (de Lama Lazzara et al. 1986; Teismann et al. 2009) or retrograde activation of corticobulbar pathways may prime the brainstem swallowing centre and cortical neurones. Early work in anaesthetised animals demonstrated that electrical stimulation of the superior laryngeal nerve branch of the vagus nerve can elicit swallowing motor activity (Doty 1951; Miller 1972) which is that of a 'stereotyped' nature (Jean 2001). In contrast, in humans stimulation with the various techniques from the periphery has shown that there is a considerable variability in the elicitation of motor components of the swallowing motor action.

In the recently published literature in humans, the increasing list of stimulation techniques have been used to providing sensory information to stimulate the sensory receptors and mechanoreceptors of the oral cavity including thermal (de Lama Lazzara et al. 1986; Gisel 2008; Rosenbek et al. 1996, 1998), tactile (Rosenbek et al. 1996, 1998) (Ali et al. 1996; Lamm et al. 2005), gustatory (Ebihara et al. 2011; Michou et al. 2012a; Rofes et al. 2013; Hamdy et al. 2003; Mistry et al. 2006), air pulses (Lowell et al. 2008; Soros et al. 2008; Theurer et al. 2005, 2009) and electrical stimulation (Power et al. 2006), the latter used on different regions, including the tongue (Lamm et al. 2005), palate (Park et al. 1997) and faucial pillars (Power et al. 2004, 2006). These paradigms provide an avenue for rehabilitation in dysphagia; however careful characterisation of the stimulation parameters has to be conducted prior to any utilisation in dysphagic patients. One example for the need of careful and methodological research to stimulation paradigms is that even though it has been observed that electrical stimulation to the faucial pillars increases cortical excitability (Power et al. 2004, 2006) and may reduce bolus transfer timings and increase swallowing safety immediately (Rosenbek et al. 1996, 1998), it does not appear to have any effect other than physiological abnormalities in dysphagia (Ali et al. 1996; Power et al. 2006). Stimulation of the tongue has not been shown to be of therapeutic benefit (Lamm et al. 2005) and palatal stimulation may be beneficial; however the studies are limited by small sample sizes (Park et al. 1997).

A problem common to all the oral stimulation techniques is that if a therapeutic benefit is produced, the effects are only short term, merely lasting for a few swallows (Rosenbek et al. 1996; Sciortino et al. 2003; Lazzara et al. 1986). Indeed, simply activating swallowing pathways either by swallowing water or flavoured solutions has been shown to significantly alter pharyngeal motor cortex excitability for up to 30 min (Mistry et al. 2006; Fraser et al. 2003) and decrease swallow speed and volume per swallow (Hamdy et al. 2003; Chee et al. 2005) (Figs. 5 and 6). Therefore, it seems that most of the paradigms delivered from

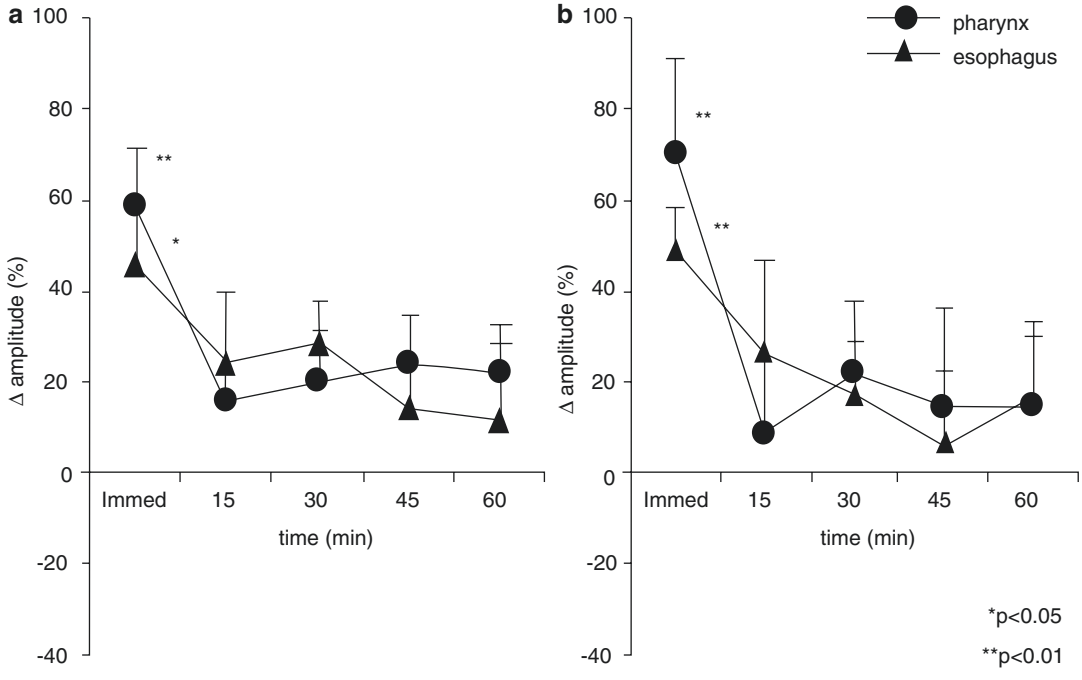


Fig. 5 Effects of volitional water swallowing on (**a**) pharyngeal (*filled circle*) and oesophageal (*filled triangle*) motor cortical responses and (**b**) craniobulbar reflexes. Group mean responses were recorded for up to 60 min after 10 min of volitional water swallowing and compared to baseline ($^{*}p < 0.05$, $^{**}p < 0.01$). Reprinted from Fraser et al. (2003)

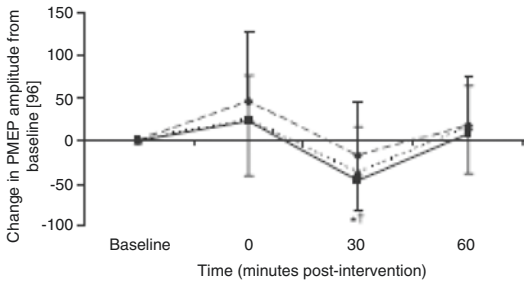


Fig. 6 Effects of swallowing neutral (water, *filled diamond*), bitter (*filled square*) and sweet (*filled triangle*) flavoured solutions on pharyngeal motor cortical responses. Group mean responses were recorded for up to 60 min after 10 min of volitional swallowing and compared to baseline ($p < 0.03$). *Reprinted from Mistry et al. (2006)

the periphery are beneficial when applied in trains or specified regimen with specific repetitions.

Air-puff pulse stimulation is a promising technique, employing bilateral repeated air-puffs to the posterior peritonsillar regions, resulting in an urge to swallow, as already investigated in young (Theurer et al. 2005) and older healthy adults (Theurer et al. 2013). In a case series proof-of-principle study air-puff stimulation increased rates of saliva swallowing in dysphagic stroke patients when applied bilaterally (Theurer et al. 2013). Neuroimaging studies examining the effects of air-puff stimulation with fMRI showed bilateral brain activation within primary somatosensory and motor cortices, thalamus, SMA and polymodal areas in the past (Lowell et al. 2008; Soros et al. 2008). Further work with controlled trials to determine the clinical efficacy of this promising technique in larger number of dysphagic patients is anticipated over the coming years.

There is also recent evidence for potential changes in neurophysiological processes by gustatory afferent stimulation. As aforementioned, afferents in the oropharyngeal areas enable the elicitation of the swallowing reflex, as information via mechanoreceptors, taste receptors, chemical receptors, etc. is received. In several research studies afferent pathway stimulation of the swallowing network has been utilised as a means to aid swallowing performance (Ebihara et al. 2011). A recent example of the effects of gustation on swallowing is the use of cannabinoids in the animal literature to facilitate swallowing reflex elicited by SLN electrical stimulation (Mostafeezur et al. 2012). Another such example is a study in healthy participants with carbonated water swallowing, which showed that carbonated liquids had a direct effect on reaction latencies of the pharyngeal swallowing and increased the number of correctly performed challenged swallows (swallows within a predetermined time window) (Michou et al. 2012a). Carbonation has been used in patients with dysphagia in the past with promising results (Sdravou et al. 2012; Bulow et al. 2003). However, according to a recent narrative review the existing evidence fails to provide clear direction for the clinical use of carbonation, and there is a need for additional studies (Turkington et al. 2017).

Moreover, there is evidence that oropharyngeal afferents express the polymodal Transient Receptor Potential Vanilloid 1 (TRPV1) (Hamamoto et al. 2009), projecting to the supramedullar structures and to the nucleus tractus solitarius in the brainstem, allowing the involuntary onset of swallow response and modulating volitional swallowing. Recently, a large case series study (Rofes et al. 2013) and a RCT (Nakato et al. 2017) observed that stimulation of TRPV1 by capsaicinoids strongly improved safety and efficacy of swallow and shortened the swallow response in older patients with dysphagia, while a 10-day regimen with capsaicin infused boluses showed comparative beneficial results to neuromuscular electrical stimulation applied externally in stroke patients in a randomised trial (Ortega et al. 2016). These findings suggest the clinical potential of capsaicinoids in dysphagia rehabilitation as a pharmacologic strategy for oropharyngeal dysphagia management.

Interestingly, there has also been an increase of the published clinical studies that employed neuromuscular electrical stimulation (NMES), which uses externally applied electrical current in the area of the anterior neck and/or in the suprahyoid area at motor or sensory threshold

levels. The rationale behind this technique is that stimulation of the muscle fibres can re-educate the functional swallow-related muscle contraction patterns (Freed et al. 2001; Bulow et al. 2008). The technique has been applied in stroke (Sun et al. 2013; Kushner et al. 2013; Beom et al. 2011) and others, head and neck cancer (Lin et al. 2011), Parkinson's disease (Baijens et al. 2012; van Hooren et al. 2014; Heijnen et al. 2012), paediatrics (Christiaanse et al. 2011) and other mixed aetiologies patient populations (Verin et al. 2011; Lee et al. 2012; Barikroo and Lam, 2011). The results of these studies, which employed various study designs (case series, cohorts, RCTs), are not conclusive since the stimulation parameters used across the studies were different. Moreover researchers have used various combinations of stimulation and behavioural interventions in their protocols (i.e. effortful swallowing (Park et al. 2012)). This heterogeneity is the direct outcome of the insufficient preliminary background work on the different parameters, such as the stimulation repetitions, optimal duration of therapeutic regimen, dosage and electrode positioning (Tan et al. 2013; Carnaby-Mann and Crary 2007). Meanwhile, a recent meta-analysis (Tan et al. 2013) showed that NMES is not superior to traditional swallowing therapy in clinical functional outcomes in stroke population, but there may be some benefit when applied to dysphagic patients of varied disease aetiologies. A later meta-analysis, however, showed that although NMES was not superior to traditional therapy, the beneficial effects following this technique were evident when used together with traditional therapy (Chen et al. 2016). We anticipate to increase our understanding of this technique in the future with neuroimaging studies, such as the one by Humbert and Joel (2012), showing that electrical stimulation on the anterior neck bilaterally at a (low) sensory level administered during swallowing did not result in any greater activation compared to still water swallowing or sour bolus swallowing or visual biofeedback.

5.2.2 Pharyngeal Electrical Stimulation

Under the umbrella of the peripheral stimulation techniques is also pharyngeal electrical stimulation (PES). PES has been studied both in healthy volunteers and the patient population. In health, short trains of intraluminal PES have been shown to increase corticobulbar excitability, without affecting brainstem responses (Fraser et al. 2003; Hamdy et al. 1998b), and increase blood-oxygen-level dependent (BOLD) fMRI responses (Fraser et al. 2002) (Fig. 7).

Studies in healthy volunteers over the recent years have increased further our knowledge of the underlying mechanism behind these results. Based on this early encouraging work (Fraser et al. 2002, 2003), Jayasekeran and colleagues (2010) sought to substantiate the mechanisms by which PES can help reverse both cortical and behavioural swallowing impairments in dysphagic stroke patients. Using the virtual lesion model of swallowing impairment described earlier, the authors studied the effects on both swallowing neurophysiology and behaviour of active or sham PES after inducing a virtual lesion in healthy volunteers. The authors were able to show reversal of the neurophysiological and behavioural effects of a virtual lesion to the inhibited pharyngeal motor cortex with PES, laying the foundation for the application of this technique in dysphagic stroke patients. In another neuroimaging study, with magnetoencephalography before and 45 min after the application of 10 min PES to healthy subjects in a randomised crossover design, changes in cortical oscillatory activity during volitional swallowing were observed reflecting stimulation-induced increased swallowing processing (Suntrup et al. 2015b). A recent randomised study in healthy volunteers, employed a single application of 10 min real compared to sham PES, showed that there was an increase of Substance P (SP), a neuropeptide known to enhance the swallow response, compared to baseline (Suntrup-Krueger et al. 2016). Lastly, one of the latest studies in healthy subjects with PES was a randomised

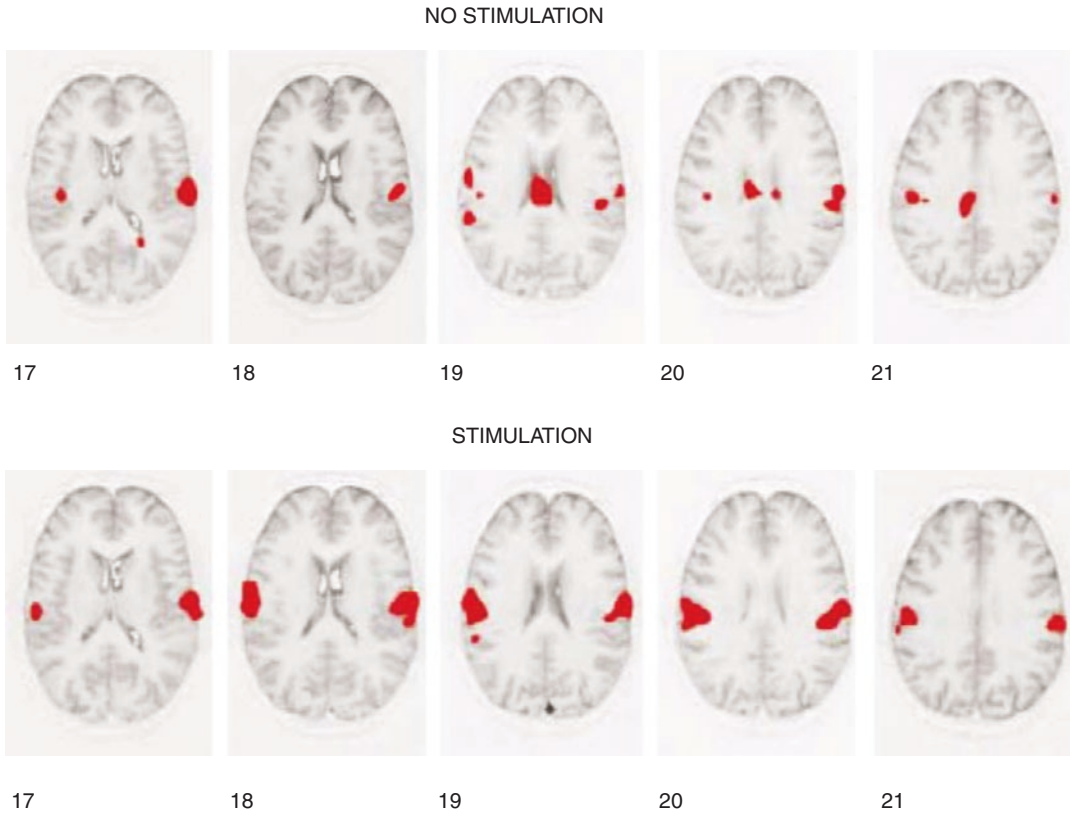


Fig. 7 Effects of pharyngeal electrical stimulation on cortical BOLD fMRI signals in healthy subjects during volitional swallowing. Group mean activation data are shown as a series of normalised transverse brain slices, with no stimulation paradigm across the top, and the stimulation paradigm across the bottom. Activated pixels in *red*, and brain slice numbers indicated below. Greater bilateral functional activation occurs within sensorimotor cortex (BA 3,4), most overt in slices 17–19, after pharyngeal stimulation compared to no stimulation ($p < 0.05$). Reprinted from Fraser et al. (2002)

crossover study with four arms exploring whether combining PES with swallowing of still water or carbonated or PES alone (plus a sham arm) can potentiate excitation in either cortical and/or brain stem areas assessed with transcranial and transcutaneous magnetic stimulation. There were immediate short-term craniobulbar amplitude changes following the swallowing paradigm of combined PES and swallowing of carbonated swallowing. Only single application of PES produced long-term changes in corticopharyngeal excitability compared to the other arms of the study (Magara et al. 2016).

In dysphagia stroke patients, preliminary data showed that following the technique an improvement of pharyngeal swallowing delay (swallowing reaction time) and penetration-aspiration scores in a small group of stroke patients is evident (Fraser et al. 2002). Jayasekeran and colleagues (Jayasekeran et al. 2010) refined the treatment parameters in a dose–response study of PES in dysphagic stroke patients and assessed swallowing outcome using VFS. They found that a stimulation regime of PES once a day for 3 days was the most practical and effective course of neurostimulation to reduce aspiration. In addition, the efficacy of PES was evaluated in a randomised clinical trial of 28 acute dysphagic stroke patients. The authors concluded that PES significantly improved swallowing performance and intriguingly reduced hospital stay (Fig. 8), compared to the control group.

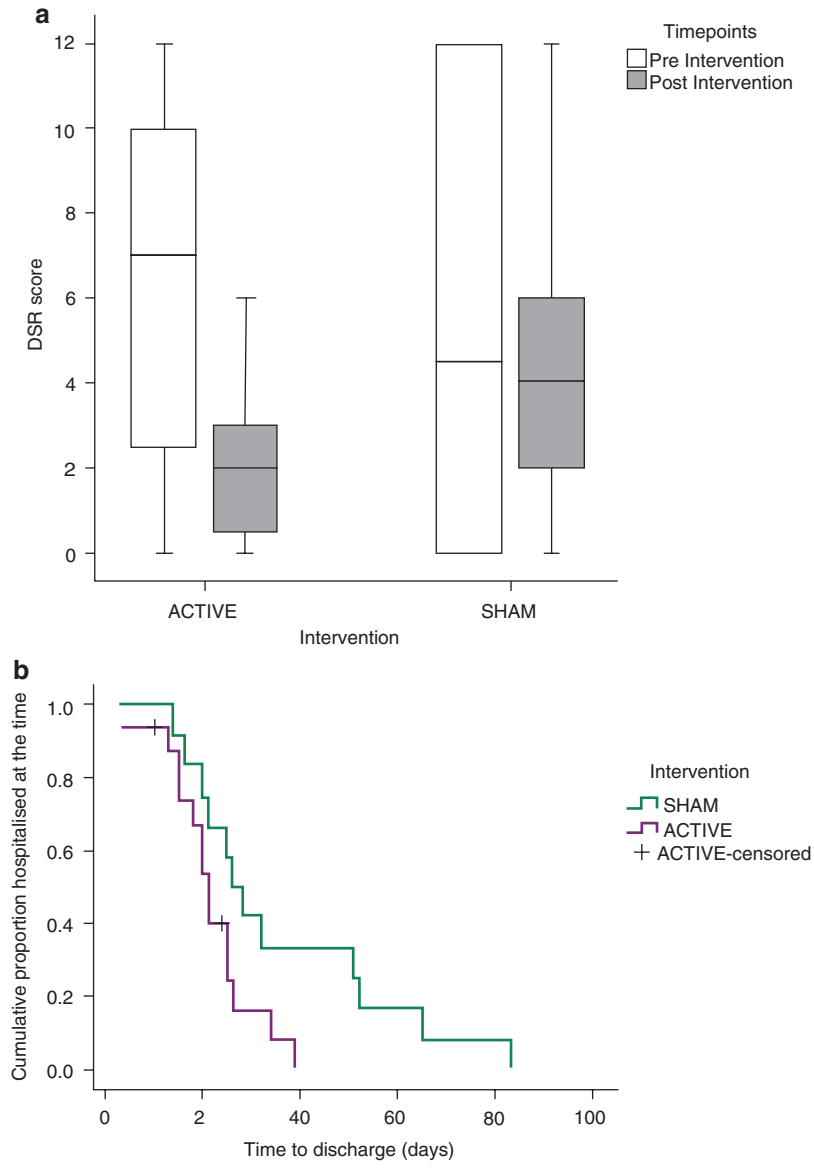


Fig. 8 Results of a randomised clinical trial of pharyngeal electrical stimulation (PES) in dysphagic stroke patients. (**a**) Comparison of Dysphagia Severity Rating Scale (DRS) scores between active and sham treatment groups ($U = 58.0$, $p = 0.04$) indicate an improved feeding status in the active group after PES. (**b**) Kaplan-Meier plot showing the period of hospitalisation following either active or sham treatment. The active treatment group have a significantly shorter period of hospitalisation compared to sham group when time to event analysis was used (log rank test $p = 0.038$). The censored data takes into account two patients who died during hospitalisation. Reprinted from Jayasekeran et al. (2010)

This pilot study by Jayasekeran et al. (2010) demonstrated that bedside neurostimulation of the pharynx can be delivered in a safe and effective manner with encouraging results on reducing swallowing impairment and prolonged hospitalisation. Another RCT in acute stroke patients ($n = 36$; median = 71 years; 61% male) (Vasant et al. 2016) showed that 3 days of PES at the bedside is tolerated, without adverse effects or associations with serious complications (chest infections/death). Also, it showed that there was a favourable outcome to PES treatment, as suggested by the consistency of the direction of the estimated effects relating to dysphagia severity at 2 weeks, the time to nasogastric tube removal, the time to discharge (Odd ratios and Hazard ratios were all > 1), and the observed improvement in the number of unsafe swallows (PAS ≥ 3) in the patients studied. The patients recruited in this second RCT (Vasant et al. 2016) were experiencing more severe swallowing problems and had higher National Institutes of Health Stroke Scale compared with the first RCT trial (Jayasekeran et al. 2010). In 2015, Scutt and colleagues (2015)

performed an individual patient data meta-analysis for all the RCT trials with PES. The results showed that compared to no/sham PES, real PES was associated with lower aspiration-penetration scores and reduced length of hospital stay. In a multicentre RCT across Europe, 162 dysphagia patients were randomly assigned to PES or sham treatment given on three consecutive days as per protocol and examined with VFS. It was shown that the results from PES did not differ to the outcomes of the sham group (clinical swallowing and functional outcomes). The authors commented that the data showed that the patients were undertreated compared to previous pilot RCTs (Bath et al. 2016). Further information regarding the use of PES at the bedside is provided by a trial in tracheostomised stroke patients (Suntrup et al. 2015c). Stroke patients were randomised into real (n = 20) or sham (n = 10) PES over 3 days. Seventy-five per cent of the patients were decannulated from the real arm compared to 20% of the sham arm, as assessed with FEES and decannulation protocol from the group. A larger study in tracheostomised stroke patients is currently underway (Dziewas et al. 2017).

Interestingly, there is also some recent evidence regarding the underlying mechanisms for the change in swallowing function in successfully PES-treated stroke patients. Sixteen dysphagic stroke patients that completed the single-blind randomised sham-controlled trial of PES (Vasant et al. 2016) within 6 weeks of their stroke were genotyped for the BDNF SNP Val66Met (rs6265) from saliva samples. The selection of this single nucleotide polymorphism (SNP) was based on the previous study that showed that BDNF, which is the most abundant growth factor in the brain and is involved in long-term brain plasticity (Thoenen et al. 1991), was associated with better motor recovery in animal models (Schabitz et al. 2004) and was partly a factor for the response to neurostimulation in healthy subjects (Jayasekeran et al. 2011b). Of relevance, a BDNF (SNP) results in the common amino acid substitution of valine (Val) to methionine (Met) at codon 66 (Val66Met; rs62565). Jayasekeran et al. (2011b) found that subjects homozygous for the Val allele demonstrated significantly altered cortical excitability after PES when compared to heterozygous/Met homozygous individuals (Met carriers) (Jayasekeran et al. 2011b). In stroke patients, in the study by Essa and colleagues (2017) patients with the Met BDNF allele demonstrated significantly greater improvements in DSRS at 3 months compared to patients homozygous for the Val allele. The aforementioned findings suggest a potential association between BDNF and PES induced swallowing recovery. Further work will be required to validate these observations and demonstrate clinical utility in patients in the future.

5.3 Transcranial Direct Current Stimulation (TDCS)

Transcranial direct current stimulation (tDCS) is a novel technique in which a weak electric current (approximately 1–2 mA) is passed over the brain. It appears to be both safe and well tolerated (Nitsche and Paulus 2000) and has already been shown to alter the excitability and function of various parts of the nervous system depending on which site is stimulated (Gandiga et al. 2006; Maeda et al. 2000). In the clinical setting, tDCS also offers other advantages; the equipment needed is small and easily transportable, therefore, making it a more viable tool.

The direction of change of excitability is dependent on the position of the electrodes; excitability increases when the anode is placed over the motor cortex and the cathode over the supraorbital ridge (‘anodal’ tDCS), whereas it decreases when the current flow is reversed (‘cathodal’ tDCS) (Fregni et al. 2005; Takeuchi et al. 2005; Nitsche and Paulus 2001; Hummel et al. 2005). These effects are also dependent on the combination of parameters such as the current strength, duration of stimulation and electrode montage. The excitatory effects in the motor cortex produced with this technique are thought to be due to neuronal depolarisation and possible hyperpolarisation of inhibitory

interneurons, whereas the inhibitory effects are thought to be caused by hyperpolarisation of motor neurones. It is a useful tool for sham-controlled studies as the current produces a mild tingling sensation on the scalp, lasting for approximately 20 s. Stimulation can therefore be given for 30 s, enough time to produce the initial sensation, but not long enough to induce any cortical changes (Nitsche and Paulus 2000).

Jefferson et al. (2009b) explored the parameters of tDCS that might be usefully applied to the swallowing regions of motor cortex. The study found that the levels of stimulation applied to hand motor cortex were not effective at changing excitability in the pharyngeal motor cortex. However, when higher or longer levels of current were applied, both excitatory (anodal) and inhibitory (cathodal) changes were induced. It is therefore conceivable that anodal tDCS could be a new therapeutic avenue to dysphagic stroke patients.

Following on from this parameter setting study, Kumar and colleagues (Kumar et al. 2011) have published data from a clinical trial of tDCS in 14 acute dysphagic stroke patients (7 real, 7 sham). In this study, the authors applied a 5-day treatment of 2 mA of anodal tDCS for 30 min a day, to the motor cortex of the unlesioned hemisphere (electrode placement was estimated using the international 10–20 EEG system for electrode placement and magnetic resonance image co-registration). Patients in both treatment arms were also given lemon flavoured lollipops to suck, asked to perform effortful swallows and were given ice chips intermittently for dryness. Changes in the dysphagia outcome and severity scale (DOSS) score pre-stimulation, compared with after the last session, were used as the main outcome measure (O'Neil et al. 1999) with videofluoroscopy assessments made intermittently, unless DOSS scores could not be obtained. The authors report that there was significant improvement in DOSS scores when comparing the actively treated group with the sham-treated group ($p = 0.019$). The authors, however, have acknowledged that they did not test the optimal parameters of stimulation as identified by Jefferson et al. (2009b) as their protocol predated its publication.

Other studies have been also published in the recent literature and were included in the recent meta-analyses (Pisegna et al. 2016; Momosaki et al. 2016b). It seems that there is a potential beneficial result following the application of tDCS in stroke patients. These studies are also summarised in Table 3. Most researchers have applied the technique for 2 weeks post-stroke as an adjunct to therapy or during swallowing. However, as with rTMS studies, there are several differences amongst the studies with the striking one being the targeted hemisphere (affected vs. unaffected) and the rationale behind the application of the technique and also the optimal dosage and electrode placement.

Meanwhile, the accumulation of evidence from the healthy volunteers' studies is continuing, mainly as far as the mechanism employed for the changes in swallowing function is concerned. One study with MEG (Suntrup et al. 2013) showed that following application of anodal tDCS (20 min, 1 mA) in 21 healthy subjects significant bilateral enhancement of cortical swallowing network activation was found in the theta frequency range after compared to sham stimulation. This bilateral increase is a promising result for the application of this technique in stroke patients. With the use of TMS, Vasant and colleagues (Vasant et al. 2014) applied the optimal parameters of tDCS (anodal, 1.5 mA, 10 min (Jefferson et al. 2009b)) contralaterally to a 'virtual lesion' (local inhibition with 1 Hz rTMS) to the strongest pharyngeal projection and compared the results to a sham arm within the same population. Active tDCS increased cortical excitability bilaterally and reversed the inhibition, alongside with changes observed in behavioural tasks. It should be recognised that as with rTMS reports, the parameters of the tDCS technique are different across the studies, making commenting on the efficiency of the technique harder. Yet, further studies will increase our knowledge on the effects of the technique in swallowing rehabilitation.

Table 3 The different parameters of the studies using tDCS are shown in this table

Study year	Demographics		Study design	Parameters							Results/comments
	Total *n* participants	Characteristics		Stimulation	Duration	Hemisphere	Location of anodal electrode pad	Location of cathode	Electrode area cm^2	Schedule	
Kumar et al. (2011)	14 (7 tDCS, 7 sham) AR:50–92 yoa	Acute hemispheric stroke	RCT (tDCS vs. sham)	Anodal tDCS 2 mA	30 min	Unaffected	Inferior sensorimotor cortex and neighbouring premotor brain regions	Contralateral supraorbital region	Anode 15 Cathode 30	Daily for five consecutive days	TDCS group showed a 2.60 point improvement in DOSS scores compared to a 1.25 point improvement in the sham group
Yang et al. (2012)	16 (9 tDCS, 7 sham)	Post-stroke dysphagia	RCT (tDCS and TT vs. sham and TT)	Anodal tDCS 1 mA	20 min	Affected	Pharyngeal region	Contralateral supraorbital region	25	Daily for 10 days	Initial improvement in FDS in TDCS and sham groups with no significant difference. At 3 months follow-up TDCS group showed improvement over sham
Shigematsu et al. (2013)	20 (10 tDCS, 10 sham) AR 54–79 years	Post-stroke dysphagia	RCT (tDCS and TT vs. sham and TT)	Anodal tDCS 1 mA	20 min	Affected	Pharyngeal region	Contralateral supraorbital region	35	10 days	TDCS groups showed improved DOSS over the sham group immediately after intervention (1.4 vs. 0.5) and at 1 month (2.8 vs. 1.2)
Ahn et al. (2017)	26 (13 tDCS, 13 sham) tDCS Group 61.62 Sham Group 66.38	Post-stroke dysphagia	RCT (tDCS and TT vs. sham and TT)	Anodal tDCS 1 mA	20 min	Bi-hemispheric	Pharyngeal region	Bilateral supraorbital regions	25	Ten sessions over 2 weeks	Anodal tDCS Immediate mean improvement of DOSS. Sham: No corresponding significant increase

Key: *AR* age range, *yoa* years of age, *TT* traditional treatment, *RCT* randomised controlled trial, *DOSS* dysphagia outcome and severity scale

5.4 Paired Associative Stimulation (PAS)

Plastic changes of the motor and somatosensory cortical areas have also been investigated using TMS in the form of paired associative stimulation (PAS). This neurostimulation technique is capable of provoking long-lasting heterosynaptic plasticity in neuronal pathways through the near synchronous combination of peripheral stimuli in the targeted muscle with cortical stimuli over the targeted muscle representational area in the motor cortex. PAS has been studied in many cerebral regions (Cruikshank and Weinberger 1996; Kelso et al. 1986) both in vivo (Baranyi and Feher 1981) and in vitro (Hess and Donoghue 1994). The concept of this technique derives from evidence that peripheral input plays an important role in plastic reorganisation of motor areas and can lead to long-lasting changes in cortical excitability of the targeted area, as already seen with the application of PES on swallowing musculature. Research in animal neocortical slices have shown that when a weak excitatory synaptic input repeatedly arrives at a neuron shortly before the neuron has fired an action potential, then the strength and efficacy of that connection is increased, whereas if the input arrives after the neural discharge, the strength of the connection is reduced (Dan and Poo 2006). Bi-directional modulation of synaptic efficacy in this manner is termed Hebbian plasticity.

Modulation of cortical networks in healthy volunteers using PAS was first described by Stefan et al. (2002), who paired low-frequency (peripheral) electrical median nerve stimulation with (central) TMS of the abductor pollicis brevis motor cortical representation. These findings for the limb muscles have since been replicated by several authors (Stefan et al. (2002); Ridding and Taylor (2001); McKay et al. (2002); Pyndt and Ridding (2004)). The exact mechanism(s) underlying the induced changes is (are) yet to be fully elucidated; however, consensus amongst researchers is currently focusing towards the existence of no single mechanism. NMDA-dependent mechanisms, such as long-term potentiation and depression, are currently the putative candidates responsible for the induction of plastic changes in sensorimotor areas through activity-dependent modification of the existing cortical synapses (Stefan et al. (2000); Wolters et al. (2003)).

However, recent studies in the swallowing motor system have contributed additional information on the origin of, and the potential mechanisms involved in the induction of cortical changes. In 2009, Singh et al. (2009) described a PAS protocol for inducing changes in pharyngeal motor cortical excitability. Using pharyngeal electrical stimuli (peripheral stimulation) and TMS (cortical stimulation) separated by a 100 ms inter-stimulus interval, Singh et al. (2009) were able to produce changes in cortical excitability that lasted for up to 2 h post-stimulation, and for up to 8 h in a separate study in two subjects. Using magnetic resonance spectroscopy, they also demonstrated that the mechanism involved changes in intracortical glutamate levels within the cortex.

Investigations into refinement of the PAS parameters have continued at our laboratory and have shown that PAS applied for just 10 min can induce changes in pharyngeal motor cortical excitability to the same magnitude as a 30-min protocol (Michou et al. 2009). Moreover, similarly to 5 Hz rTMS and PES, it is also capable of reversing the effects of a virtual lesion in both hemispheres when applied to the unaffected hemisphere (Michou et al. 2012b).

Paired associative stimulation was applied in a small group of chronic dysphagic stroke patients showing promising results on neurophysiological and functional measurements in a sham-controlled randomised study (Michou et al. 2012b). Additionally, using magnetic resonance spectroscopy (MRS), we can quantify the concentrations of neurotransmitters. Recently, we have also observed changes in the major inhibitory neurotransmitter, GABA, when PAS is applied in health (Michou et al. 2015). This latest study was a combined fMRI and MRS study aiming to investigate the whole brain changes following PAS delivered to the dominant pharyngeal motor map as well as the changes in GABA concentrations. Interestingly, following the application of PAS to the dominant pharyngeal motor representation, blood-oxygen-level dependent (BOLD)

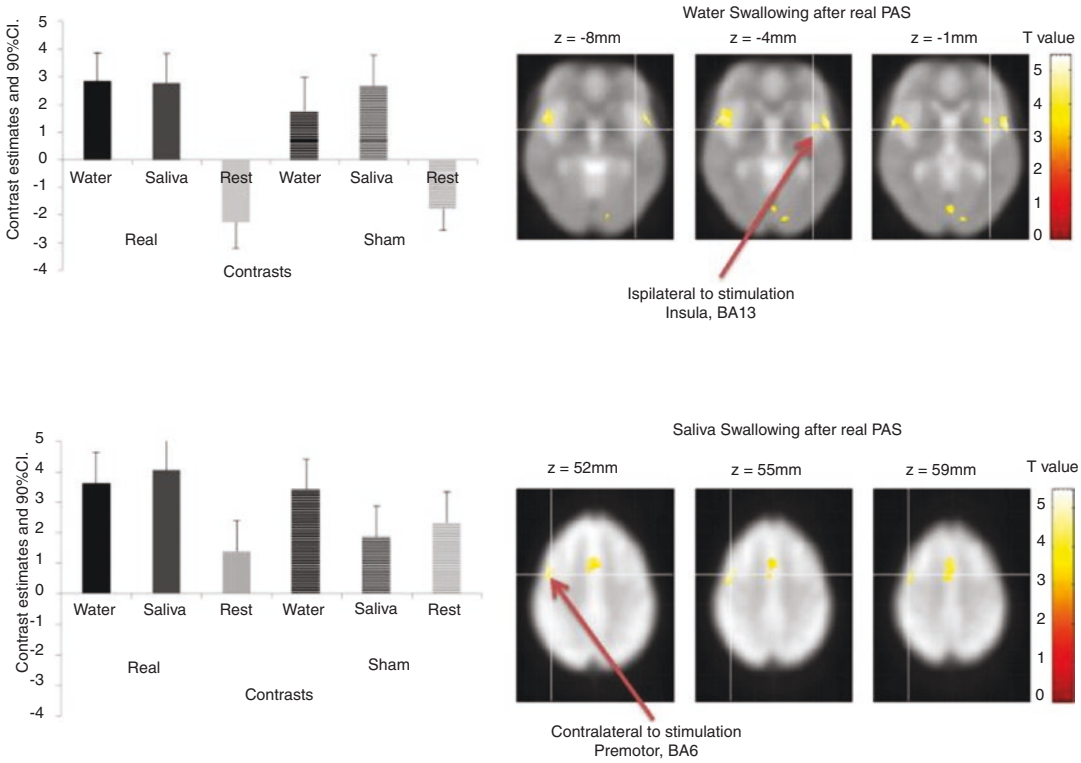


Fig. 9 Here the effect sizes of peak activations for the ipsilateral to PAS application insula (Brodmann area 13) in the water swallowing blood-oxygen-level dependent level change, following real PAS, and contralateral to stimulation for saliva swallowing following real PAS. Reprinted from Michou et al. (2015)

signal was increased in contralateral (to stimulation) hemispheric areas that are of importance to the swallowing neural network (premotor cortex) as well as ipsilateral areas, such as insula (Fig. 9). Changes in levels of GABA were also observed following the application.

This is perhaps one of the few neurostimulation paradigms in swallowing neurorehabilitation that has fully and systematically investigated, with research studies examining not only the parameters (repetition within a treatment session, frequency, duration (Singh et al. 2009; Michou et al. 2012b), repeated application for responders vs. non-responders to a single application (Michou et al. 2013)), but also the underlying mechanisms to account for the changes observed in health and dysphagic stroke patients. This bodes well for the application of PAS as a strong potential candidate therapeutic intervention for dysphagia neurostimulation in stroke patients.

Conclusion

Direct and indirect forms of experimental neurostimulation therapies are developing rapidly and now provide new avenues for successful neurorehabilitation, founded on an understanding of how the brain reorganises and compensates following injury. There remain challenges however with regards to the clinical utilisation of these techniques, the type of patients that would benefit and the logistics of how such treatments can be embedded into a health care system.

Nonetheless, these approaches should lay the foundation for the design of future large-scale randomised controlled trials of non-invasive cortical and peripheral stimulation in dysphagic stroke patients and provide useful correlates for its potential application in neurogenic dysphagia. It is hoped that such studies will provide more information as to whether neurostimulation can be a useful

therapeutic tool or an adjunct to current clinical practice in the care of patients with dysphagia, so reducing the suffering and mortality associated with this distressing condition.

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Sensory Stimulation Treatments for Oropharyngeal Dysphagia

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Contents

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Abstract

One of the main causes of dysphagia in older and neurological patients is the impairment on oropharyngeal sensory function. Over the last decade, a better understanding of how sensory stimuli are perceived in the human oropharynx and processed in the CNS has led to several new therapeutic strategies based on the sensory stimulation of the oropharynx in the treatment of dysphagia. The goal of these new strategies is not only to prevent safety impairments during deglutition but to improve the oropharyngeal swallow response to move from compensation to recovery of the swallowing function. This chapter will cover the neurophysiological, anatomical and molecular bases for these sensory stimulation treatments and provide an updated list of therapies that have been validated on patients with dysphagia, including pharmaceutical, physical and electrical stimulation of the oropharynx.

1 Introduction

One of the main causes of dysphagia in older patients and those with stroke and neurodegenerative diseases is the impairment on oropharyngeal sensitivity. Oropharyngeal sensitivity may be reduced by varying mechanisms between these groups, but all are closely related to delayed oropharyngeal swallow response (OSR) and safety impairments.

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Oropharyngeal sensitivity is known to decrease with age, with close correlation between age and sensory threshold for mechanical stimulation (Aviv et al. 1994). This has been explained by the observation that the ageing process reduces the number of small diameter myelinated fibres in the internal superior laryngeal nerve (ISLN) (Mortelliti et al. 1990; Tiago et al. 2007). Electroencephalographic (EEG) studies have also shown how older people present lower amplitude and greater latency in their pharyngeal sensory evoked potentials (PSEP) than young volunteers. This could be due to both a decreased afferent input from the pharynx and disrupted connection within the cortex (Rofes et al. 2017). Pharyngeal sensory loss is even greater in older dysphagia patients; this oropharyngeal sensory impairment is related to increased prevalence of laryngeal vestibule penetrations and aspirations (Aviv et al. 1994; Rofes et al. 2017).

Oropharyngeal sensitivity can be affected by stroke, supratentorial or infratentorial, and stroke patients with decreased pharyngeal sensitivity are at high risk of aspiration, which can lead to aspiration pneumonia (Aviv et al. 1996, 1997). Although the oropharyngeal motor representation in the cortex is asymmetrical and thus only a stroke on the dominant hemisphere affects the motor aspect of swallow response (Hamdy et al. 1997; Singh and Hamdy 2006), the oropharyngeal sensory representation in the cortex can be affected independently of the dominant hemisphere, and oropharyngeal sensitivity can be reduced in the contralateral side of the pharynx (Aviv et al. 1997; Cabib et al. 2017).

Oropharyngeal sensitivity is also impaired in patients with neurodegenerative diseases such as Parkinson's disease (PD), which accounts for a lack of self-awareness of swallowing disorders in these patients (Hammer et al. 2013). Impaired oropharyngeal sensitivity in neurodegenerative diseases is due not only to damage in the central nervous system (CNS) but also to damage in the peripheral sensory nerves innervating the oropharynx (Mu et al. 2013, 2015); Lewy pathology has been found in sensory nerve fibres innervating the oropharynx and larynx, specially in the ISLN of PD patients with dysphagia symptoms. Damage to the peripheral sensory nerves has also been found in other Lewy body disorders, such as Alzheimer's disease and dementia with Lewy bodies (Beach et al. 2010).

Oropharyngeal sensory inputs play a major role in the generation of the swallow response. Decreased oropharyngeal sensitivity described in older, stroke and neurodegenerative disease patients is thus a critical component of the impaired OSR in dysphagia patients that can be and must be targeted to treat oropharyngeal dysphagia.

2 Swallow Neurophysiology

The proper generation of a coordinated OSR requires the interaction and connection of several areas and elements from the CNS and the peripheral nervous system. It also requires structural integrity of the oropharynx and larynx, proper function of 30 pairs of muscles and coordination with the respiratory system (Fig. 1).

Stimuli from the alimentary bolus are perceived by the peripheral sensory receptors during deglutition; this information is sent by the afferent nerves (cranial nerves V, VII, IX and X) to the central pattern generator (CPG) located in the medulla oblongata of the brainstem and to the somatosensory cortex and subcortical structures such as the amygdalae and the basal ganglia (Clavé and Shaker 2015).

The voluntary control of the oral phase and part of the pharyngeal phase of deglutition are conducted in cortical areas of the brain such as the precentral and inferior frontal gyri as well as other adjacent cortical areas of the sylvian fissure and the lateral and precentral cortex (Schindler and Kelly 2002). In healthy individuals, deglutition activates these cortical areas in a bilateral but asymmetric fashion, which implies the existence of a dominant hemisphere (Hamdy et al. 1996; Teismann et al. 2011).

The OSR of the pharyngeal phase of deglutition is produced in the CPG found in the medulla oblongata of the brainstem. The CPG is composed of two well-communicated groups of interneurons: the dorsal swallowing group (DSG) and

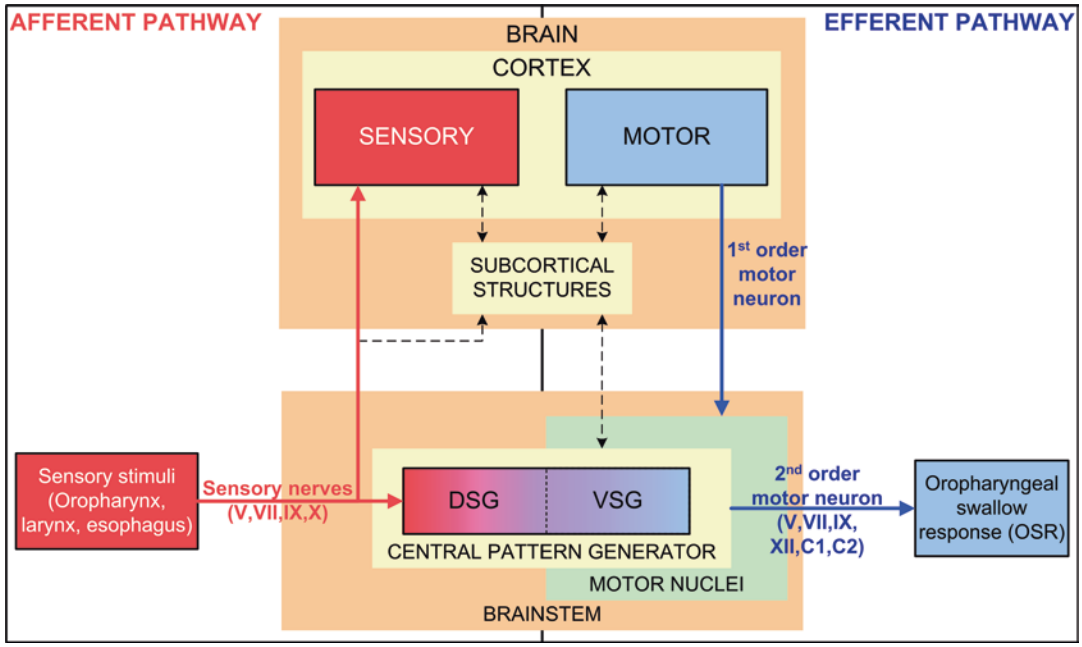

Fig. 1 Swallow neurophysiology. *DSG* dorsal swallowing group; *VSG* ventral swallowing group

the ventral swallowing group (VSG). The DSG is found in the nucleus tractus solitarius within the medulla oblongata and integrates the afferent information from the peripheral nerves and the modulating signals coming from cortical and subcortical structures to generate the swallowing motor pattern. The VSG is found in the ventrolateral aspect of the medulla oblongata above the nucleus ambiguus and, upon activation by the DSG, distributes the swallowing motor pattern among the different motor nuclei (Jean 2001).

The motor nuclei controlling the deglutition muscles are found in the pons of the brainstem (trigeminal motor nucleus and facial nucleus), in the medulla oblongata (nucleus ambiguus and hypoglossal nucleus) and in the cervical spinal cord (C1–C2). Motor neurons innervating oropharyngeal muscles project from these nuclei through the cranial nerves V, VII, IX, X and XII and the cervical spinal nerves (C1, C2 and C3) composing the cervical plexus.

The muscles that participate in deglutition are the masticatory, the lingual, the soft palate, the pharyngeal, the laryngeal, the suprahyoid and the infrahyoid muscles. During the oral phase, the masticatory muscles are innervated by the cranial nerves V and VII, and the lingual muscles are innervated by the cranial nerve XII. During the pharyngeal phase, the soft palate, the pharyngeal and the extrinsic laryngeal muscles are innervated by the pharyngeal plexus composed by the cranial nerves IX and X, the suprahyoid muscles are innervated by the cranial nerves V, VII and XII, the intrinsic laryngeal muscles are innervated by the recurrent laryngeal nerve (cranial nerve X) and the infrahyoid muscles are innervated by the cervical plexus.

3 Sensory Innervation of the Oropharynx and Larynx

The human oropharynx and larynx are innervated by afferent fibres of the lingual branch of the cranial nerves V and IX, the chorda tympani of the cranial nerve VII, the pharyngeal branch of the cranial nerves IX and X and the laryngeal branch of the cranial nerve X (Fig. 2).

The tongue is innervated by afferent fibres of the lingual branches of the cranial nerves V, VII and IX (L-IX). The base of the tongue and the

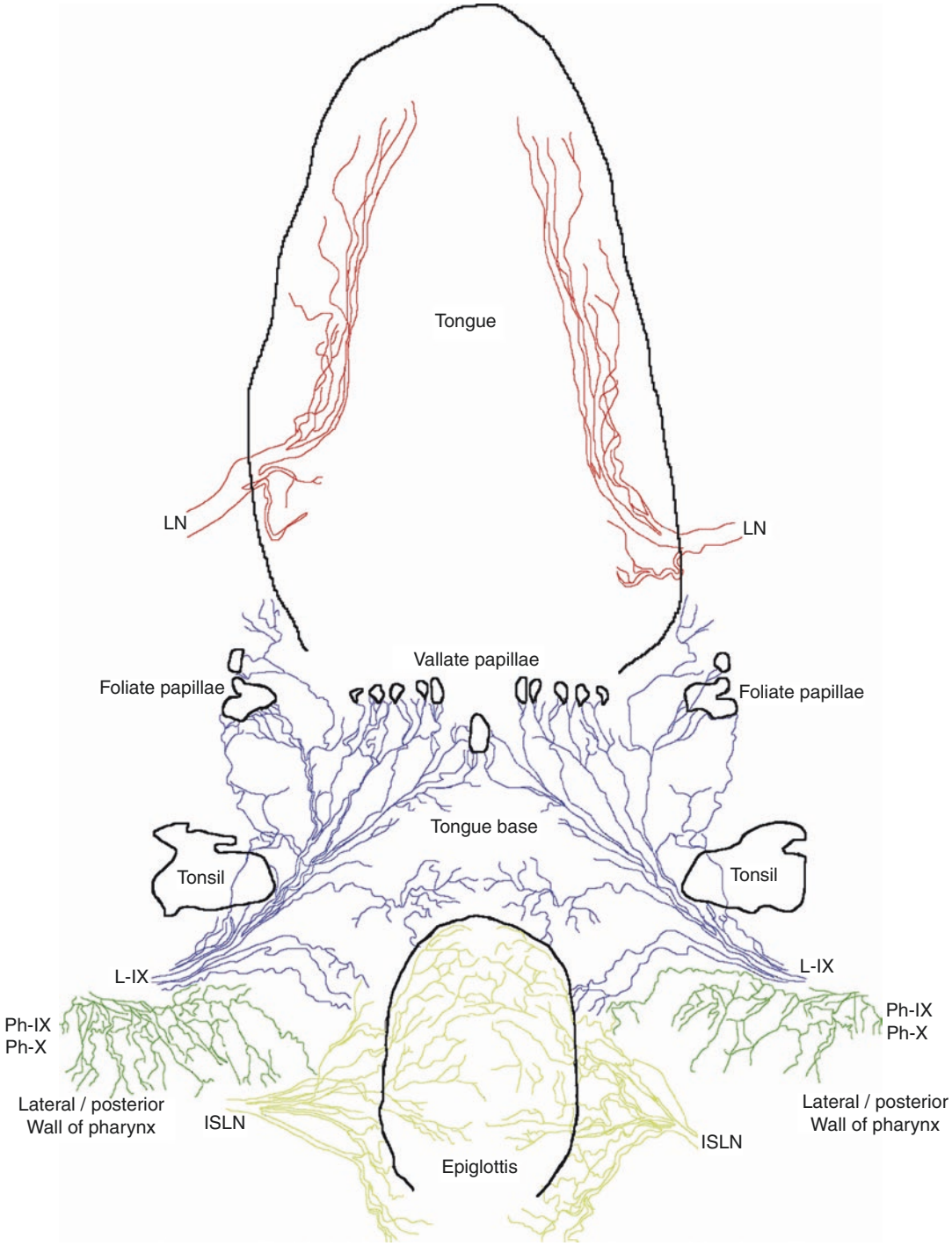

Fig. 2 Distribution of the oropharyngeal sensory innervation. Schematic representation of the distribution of the sensory branches of CN V, VII, IX and X innervating the oropharyngeal mucosa. *LN* lingual nerve, *ISLN* internal superior laryngeal nerve. Based on the Sihler's stain images from (Sanders and Mu 1998; Mu and Sanders 2000; Zur et al. 2004). Reproduced from Alvarez-Berdugo et al. (2016a)

circumvallate and foliate papillae are innervated by two of the four major subdivisions of the L-IX. The subdivision of the L-IX that innervates the base of the tongue mucosa is divided into tertiary branches and twigs that run towards the medial axis of the tongue where they meet with the fibres coming from the opposite side. The subdivision of the L-IX that innervates the papillae is divided in lateral and medial branches; lateral branches innervate the foliate papillae and some of the lateral circumvallate papillae, medial branches ipsilaterally innervate most of the circumvallate papillae. The central circumvallate papilla is innervated by fibres coming from medial branches from both sides (Mu and Sanders 2000). The two anterior thirds of the tongue are innervated by the lingual nerve (LN) composed of the lingual branch of the cranial nerve V and some afferent fibres from the chorda tympani. The LN penetrates the tongue anterior to the circumvallate papillae and subdivides into medial and lateral branches; the medial branches innervate the ventrolateral mucosa of the tongue, and the lateral branches innervate the lateral part of the tongue and its tip (Zur et al. 2004).

The oropharyngeal mucosa is innervated by afferent fibres of the lingual (L-IX) and pharyngeal (Ph-IX) branches of the cranial nerve IX and the pharyngeal branch of the cranial nerve X (Ph-X). The mucosa of the tonsil and peritonsillar area and the lingual surface of the epiglottis are innervated by two of the four subdivisions of the L-IX. The subdivision of the L-IX that innervates the tonsil and peritonsillar area is split into two or three tertiary branches that surround the tonsil. The subdivision of the L-IX that innervates the epiglottis is also split into two or three tertiary branches; one of them innervates the mucosa of the lingual surface of the epiglottis, and the others form anastomosis with afferent fibres from the laryngeal sensory branch of the cranial nerve X, the internal superior laryngeal nerve (ISLN). The lateral and posterior walls of the pharynx, including the pharyngopalatine arch, are innervated by the three subdivisions of the Ph-IX together with the afferent fibres of the Ph-X; all these afferent fibres form a dense nervous plexus in the mucosa of this region (Mu and Sanders 2000).

The mucosa of the hypopharynx and larynx is innervated by the ISLN, which penetrates the thyrohyoid membrane and splits into three branches. The laryngeal surface of the epiglottis is innervated by the superior branch of the ISLN, which penetrates the epiglottis through the aryepiglottic fold and subdivides into twigs that form a dense network with the fibres arriving from both sides. The aryepiglottic fold, the laryngeal vestibule and the vocal folds are innervated by the middle branch of the ISLN, which splits into interconnected twigs that form a network under the mucosa. The other parts of the hypopharynx are innervated by the inferior branch of the ISLN, the one with greatest diameter and most complex distribution: the superior subdivision of which innervates the arytenoid cartilage, the middle subdivision innervates the region posterior to the arytenoids and the interarytenoid muscles and the inferior subdivision innervates the mucosa over the anterior wall of the hypopharynx (Yatake and Hiroto 1968; Sanders and Mu 1998).

4 Sensory Structures of the Oropharynx Involved in Swallow Function

The afferent fibres innervating the human oropharynx perceive chemical (taste and pungency), thermal and mechanical stimuli. Mechanical, thermal, chemical (excluding taste) and painful stimuli are perceived in the oropharynx by the corresponding branches of the cranial nerves V, IX and X. Taste is perceived by the afferent fibres of the chorda tympani (cranial nerve VII) that innervate the fungiform papillae of the anterior two thirds of the tongue and by the afferent fibres of the L-IX branch that innervate the circumvallate and foliate papillae of the tongue base. The sensory structures that perceive all these stimuli are the Meissner's corpuscles, the Merkel cells, the Pacini corpuscles, the Krause bulbs, the free nerve endings and the taste buds (Alvarez-Berdugo et al. 2016a) (Fig. 3).

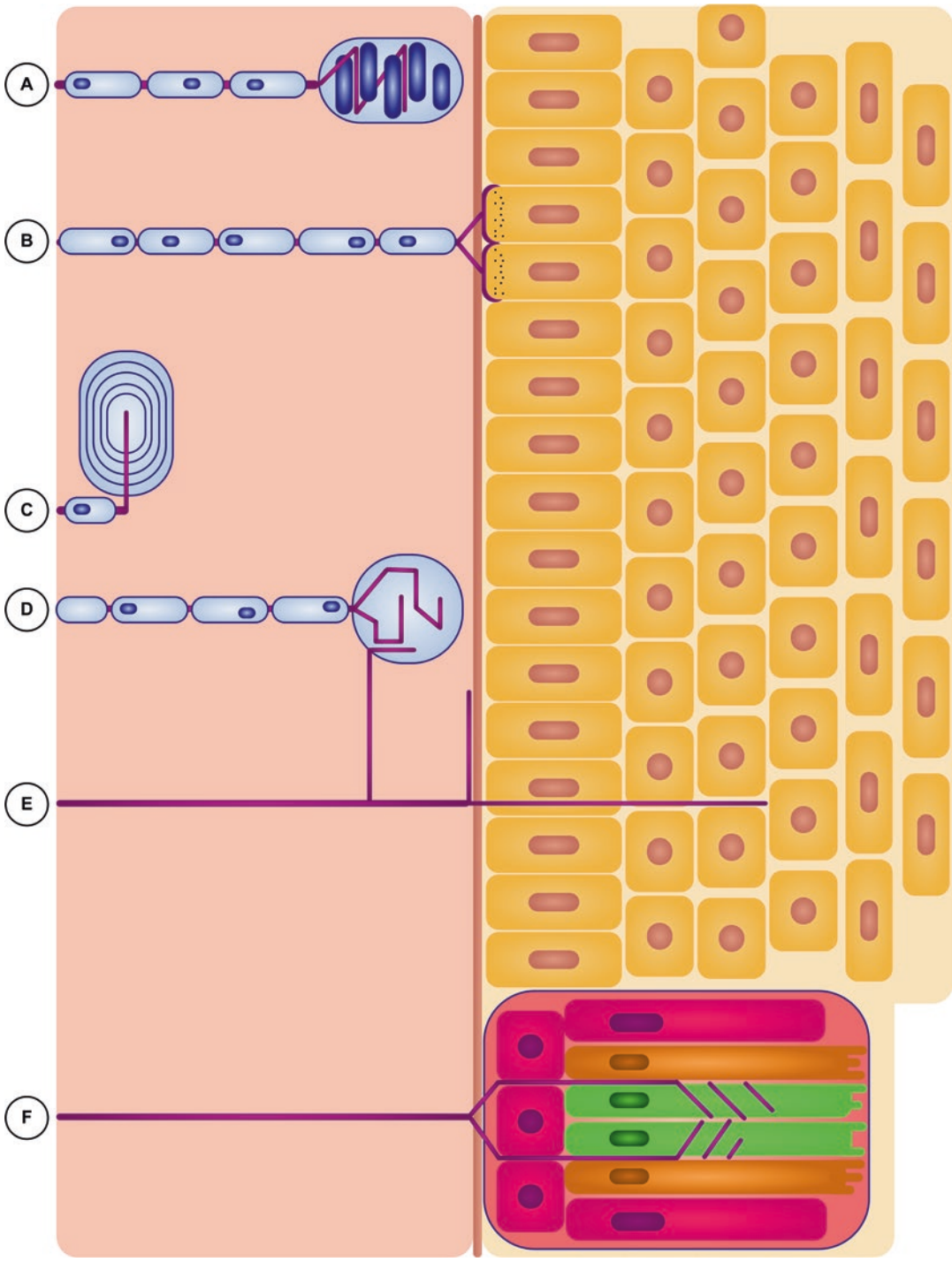

Fig. 3 Specialized sensory terminals found in the mucosa. Schematic representation of the specialized sensory terminals perceiving mechanical, thermal and chemical stimuli in the oropharyngeal mucosa. (**a**) Meissner's corpuscles, (**b**) Merkel cells, (**c**) Pacini corpuscle, (**d**) Krause bulb, (**e**) free nerve ending, (**f**) taste bud. Reproduced from Alvarez-Berdugo et al. (2016a)

4.1 Meissner's Corpuscles

Meissner's corpuscles (Fig. 3a) perceive painless light mechanical stimuli. They are found in groups within the papillae disposed in different directions. They are supplied by one to three myelinated nerve fibres that lose their myelin sheath on entering the corpuscle and then divide into branches or form a discoid shape. The nerve endings are covered with several lamellar layers separated by collagen fibre-filled interspaces. The corpuscles are covered with a collagen capsule that keeps them separated from the basal lamina of the epithelium (Watanabe 1982; Watanabe and Yamada 1983, 1985).

4.2 Merkel Cells

Merkel cells (Fig. 3b) perceive the lightest touch without pain. They are found alone or in groups in the basal layer of the epithelium, always bound to the basal lamina. They are innervated by nerve endings that penetrate the basal lamina after losing their myelin sheath and surround the base of these cells. Merkel cells present granules in the basilar end and protrusions of cytoplasm that contact neighbouring epithelial cells at the apical end (Smith 1970; Hashimoto 1972; Toyoshima et al. 1987; Bengoechea et al. 1989).

4.3 Pacini Corpuscles

Pacini corpuscles (Fig. 3c) perceive deep mechanical stimuli without pain. They are found in the deepest layer of the submucosa. They are innervated by a single myelinated nerve end that penetrates the corpuscle in a straight line. Pacini corpuscles are lamellar structures (Munger and Ide 1988; Watanabe 2004).

4.4 Krause Bulbs

Krause bulbs (Fig. 3d) perceive light touch and cold stimuli. They are found within the papillae. They are innervated by one to three myelinated or not myelinated nerve endings, when both kinds of nerve endings penetrate the same bulb they never contact each other. Once the nerve endings have penetrated the bulb, they run in coils and split into several axon terminals. Krause bulbs are covered by a capsule composed of fibroblasts and collagen fibres (Chouchkov 1973; Lawrenson and Ruskell 1991).

4.5 Free Nerve Endings

Free nerve endings (Fig. 3e) perceive painful, chemical and thermal stimuli. They split into branches and reach the basal lamina of the epithelium where, in some cases, the Schwann cells that surround these terminals and the basal lamina establish close contact and become thinner so the axon terminal can penetrate the epithelium. However, intraepithelial sensory fibres are scarce in the oropharyngeal mucosa. Free nerve endings are generally type Aδ and C nerve fibres (Bengoechea et al. 1989; Munger 1965; Chiba et al. 1985).

4.6 Taste Buds

Taste buds (Fig. 3f) distinguish between the five basic tastes: salt, sweet, bitter, sour and umami, the taste elicited by the presence of glutamate and ribonucleotides such as IMP and GMP in the food. They are found on the fungiform papillae of the two anterior thirds of the tongue and the soft palate, in the rifts of the circumvallate papillae and on the foliate papillae of the tongue base. Taste buds are onion-like structures formed by specialized epithelial cells (Stone et al. 1995; Okubo et al. 2009; Roper 1989), which can be classified according to their morphology and function as Type I, II and III. Type I cells are the most abundant (50–75% of the taste bud cells) and provide cellular support to the other cells; they also transduce the salt taste (Chaudhari and Roper 2010; Vandenbeuch et al. 2008). Type II cells transduce the sweet, bitter and umami tastes, depending on the specialized receptor they express (Zhang et al. 2003; Tomchik et al. 2007).

Type III cells establish a synaptic union with the nerve endings that supply the taste buds and transduce salt and sour tastes (Yee et al. 2001; Tomchik et al. 2007). All these taste bud cell types are connected; Type I cells provide support to the perception and synaptic communication of Type II and III cells. Type II cells finely perceive tastes and send signals to Type III cells that will transmit the stimulus information to the nerve endings (Chaudhari and Roper 2010). The nerve fibres supplying the taste buds penetrate the basal lamina of the epithelium and form protrusions that surround Type III cells to establish synapse (Yee et al. 2001; Witt and Reutter 1997).

5 Sensory Receptors of the Oropharynx

Perception of thermal and chemical stimuli is achieved through the presence of molecular receptors expressed in the sensory nerves that innervate the oropharyngeal mucosa. The activation of these receptors will initiate the transmission of a sensory input towards the CNS. The main family of sensory receptors found in the human oropharynx are the transient receptor potential (TRP) channels which perceive a wide spectrum of temperatures and chemical substances (Alvarez-Berdugo et al. 2016a) (Table 1).

5.1 TRPV1

The transient receptor potential channel subfamily V member 1 (TRPV1) was the first TRP receptor identified. It was characterized as the vanilloid receptor from a cDNA library expressed in mammalian cells (Caterina et al. 1997). This receptor is mainly expressed in the afferent Aδ and C fibres, together with the pro-inflammatory neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP). Furthermore, its expression has been found in multiple human tissues, both in nerve (such as dorsal root ganglia and trigeminal ganglia) and non-nerve tissue (such as epithelial cells of the urinary bladder and the skin) (Cortright et al. 2001; Ugawa et al. 2005; Denda et al. 2001; Shabir et al. 2013).

TRPV1 was found in the plasma membrane of the oropharyngeal and epiglottis lingual surface mucosa epithelial cells, with stronger signal in the basal and intermediate layer cells than in the more superficial layer cells of the epithelium. It

Table 1 Natural agonists and physical activators of TRPV1, TRPA1 and TRPM8

TRPV1	TRPA1	TRPM8
Temperature (≥43 °C)	Temperature (≤17 °C)	Temperature (≤25 °C)
Acidic pH	1,4-Dihydropyridines	Eucalyptol (eucalyptus)
2-APB	Allicin (garlic)	Geraniol (geranium, lemon)
Allicin (garlic)	Allyl isothiocyanate (mustard)	Icilin
Anandamide	Bradykinin	Linalool (tejpat)
Camphor (camphor laurel)	Cannabichromene (cannabis)	Menthol (peppermint)
Cannabidiol (cannabis)	Cannabidiol (cannabis)	
Cannabigerol (cannabis)	Cannabinol (cannabis)	
Capsaicin (chilli peppers)	Capsiate (chilli peppers)	
Eugenol (cloves)	Cinnamaldehyde (cinnamon)	
Gingerol (ginger)	Curcumin (turmeric)	
Hydrogen sulphide	Eugenol (cloves)	
Nitric oxide	Gingerol (ginger)	
Piperine (black pepper)	Hydrogen sulphide	
Polygodial (Dorrigo pepper)	Icilin	
	Nitric oxide	
	Tetrahydrocannabinol (cannabis)	

Reproduced from Alvarez-Berdugo et al. (2016a)

was also found in the nociceptive Aδ fibres innervating the oropharyngeal mucosa and in polymorphonuclear leukocytes in the submucosa, near the basal lamina. In the lingual mucosa, TRPV1 was mainly found on the membranes of the stratum basale and stratum spinosum cells of the filiform papillae epithelium; similarly to the oropharyngeal mucosa, TRPV1 immunoreactivity was weaker in the more superficial layers (stratum granulosum and stratum corneum) (Alvarez-Berdugo et al. 2016b).

The main function of TRPV1 channels is to open upon perception of harmful stimuli. This receptor is activated by harmful temperatures (>43 °C), acid solutions (pH < 5.5) and several endogenous and exogenous chemical compounds, such as capsaicin, one of the better known chemical agonists of TRPV1 (Szallasi et al. 2007).

TRPV1 ion channels are homotetramers and each subunit has six transmembrane domains with the C-terminal and N-terminal in the cytosolic space. The pore of the channel is formed by two of these transmembrane domains, and the sensory function is performed by the other four (vanilloid binding site). The cytosolic domains allow specific protein-protein interactions due to the presence of four to six ankyrin repeats. Among these interactions, calmodulin is the most important, regulating the function of the channel according to the intracellular calcium levels (Kedei et al. 2001; Mosavi et al. 2002; Rosenbaum et al. 2004). There are other modulators that interact with the cytosolic domains of TRPV1, such as PIP2, which inhibits the channel activation, and PKA and PKC phosphatases, which sensitize the channel by phosphorylating their target amino acids (Rathee et al. 2002; Rosenbaum and Simon 2007).

The mechanism through which TRPV1 is activated depends on the stimulation agent. While high temperatures seem to affect several domains of the channel, chemical agonists interact with the vanilloid binding site (Voets 2014):

- Acid: The opening of the channel depends on the oropharyngeal acidity. When the pH is below 6, the pore opens due to the action of H+ ions on the extracellular domain (Glu-648, Val-538 and Thr-633). When the pH is between 6 and 7, H+ ions act on the Glu-600 reducing the concentration threshold for other agonists to activate the channel (Geppetti and Trevisani 2004; Nilius et al. 2007).
- Pungency: The activation of TRPV1 by capsaicin and other vanilloids might increase the sensory input to the brainstem and cortical areas, activating the CPG and eliciting the swallow response. In addition, the release of neuropeptides, such as SP and CGRP, may produce local effects through paracrine and autocrine mechanisms. SP is released after the activation of TRPV1 by its agonists; SP then mediates the phosphorylation of TRPV1 via PKC and thus sensitizes the receptor and decreases its activation threshold. The release of SP into the larynx, either through direct action on sensory terminal nerves or through the action of pro-inflammatory substances, can also sensitize primary sensory neurons and thus facilitate the motor swallow response. SP also plays a major role in the cough reflex (Nakagawa et al. 1995; Rofes et al. 2014a).

5.2 TRPA1

Following the identification of the TRPV1, other nociceptive receptors were identified, among them the transient receptor potential channel subfamily A member 1 (TRPA1), formerly called ANKTM1, as the noxious cold stimuli receptor. TRPA1 is expressed in a subpopulation of C-fibre sensory neurons from the nodose, trigeminal and dorsal root ganglia that also expresses TRPV1, as well as SP and CGRP neuropeptides (Story et al. 2003; Bautista et al. 2005; Kobayashi et al. 2005; García-Añoveros and Duggan 2007). TRPA1 expression has also been found in fibroblasts and epithelial cells of the skin and the bronchial walls, as well as in ear ciliated cells (Corey et al. 2004; Atoyan et al. 2009; Mukhopadhyay et al. 2011).

Within the oropharynx, TRPA1 can be found below the basal lamina, in sensory nerve fibres that are just below the epithelium. It is also found within the epithelium, either in the nerve fibres

that penetrate it or in the Langerhans cells of the stratum spinosum of the lingual mucosa or the intermediate layer of the pharyngeal and lingual surface of the epiglottis mucosa. TRPA1 can also be found in the sensory fibres that innervate the blood vessels that irrigate the submucosa (Alvarez-Berdugo et al. 2016a, b).

TRPA1 is the receptor of noxious cold temperatures (<18 °C) and natural and synthetic irritant substances such as allyl isocyanate (mustard), cinnamaldehyde (cinnamon), piperin (black pepper), allicin and allyl disulphide (garlic), and it can also be activated by low concentration of menthol (Bandell et al. 2004; Karashima et al. 2007). In addition to chemical and thermal perception, TRPA1 is also involved in mechanoreception in ear ciliate cells (Sotomayor et al. 2005).

The TRPA1 ion channels are homotetrameric and each subunit has six transmembrane domains. The pore of the channel is formed by one of these transmembrane domains from each subunit. What distinguishes TRPA1 from other TRP receptors is its N-terminal end, a cytosolic domain in the shape of a spring due to its 17 ankyrin repeats. It is believed that this structure allows mechanoreceptor function in ear ciliate cells (Sotomayor et al. 2005).

5.3 TRPM8

The transient receptor potential subfamily M member 8 (TRPM8) is another important sensory receptor related with thermal and chemical perception in the human oropharynx. At the neuronal level, TRPM8 expression is concentrated in a subpopulation of peripheral sensory neurons of small diameter, in which there is no co-expression with the TRPV1 receptor or CGRP (Peier et al. 2002). Outside the nervous system, the presence of TRPM8 has been described in different types of solid tumours and has an important role in the survival, proliferation and invasion of tumour cells (Yee 2015).

Within the oropharynx, TRPM8 is mainly located in the nerve fibres that innervate the lingual, oropharyngeal and epiglottis lingual surface mucosa. These nerve fibres are generally located below the epithelium, either in nerve bundles or individually, although they can also trespass the basal lamina and penetrate the deeper layers of the epithelium. TRPM8 has also been found in corpuscular structures under the epithelium and on nerve fibres that innervate the blood vessels that irrigate the submucosa.

TRPM8 is activated by non-harmful cold stimuli (15–30 °C) and chemical substances with a refreshing effect such as menthol, icyline and eucalyptol.

TRPM8 structure is similar to other TRP receptors, but its cytosolic domains do not present ankyrin repeats. Instead it has major homology regions (MHR), which allow the formation of the channel by the union of different subunits of the receptor (Phelps and Gaudet 2007).

5.4 Other TRP

In addition to TRPV1, TRPA1 and TRPM8, there are other TRP receptors involved in the sensory perception of other kinds of stimuli. For instance, TRPV2 is activated by extremely hot temperatures (>52 °C), and TRPV3 perceives temperature changes within the physiologic range (22–40 °C). Furthermore, osmotic changes are perceived by TRPV4 which, along with TRPC1 and TRPC6, can also perceive harmful mechanical stimuli. Little is known about the presence of these receptors in the human oropharynx, however, TRPV2 has been found in rat pharyngeal mucosa, soft palate, epiglottis and larynx. Like TRPV1, TRPV3 has also been found in mouse keratinocytes and neurons. TRPV4 has been found in trachea and salivary glands. (Caterina et al. 1999; Delany et al. 2001; Peier 2002; Xu et al. 2002, 2006; Alessandri-Haber et al. 2003, 2009; Chung et al. 2004; Sasaki et al. 2013).

5.5 ASICs

ASICs are another family of sensory receptors. ASIC family receptors perceive acidic and mechanical stimuli and have been localized in the taste

buds and in the digestive tract (Page et al. 2005; Huque et al. 2009). Among this family of receptors, ASIC3 is thought to be one of the main receptors to perceive acidic stimuli in the oropharynx.

Within the oropharynx, ASIC3 is primarily found in the sensory nerve fibres that innervate the lingual, oropharyngeal and epiglottis lingual surface mucosa. These nerve fibres can be found below the basal lamina, running parallel to the epithelium or innervating the blood vessels that irrigate the submucosa.

ASICs form heteromeric channels between the members of the same family of receptors, which can differentiate between ranges of acidity (Huque et al. 2009). ASICs respond to lower pH ranges than TRPV1 and rapidly inactivate inward Na + currents (Leffler et al. 2006).

6 Sensory Stimulation Treatments

The new stimulation treatments for OD target the reduced oropharyngeal sensitivity in OD patients. The development of these new strategies is possible thanks to greater understanding of swallow neurophysiology and sensory perception in the oropharynx. Most of these strategies aim to activate sensory receptors to increase the oropharyngeal sensory input to the CNS and thus improve the oropharyngeal swallow response. During the last decade, several groups have tested therapeutic strategies based on sensory stimulation in OD patients.

6.1 Mechanical and Thermal Stimulation

Mechanical and thermal stimuli have been used in the past to find the pharyngeal sensory areas that trigger deglutition and to measure the loss of pharyngeal sensitivity in OD patients and populations at risk of dysphagia (Pommerenke 1927; Aviv et al. 1994, 1996, 1997). They have also been used in acute treatments of neurogenic patients with OD to improve swallowing physiology. For instance, cold and mechanical stimulation of the glossopharyngeal innervated regions significantly reduced total transit time in neurogenic OD patients (de Lama Lazzara et al. 1986). These results were reproduced with a metallic instrument that provided 0–3 °C tactile and cold stimuli in the same area in patients with idiopathic Parkinson's disease and OD (Regan et al. 2010). Mechanical stimuli with air pulses have been used as a treatment for stroke patients with OD and were found to improve the swallowing rate (Theurer et al. 2013). Mechanical thermal stimulation of the oropharynx improves the OSR of neurogenic OD patients by increasing the sensorimotor cortical activation (Teismann et al. 2009).

6.2 Chemical and Pharmacological Stimulation

- Acid: One of the first approaches to use chemical sensory stimulation as a therapeutic strategy to treat OD was with sour boluses (50% v/v citric acid from lemon juice). It was found to reduce the prevalence of aspirations by shortening the pharyngeal swallow delay in patients with neurogenic OD, but the high concentration of citric acid was not well tolerated (Logemann et al. 1995). Later studies proved that an equivalent concentration of citric acid (2.7% w/v) achieved a similar therapeutic effect, but mixing citric acid and sucrose (1.11% and 8% w/v, respectively) did not significantly improve OD symptoms or swallow response parameters (Pelletier and Lawless 2003). Finally, stimulating with both cold (2–8 °C) and acid stimuli (citric acid from lemon juice) reduced the pharyngeal swallowing time in stroke patients (Hamdy et al. 2003; Cola et al. 2012).
- TRP agonists: Another early attempt to use chemical stimulation of the swallow reflex was with capsaicin (10^{-6}–10^{-9} M), the pungent substance found in red chilli peppers. Drops were directly instilled into the pharynx and reduced the swallow reflex latency in stroke and dementia patients in a dose-dependent manner (Ebihara et al. 1993). Some years later, capsaicin and other pungent

molecules such as piperine, the pungent substance found in black pepper, were used on patients with OD caused by either age, stroke or neurodegenerative diseases. In both in acute and subacute clinical trials, capsaicin and capsaicinoids (10^{-5} M) were administered in the bolus to OD patients and reduced both safety and efficacy impairment prevalence by shortening the laryngeal vestibule closure time and increasing the bolus velocity (Ebihara et al. 2005; Rofes et al. 2013a; Ortega et al. 2016). Olfactory stimulation with black pepper oil and oral stimulation with piperine within the bolus (10^{-4}–10^{-3} M) also significantly reduced safety impairment prevalence in OD patients (Ebihara et al. 2006a, Rofes et al. 2014a, b), and, when applied during a long period of time (30-day study), it even enhanced neural plasticity in the left insular cortex (Ebihara et al. 2006a). Finally, the use of menthol, either instilled into the pharynx (10^{-4}–10^{-2} M) or mixed with the bolus (10^{-3}–10^{-2} M), reduced the prevalence of safety impairment by improving the swallow response (Ebihara et al. 2006b; Alvarez-Berdugo et al. 2017). However, compared to the therapeutic effect of capsaicinoids or piperine, menthol is the least effective of these agonists (Alvarez-Berdugo et al. 2017). A combination of all these treatments was used in OD patients admitted to hospital with recurrent pneumonia prior to reintroducing oral feeding. Starting with 3 days of olfactory stimulation with black pepper oil once pneumonia had been cured, capsaicin troches were then administered for 5 days, and, finally, a menthol-flavoured jelly was fed to patients prior to oral feeding introduced in a step-by-step manner (Ebihara et al. 2010). Although acute clinical trials have been done as proof of concept to assess the therapeutic effect of these chemical and pharmacological strategies, more mid- and long-term studies will be needed to assess the long-term effect of a chronic treatment using these strategies. Long-term studies are also needed to confirm the effect of these strategies on the CNS.

- Carbonation: Some clinical studies have tested the use of carbonated fluids (obtained by mixing citric acid and sodium bicarbonate) in neurogenic OD patients; analysing deglutition with VFS, these studies proved that carbonated fluids reduce the prevalence of laryngeal vestibule penetrations and pharyngeal residues by improving the OSR (Bülow et al. 2003; Sdravou et al. 2012; Larsson et al. 2017). Studies on healthy volunteers have shown that stimulation with carbonated liquids increases corticobulbar excitability, which would explain the OSR improvement in OD patients (Elshukri et al. 2016).

6.3 Electrical Stimulation

The swallow response can be elicited by direct electrical stimulation of the Ph-IX nerve and the ISLN. On the other hand, electrical stimulation of the L-IX nerve inhibits swallow, and electrical stimulation of the Ph-X nerve has no effect on swallow response (Kitagawa et al. 2002). Voltage-dependent channels of the sensory neurons of these nerves might be activated by sensory electrical stimulation and thus the input signal conducted to superior areas of the CNS.

Electrical stimulation therapies are currently being performed in two different modalities: through intrapharyngeal electrical stimulation or through transcutaneous electrical stimulation.

- *Intrapharyngeal electrical stimulation*: Intrapharyngeal electrical stimulation applies electrical stimuli on the pharynx using intrapharyngeal electrodes. The application of 5 Hz electrical stimuli during 10 min in acute post-stroke dysphagic patients showed a significant reduction in the pharyngeal transit time, swallowing response time and prevalence of aspirations, by increasing pharyngeal corticobulbar excitability and topographic representation in the undamaged hemisphere (Fraser et al. 2002). When this stimulation was carried out for three consecutive days (5 Hz, 10 min/day), it improved airway protection, reduced aspirations, improved feeding status and shortened time to decannulation and hospital discharge

after the intervention (Jayasekeran et al. 2010; Suntrup et al. 2015). A meta-analysis of three small clinical studies determined that intrapharyngeal electrical stimulation on stroke patients with OD reduced aspiration prevalence and hospital stay but demanded bigger studies to confirm these results (Scutt et al. 2015). A multicentre prospective single-blinded randomized controlled trial is currently being performed to validate previous findings (Dziewas et al. 2017).

- *Transcutaneous electrical stimulation*: Transcutaneous electrical stimulation is used to activate the muscles involved in swallowing function through the peripheral motor nerves (neuromuscular electrical stimulation, NMES) (Freed et al. 2001). However, their effectiveness and safety is still under discussion due to the inconsistent results (Logemann 2007; Ludlow et al. 2007; Oh et al. 2007; Rofes et al. 2013b). In addition to neuromuscular electrical stimulation, transcutaneous electrical stimulation has also been used as a sensory strategy, using lower electrical intensity to avoid muscle contraction during treatment. This approach has showed significant improvement in several swallow parameters, such as reduced swallow response time and prevalence of aspirations in chronic post-stroke dysphagic patients (Gallas et al. 2010; Rofes et al. 2013b) but not in Parkinson's disease patients with dysphagia (Baijens et al. 2013).

7 Future of Sensory Stimulation Treatment

This chapter has exposed the new generation of OD treatments based on the sensory stimulation of the OSR.

Older, stroke and neurodegenerative disease patients with OD present lower oropharyngeal sensitivity. This sensory loss is caused by either peripheral damage to the sensory innervation or impaired connectivity and activation within the CNS. Impaired oropharyngeal sensitivity is closely related to delayed OSR and weak tongue propulsion which cause the safety and efficacy impairments of deglutition in this population. That is why this new generation of treatments for OD are based in enhancing sensory perception.

These new sensory stimulation treatments are not only improving the OSR in OD patients in the short term but may have mid- and long-term effects on peripheral sensitivity and neurophysiology. As previously stated, long-term sensory stimulation of the oropharynx may promote the release of neuropeptides such as SP and CGRP that sensitize sensory receptors and thus improve peripheral sensitivity (Suntrup-Krueger et al. 2016; Nakato et al. 2017). Similarly, mid- and long-term sensory stimulation of the oropharynx has been shown to increase neuron excitability and cortical representation and activation, thus improving swallow response through neural plasticity mechanisms (Bonham et al. 2006; Ebihara et al. 2010). This neural plasticity could be related to the creation of new synaptic connections due to the long-term potentiation effects of sensory stimulation (Purves et al. 2012).

Despite its promising effects, not all OD patients may benefit from sensory stimulation treatments (Ortega et al. 2016; Nakato et al. 2017). The reason why some patients are non-responders to sensory stimulation can only be hypothesized. Sensory stimulation might be ineffective for patients with unaltered sensitivity and cortical activation or for patients with irreversible damage to afferent pathways and central sensory areas. Developing methods to predict responsiveness of patients to sensory stimulation treatment will be a milestone in the future treatment of OD patients.

In summary, the future of sensory stimulation treatment will be supported by two major pillars: on one hand, the research of new targets and the development of new sensory stimulation treatments; on the other hand, the development of non-invasive predictive tests of the responsiveness of patients to these therapeutic strategies.

Future treatment of older and neurological disease patients with OD will be personalized, with a comprehensive pathophysiological study that leads to the most suited therapeutic strategy for each patient. Future directions will take us

from current compensation of swallow disorders to the rehabilitation of the swallowing function with these future treatments.

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Pharmacologic Treatment of Esophageal Dysmotility

Caryn Easterling, Venelin Kounev, and Reza Shaker

Contents

Abstract

Esophageal dysmotility is a medical term that refers to an interruption in the bolus propagation through the esophagus. This chapter provides a description of the esophageal anatomy and physiology, the causes (if known) of esophageal dysmotility, and the current pharmacologic treatments.

1 Introduction

The esophagus is a tubular structure anatomically connecting the oropharynx with the stomach. The main function of the esophagus is to transport food and oral secretions from the pharynx to the stomach. It also supports decompression of the upper gastrointestinal tract by allowing physiologic eructation or emesis. The esophagus is collapsed during interdeglutitive periods and varies in length depending upon body size, ranging from 20 to 22 cm. The esophagus is comprised of the esophageal body and two sphincters, creating high-pressure zones at the proximal and distal ends. At the proximal esophageal end lies the tonically contracted 2–4 cm high-pressure zone called the upper esophageal sphincter (UES). The UES is comprised of striated muscles that is the cricopharyngeus and the inferior pharyngeal constrictor muscle, while the lower esophageal sphincter is comprised of smooth muscle. Both esophageal sphincters

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are important in maintaining esophageal function and preventing gastroesophageal reflux. The UES also prevents air from entering the GI tract and refluxate from entering the airway (Sivarao and Goyal 2000). In contrast, the lower esophageal sphincter (LES) prevents gastric contents from entering the esophagus by maintaining a tonic basal pressure. This resting pressure is under neurologic control via cholinergic innervation mediated by the neurotransmitter acetylcholine. The resting pressure is influenced by intracellular calcium influx and can be affected by a variety of hormones, neurotransmitters, and pharmacologic agents (Mittal and Balaban 1997).

The structure of the esophageal body and lower esophageal sphincter includes the inner circular and outer longitudinal smooth muscles with the myenteric plexus located between the two muscular layers. These inner circular and outer longitudinal muscular layers produce lumen occluding contraction and esophageal shortening, respectively (Christensen and Robison 1982). Coordination of these contracting muscular layers produces peristalsis that contributes to esophageal motility. The efficient transport of a food bolus through the esophagus requires coordinated relaxation of the upper esophageal sphincter, sequential contractions of the esophageal body, and relaxation of lower esophageal sphincter. Esophageal dysmotility is a medical term that refers to an interruption in the bolus propagation through the esophagus.

The human esophagus is comprised of two portions designated by location: the cervical and thoracic esophagus. Because the esophagus is composed of striated and smooth muscle segments the neuromuscular mechanism that orchestrates esophageal peristalsis differs in these muscle types. Deglutitive function of the striated portion of the esophagus is primarily mediated through central innervation while the smooth muscle portion of the esophagus is mediated by peripheral and central neural stimulation. Likewise, local and systemic disease processes affect these distinct muscle types in different ways.

2 Normal Esophageal Motility and How Does it Occur?

Esophageal bolus transit is composed of a series of highly coordinated events that move a liquid or solid bolus to the stomach. The esophageal transit is orchestrated by control mechanisms originating from the central nervous system, enteric nervous system, and musculature of the esophagus. These control mechanisms also coordinate the motor function of the esophagus with the activity in the oropharynx, LES, stomach, and pulmonary systems (Goyal and Chaudhury 2008).

Bolus transport through the esophagus after a swallow is performed in the upright position assisted by gravity and peristalsis. A large portion of a liquid bolus may pass through the esophagus because of gravity while solid boluses and residual liquid boluses will require intact esophageal peristalsis to pass into the stomach. Primary peristalsis is stimulated by the oropharyngeal swallow while secondary peristalsis is stimulated by the presence of a bolus within the body of the esophagus (Figs. 1 and 2).

Contraction of the striated portion of the esophagus occurs following UES relaxation and is directed by sequential activation of neurons originating in the nucleus ambiguous that travel to the vagal nerve fibers synapsing with striated nerve fiber motor endplates within the myenteric plexus (Roman and Car 1970; MacGilchrist et al. 1991). The striated muscle portion is measured from the lower margin of the UES and makes up approximately 5% of the esophageal body.

The striated muscle joins the smooth muscle to make up the transition zone of the esophagus. The transition zone makes up 30–35% of the esophageal body and it has been characterized as a lower amplitude peristaltic pressure wave profile compared to other esophageal area, that is, primarily striated or smooth muscle areas. The transition zone has been defined by high-resolution manometry (HRM) (Fig. 3) to have nadir pressure that may fall below 30 mmHg isobaric contour in 60% of swallows in normal subjects (Kumar et al. 2009).

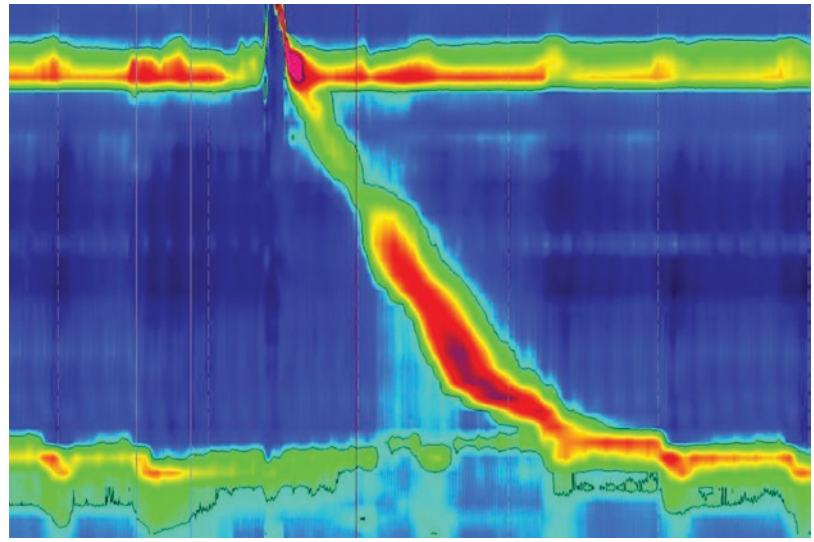

Fig. 1 HRM-pressure topography of a normal swallow. Esophageal peristalsis is triggered by an oropharyngeal swallow

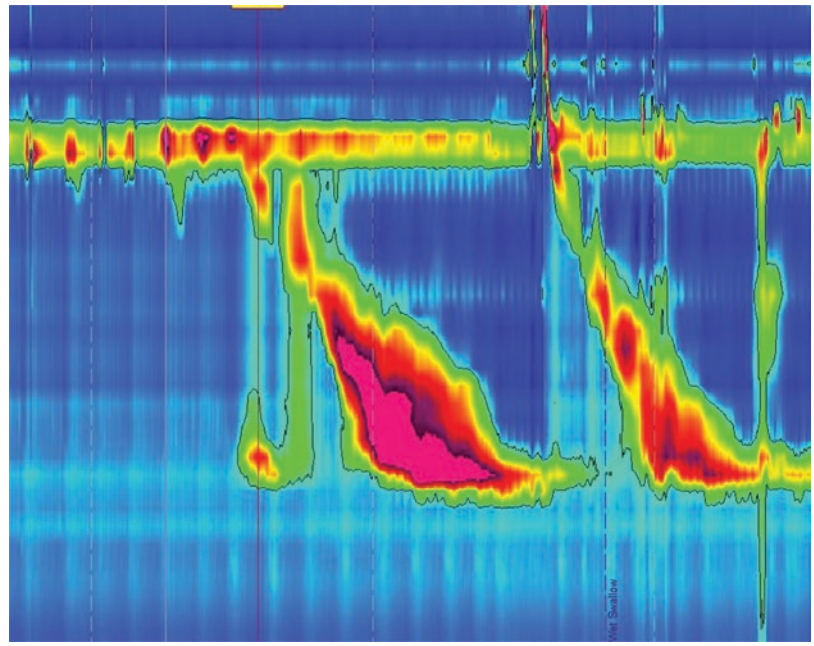

Fig. 2 HRM-pressure topography of a secondary peristalsis triggered by a reflux event

If the transition zone pressure trough is prolonged or elongated on HRM these findings are associated with abnormal bolus transit or esophageal dysmotility (Ghosh et al. 2008a, b). The distal 50–60% of the esophagus is composed entirely of smooth muscle.

Deglutition is a complex process which depends on the interplay among the CNS, myenteric plexus, and smooth muscle (Roman and Car 1970). There are two types of esophageal intramural neurons—inhibitory and excitatory neurons. The myenteric plexus receives input from the central nervous system providing innervation to the smooth muscle of the esophagus. Primary esophageal peristalsis begins with deglutitive inhibition followed by excitation. Esophageal smooth muscle has a unique function orchestrating bolus movement through sequential myogenic relaxation and contraction. A rebound

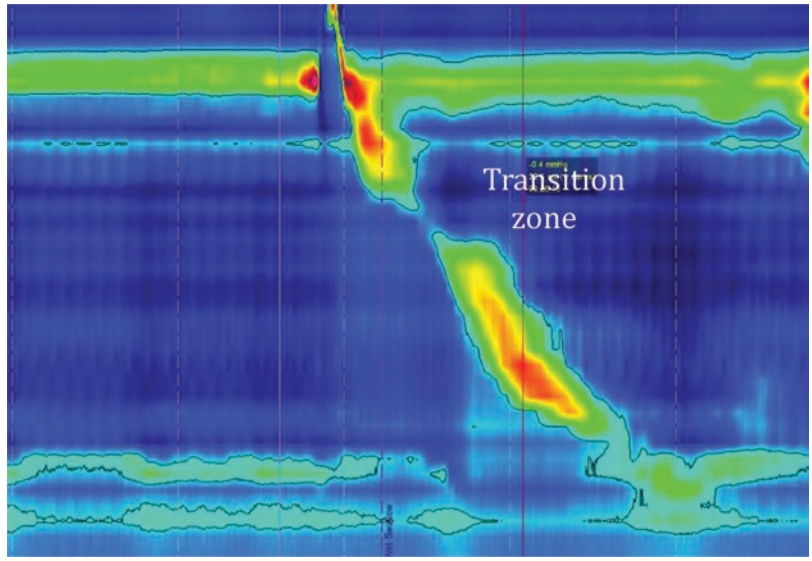

Fig. 3 HRM-example of transition zone with short peristaltic break

contraction and latency gradient are unique to the smooth muscle portion of the esophagus (Weisbrodt and Christensen 1972). The contraction of the smooth muscle occurs upon cessation of the bolus as a stimulus, after esophageal distention, esophageal deflation, and contraction occur. Christensen concluded that esophageal circular muscle contraction was an example of rebound following stimulation of the inhibitory nerves. The latency gradient is part of the smooth muscle layer of the esophagus. This gradient is responsible for the peristalsis of the esophageal smooth muscle (Weisbrodt and Christensen 1972). Hyperpolarization of the smooth muscle membrane during the latency period of peristaltic contraction supported the hypothesis that the latency observed was associated with inhibition (Rattan et al. 1983). Unlike striated muscle of the esophagus, the smooth muscle receives nonsequential, simultaneous activation of the myenteric neurons (Mukhopadhyay and Weisbrodt 1975). Early studies revealed that vagal stimulation produced cholinergic and non-cholinergic esophageal contractions as well as is influential in the esophageal peristaltic pressure and velocity (Dodds et al. 1978; Gidda et al. 1981). Repeated vagal simulation provides quiescent esophageal state until the last stimulation is provided and then an esophageal contraction occurs (Gidda and Goyal 1983).

3 What Are the Characteristics of Esophageal Dysmotility?

Esophageal dysmotility can be instigated by myopathic or neuropathic conditions that affect the esophagus such as problems with control of inhibitory or excitatory innervation and control of smooth muscle that may affect the robustness of the esophageal contractions and the tone of the lower esophageal sphincter (Goyal and Chaudhury 2008).

Specifically, inhibitory innervation is responsible for the degree of esophageal contraction and relaxation of the lower esophageal sphincter. Examples of disorders of impaired inhibitory innervation are diffuse esophageal spasm (DES) and achalasia. DES involves the esophageal body alone, while achalasia involves both-the LES and the esophageal body.

Excitatory innervation is responsible for transient lower esophageal sphincter relaxation (TLESR). Excitatory innervation deficiency has been thought to be responsible for hypotensive contractions, hypotensive LES, and gastroesophageal reflux disease. Examples of deficiency of excitatory innervation may lead to hypotensive contractions and hypotensive LES and

gastroesophageal reflux disease. Scleroderma is an example of a systemic disease that causes hypotensive peristalsis and LES resting pressure. Overactive excitatory innervation can cause abnormally high-pressure peristaltic pressure waves and high LES resting pressure such as in jackhammer esophagus.

4 Disorders of Inhibitory and Excitatory Innervation and Smooth Muscle

4.1 Achalasia

Achalasia can be a primary or a secondary motility disorder. The disease was first described in 1674 by Sir Thomas Wilson and the term achalasia (from Greek meaning lack of relaxation) was first used by Arthur Hurst in 1927 (Hurst 1927). Achalasia is a rare disease affecting both genders equally primarily in the third and seventh decades of life with prevalence less than 1/10,000 people and incidence between 0.03 and 1/100,000 people per year (Mayberry 2001).

Achalasia is characterized by the diminished or absent esophageal peristalsis and outflow obstruction characterized by absence of esophagogastric junction relaxation secondary to alteration in inhibitory innervation control (Gyawali 2016). The main symptoms related to achalasia are dysphagia for liquids and solids, as well as complaints of chest pain and regurgitation. Achalasia affects primary and secondary esophageal peristalsis. The cause of primary achalasia is not well defined or understood but studies have suggested association with viral infection. In some individuals achalasia has been linked to an autoimmune response that results in inflammation and ganglion loss (Gyawali 2016; Park and Vaezi 2005). The primary neuropathology of achalasia is varying degrees in the loss of ganglion cells from the wall of the esophagus. The loss begins distally and progresses proximally over the duration of the disease. Inflammation has been noted within the myenteric plexus corresponding to ganglion cell loss. The chemical changes that are hallmark in the disease are decreased nitric oxide synthase, loss of vasoactive intestinal peptide, and loss of intrinsic acetylcholine-containing nerves (Pressman and Behar 2017; Eckardt and Eckardt 2009). Extrinsic nerves are also affected with degeneration of the axoplasm and myelin sheaths within the vagus nerve and the dorsal motor nucleus. The appearance of a thickened circular muscle layer at the level of the LES has also been noted in achalasia.

The diagnosis of achalasia is suspected based on the type of dysphagia symptoms. Radiologic imaging studies support an initial diagnosis of achalasia and have been used to detect preclinical symptomatic recurrence. The typical characteristics noted on a barium esophagram or "timed barium esophagram" (Fig. 4) are smooth tapering in the distal esophagus with typical bird's beak appearance, dilatation of the esophageal body above the gastroesophageal junction, lack of primary peristalsis noticed during fluoroscopy, and formation of a contrast column above the LES

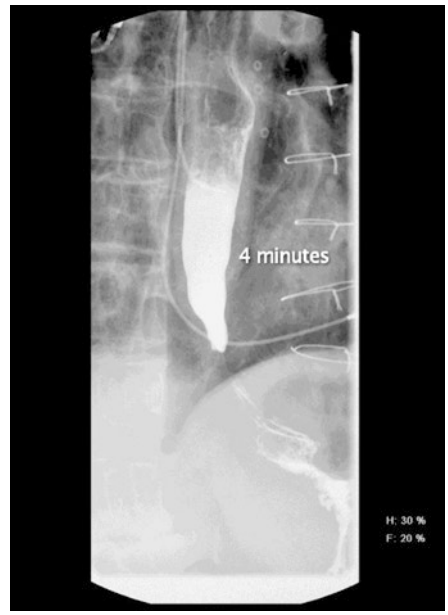

Fig. 4 Timed barium esophagram showing a column of barium at 4 min after ingestion in a patient with achalasia

(Vaezi et al. 2002). However, these radiographic characteristics may not be present in the early stages of the disease.

Endoscopy is considered to have a poor sensitivity and specificity in diagnosis of achalasia but has a role in ruling out secondary causes of achalasia.

High-resolution manometry (HRM) remains the gold standard in diagnosing achalasia. There are three distinct phenotypes of achalasia defined by HRM. Type I and II achalasia are characterized by absence of peristalsis and slow progression of the disease (Park and Vaezi 2005). Previously described abnormalities of the esophageal smooth muscle function in patients with type I and II achalasia may explain the dilated appearance of the esophageal body, also caused by high-grade outflow obstruction observed in the end stages of the disease. End-stage achalasia occurs in 5% of patients affected with type I achalasia and it is believed to be a progression of type II achalasia. Type III achalasia is also characterized by outflow obstruction along with rapid peristalsis which has been suspected to be the result of inflammation involving the myenteric plexus. Type III achalasia may also be caused by chronic use of certain pharmacologic agents such as persistent use of opioid medications resulting in physiologic changes at the esophagogastric junction (EGJ) (Pressman and Behar 2017).

The hallmark of achalasia defined by high-resolution pressure topography is EGJ outflow obstruction or elevated integrated relaxation pressure (IRP) accompanied by absence of peristalsis or non-peristaltic esophageal pressurization. The three types of achalasia differ pathophysiologically by the degree of esophageal body dysfunction as defined by high-resolution pressure topography. Type I or classic achalasia has been outlined as having 100% failed contractions and absence of esophageal pressurization; type II achalasia is defined as panesophageal pressurization occurring with at least 20% of the swallows; and type III achalasia is described as presence of preserved fragments of distal esophageal peristalsis or rapid esophageal contractions in at least 20% of the swallows (Pandolfino et al. 2008).

Amyl nitrate, a potent smooth muscle relaxant, has been used to differentiate between the diagnoses of primary versus secondary achalasia. Amyl nitrate can be administered during manometric studies when the diagnosis of achalasia is in doubt. When amyl nitrate is used in patients with primary achalasia the EGJ pressure abates as the smooth muscle relaxes. If the condition is due to secondary achalasia (e.g., due to neoplasm in the cardia or scar tissue at the LES or hiatus) the LES pressure will remain unchanged with administration of amyl nitrate.

Another pharmacologic intervention that has been used in establishing the diagnosis of achalasia is administration of intravenous (IV) cholecystokinin (CCK) during esophageal manometry. In non-achalasia patients administration of IV CCK causes relaxation of LES due to greater effect on the inhibitory myenteric plexus neurons. Due to the absence of inhibitory myenteric plexus neurons in patients with achalasia, administration of IV CCK causes a paradoxical increase in LES pressure.

4.2 Management of Achalasia

The goal in management of achalasia is early diagnosis before the condition reaches end stages when esophageal function is severely impaired and an esophagectomy may be the only option to consider. The main purpose of pharmacologic, endoscopic and surgical therapy of achalasia is to decrease the abnormal pressure of the EGJ and hence relieve the outflow obstruction. Since the etiology of achalasia is yet undefined there are no pharmacologic interventions that can prevent progression of esophageal body smooth muscle weakness or improve the esophageal body function to facilitate bolus transport across the LES (Cheatham and Wong 2011).

Pharmacologic treatments offer only transient symptom improvement at best while endoscopic and surgical treatments continue to have the best outcomes. The pharmacologic treatment includes smooth muscle relaxants such as botulinum toxin, calcium channel blockers, nitrates, and phosphodiesterase inhibitors. The mechanism of these drugs is aimed to reduce LES pressure.

Calcium channel blockers taken before meals have been evaluated extensively in achalasia patients (Triadafilopoulos et al. 1991). A meta-analysis studying the use and effectiveness of nitrates for treatment of achalasia found few controlled studies, heterogeneous data, and many reported side effects with use of pharmacologic agents (Wen et al. 2004). There have only been a few small studies reporting the use of the phosphodiesterase inhibitors.

Clinically available oral pharmacologic therapies have limited use in treating achalasia (Pohl and Tutuian 2007). Oral pharmacologic therapies have been used primarily in patients who are not candidates to undergo other more effective treatments such as botulinum toxin injections at the LES (Annese et al. 2000; Dughera et al. 2005), pneumatic dilation (Wong 2004; Zerbib et al. 2006), and/or myotomy (Vela et al. 2006).

The most effective treatment focuses on reducing the LES pressure and obstruction to outflow achieved through mechanical disruption of the lower esophageal sphincter fibers by laparoscopic Heller myotomy or endoscopic pneumatic dilation. New approaches such as the peroral endoscopic myotomy (POEM) have been utilized to safely treat patients with symptomatic achalasia (Swanstrom et al. 2011).

Based on the manometrically defined subtypes of achalasia, that is, manometric determination of type I, II, or III, the outcome of pneumatic dilation versus laparoscopic Heller myotomy varies. A higher number of patients with type II achalasia are treated successfully with pneumatic dilation or laparoscopic myotomy than patients with type I or III. Success rates in type II achalasia have been reported to be significantly higher. Patients with type III achalasia would probably benefit from therapy with laparoscopic Heller myotomy (Rohof et al. 2013).

4.3 Diffuse Esophageal Spasm (DES)

Diffuse esophageal spasm is a primary spastic motility disorder of the inhibitory nerves causing disorganized and nonefficient esophageal peristaltic pressure waves secondary to simultaneous onset of esophageal contractions in the smooth muscle segment of the esophagus. The contractions may be primary, in response to a swallow, or spontaneous as secondary peristalsis. In DES the deglutitive EGJ relaxation is usually normal with minor variations from normal range pressure; however the simultaneous esophageal body contractions may be manometrically hypotensive, hypertensive, or normal.

The cause of DES is not completely understood and continues to be debated in the literature. It has been proposed that DES is caused by impaired neuronal inhibition of the distal esophageal body. Since DES and spastic achalasia share similar pathophysiology it has been suggested by some investigators in the field of deglutition that DES may be a predecessor of achalasia or may even represent early stages of achalasia. DES can be appreciated on radiographic imaging, specifically a barium esophagram where the esophageal body contour has a corkscrew appearance (Fig. 5).

HRM is the standard for making the diagnosis of DES. According to the Chicago Classification (CC) the diagnosis of DES depends upon identification of rapid, premature, or simultaneous contractions defined by reduced distal latency of less than 4.5 s occurring in more than 20% of wet

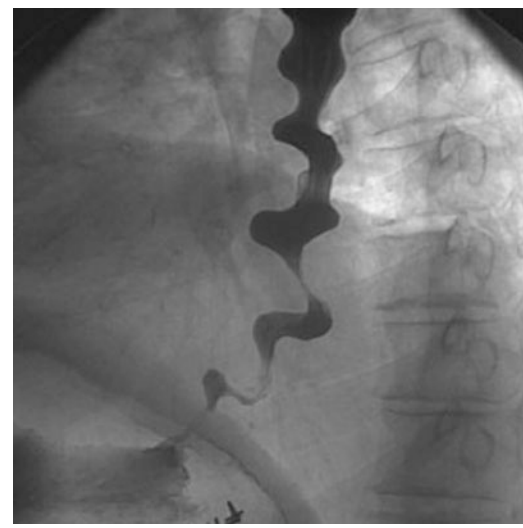

Fig. 5 Barium esophagram image of DES

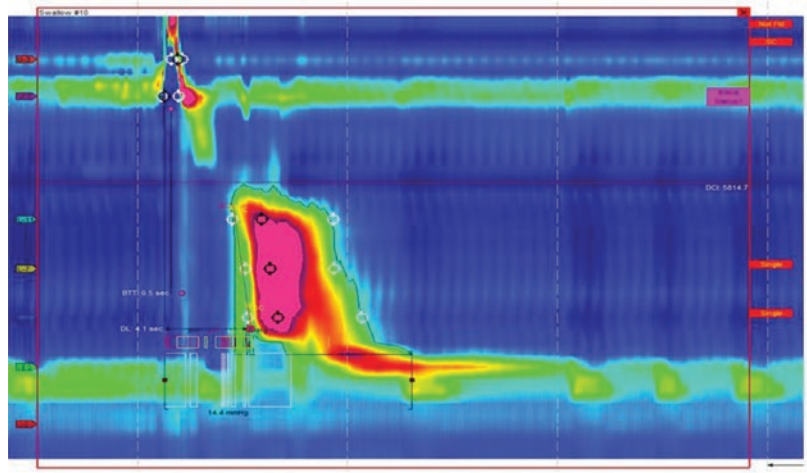

Fig. 6 High-resolution manometry of diffuse esophageal spasm (DES)

swallows (Fig. 6) which physiologically represents attenuation of esophageal inhibition (International High Resolution Manometry Working Group 2015).

DES is an uncommon esophageal motility disorder with 3–10% prevalence in patients with dysphagia (Bashashati et al. 2010). DES is diagnosed equally in both genders with the most common symptoms being solid and liquid dysphagia, chest pain, and weight loss. Dysphagia for solids and liquids may occur in the absence of chest pain. Chest pain is prevalent in patients who have manometrically confirmed hypercontractile simultaneous esophageal peristalsis. The contribution of acid stimulation on development of DES symptoms merits consideration, although the role of acid suppression is not well understood.

The goal of medical treatment of DES is to compensate for deficient inhibitory neural function. Medications to treat DES reported in case studies and small uncontrolled group reports include smooth muscle relaxants, proton pump inhibitors, and antidepressants. These medications can produce some change in the degree of chest pain but dysphagic symptoms may remain. Due to lack of controlled clinical trials the effectiveness of these medications in the management of symptomatic patients with DES has been disputed. Medication such as sildenafil designed to block nitric oxide degradation and increase tissue bioavailability of nitric oxide, which allows for prolongation of esophageal muscle relaxation, has been used with promising outcomes (Roman and Kahrilas 2012). Additionally botulinum toxin has been injected into the esophageal muscle of patients with DES with some degree of success and decrease of patient's symptoms (Bashashati et al. 2010). The use of botulinum toxin esophageal injection has been shown to be superior to placebo in patients with DES.

Since association of DES with GERD has been suspected it is reasonable to initiate antisecretory therapy early in the management of symptomatic patients with DES.

Another pharmacologic intervention, which has been studied in patients with DES, is the use of peppermint oil. Peppermint oil has been found to completely abolish premature simultaneous esophageal contractions in patients with DES while preserving deglutitive esophageal peristalsis (Pimentel et al. 2001).

Peroral myotomy is an emerging technique which may be considered in patients with DES who failed pharmacologic intervention. Surgical techniques such as POEM have yielded positive patient symptom reduction and health-related quality-of-life issues in patients with DES (Roman and Kahrilas 2012; Khan et al. 2017; Almansa et al. 2012; Burmeister 2013).

4.4 Ineffective Esophageal Motility (IEM)

IEM is the most common abnormality on esophageal manometry, with an estimated prevalence of 20–30% of motility disorders (Tutuian and Castell 2004; Conchillo et al. 2005). The pathophysiology of IEM is unknown. It is thought that IEM may be caused by collagen vascular diseases such as scleroderma or amyloidosis and by drug effects specifically those with anticholinergic influence. It is believed that the cholinergic excitatory activation is suppressed in patients with IEM causing the reduction of pressure-wave amplitude and duration in esophageal contractile profile.

High-resolution manometry is the method of choice to differentially diagnose IEM. The cardinal characteristic of IEM is poor bolus transit in the distal esophagus which can also be appreciated using multichannel intraluminal impedance testing (Tutuian and Castell 2004). Prior to the use of HRM IEM or hypotensive peristalsis was observed in response to a swallow on a barium esophagram. The barium esophagram verifies a delayed bolus transit in the distal esophagus with proximal escape of the barium bolus. If hypotensive LES is also present there will be free flow of barium from the stomach to the esophageal body.

The hypotensive esophageal contractions in IEM are characterized by pressure-wave amplitudes less than 10 mmHg at 3 or 8 cm above the LES (Blonski et al. 2008). The proposed definition of ineffective esophageal motility by the Chicago Classification refers to the distal contractile integral (DCI) of less than 450 mmHg/s/cm with less than or equal to 50% ineffective wet swallows (International High Resolution Manometry Working Group 2015).

Ineffective motility commonly coexists with GERD. Patients with IEM can develop severe esophagitis and peptic strictures secondary to gastroesophageal reflux along with poor peristaltic pressure and bolus clearance. There are no standard therapies for IEM; however GERD symptoms are usually treated with acid-suppressive therapy. If hypotensive LES is present fundoplication has been an effective option for reduction of gastroesophageal reflux and prevention of esophagitis and stricture formation; however, the risk of developing postsurgical dysphagia in this group of patients is high (Broeders et al. 2011). Treatment of IEM using pharmacologic therapies has been ineffective due to lack of promotility agents that improve esophageal contractile function (Abdel Jalil and Castell 2016) (Table 1).

Table 1 Motility disorder/pharmacologic agent and the mechanism of action

Motility disorder	Pharmacologic agent	Mechanism of action
Achalasia	Calcium channel blockers *Nitrates* Phosphodiesterase inhibitors *Botulinum toxin*	Relaxation of LES pressure to alleviate outflow obstruction
	Cholecystokinin (diagnostic agent administered during HRM)	Paradoxical increase in LES pressure
	Amyl nitrate (diagnostic agent administered during HRM)	Reduction of LES pressure
Diffuse esophageal spasm and hypercontractile esophagus	*Proton pump inhibitors*	Reduction of esophageal acid exposure
	Low-dose antidepressants	Symptomatic relief of atypical chest pain
	Calcium channel blockers *Nitrates* Phosphodiesterase inhibitors *Peppermint oil* Botulinum toxin	Relaxation of esophageal body smooth muscle
Ineffective esophageal motility	Proton pump inhibitors	Reduction of esophageal mucosa acid exposure

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The Importance of Enteral Nutrition

Christina Stene and Bengt Jeppsson

Contents

Abstract

Many neurological diseases are followed by a disturbance of nutritional intake to some extent and thus constitute the most common indication for nutritional support and enteral access. Several studies have shown that malnutrition is a common condition, with as many as 40% of admitted patients being identified as undernourished and 78% of these further found to be deteriorated in their nutritional status during hospital stay (McWirtrer and Pennington, BMJ 308:945–948, 1994). Malnutrition, being a preventable disorder, is thus of great importance to identify patients at risk of malnutrition and prevent impairment of nutritional status. With adequate nutritional care, improved healing is augmented, resulting in better care and quality of life, lowered costs due to reduced length of hospital stay, fewer complications, and decreased mortality. Gut starvation hampers the immunological response. Even small amounts of enteral nutrition maintain gastrointestinal mucosal integrity and improve barrier function, thus minimizing immunological complications and enhancing clinical recovery.

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1 The Importance of Enteral Nutrition

The value of nutritional support and the risks and implications of malnutrition of sick patients who are to undergo elective surgical intervention have been well documented in the literature in recent decades. Neurological diseases constitute the most common indication for nutritional support and enteral access since a wide variety of neurological conditions result in dysphagia, aspiration, swallowing disorders, or a combination of these symptoms (Phillips and Ponsky 2011).

Malnutrition is common prior to or after stroke, with dysphagia—a frequent manifestation of stroke—adding to nutrition risk (Corrigan et al. 2011). Malnutrition is a preventable disorder. During the acute and rehabilitation phases of stroke, nutritional intervention is the mainstay of the interdisciplinary approach to the care and treatment of these patients.

When cognitive functions are affected, such as visual neglect, or there is a concomitant depressive state where the patient is reluctant to eat, or there is a neurological deficit, e.g., paresis of the upper extremities or apraxia, the patient's ability to ingest food will be hampered, thus influencing nutritional intake and increasing the risk of malnutrition (Corrigan et al. 2011).

In elderly multimorbid patients, nutritional and fluid intake is often compromised and preventive nutritional support has to be considered at an early stage as restoration of body cell mass here is more difficult than in younger persons. Further, difficulties in performing assisted feeding are more pronounced in the elderly (Volkert et al. 2006).

For patients with a normal-functioning gastrointestinal tract who require nutritional support, enteral access is the preferred mode through which to administer nourishment. Enteral nutrition has been proven to be safe and possesses a clear cost advantage as well as gives metabolic and immunity-linked benefits. Enteral access encompasses local nasogastric or nasoenteric tubes, endoscopic options comprising percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy, and a surgical approach (gastrostomy, e.g., Witzel technique, or jejunostomy), the latter confined to patients who opted for or were chosen for abdominal surgery or in cases where the endoscopic procedure is deemed not feasible.

Parenteral nutrition should be restricted to patients with contraindications for the use of the enteral pathway, e.g., with a nonfunctioning gastrointestinal tract due to ileus/mechanical obstruction, fistulas of the upper gastrointestinal tract, or a reduced visceral blood flow.

To evaluate or assess the nutritional status of a patient, the specific demands of that individual must be reflected upon to form a basis for selection of the optimal treatment strategy for the patient on his or her journey through the disease (Howard et al. 2006). Knowledge of the various treatment methods, risks, and advantages associated with the different options is a prerequisite for being able to lead the patient through the most effective and tailored nutritional support.

Satisfactory supply of nutrients is important for the many tasks of the gastrointestinal tract. In addition to its role in digestion of food and the absorption of nutrients, it also constitutes a barrier between the luminal content and the blood circulation and lymphatics, and also houses a large proportion of the immune system of the body. This explains the importance of maintaining the gut in as good a condition as possible during periods of disease and reduced ability in providing the body with a normal dietary intake.

Technical progress concerning access to the gastrointestinal tract as well as the diverse formulae suitable for upgrading a variety of states of impaired nutritional needs have now made it unacceptable to allow patients who are unable to maintain nutritional support in a normal way or other ways to become malnourished and for this to result in any complications, distress, or even death by starvation (Dudrick and Palesty 2011).

If 7 days have elapsed without the patient being able to achieve a sufficient oral intake of aliments or if the patient has been unable to take in at least 60% of the estimated daily nutrient demands, nutritional support should be initiated without delay, in the first instance by the enteral route (Arends et al. 2006; Jayarajan and Daly 2011). Nutritional support is indispensable for

patients who cannot achieve full supply of energy and substrate demands.

Early enteral feeding has largely shown positive results compared with the parenteral feeding, resulting in a better outcome, with a reduction in the complication rate, lower incidence of infections and sepsis, improved wound healing, and a decreased length of hospital stay. Immunological benefits are also seen in enteral feeding. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have recommended gut feeding as the method of choice when the gastrointestinal tract is able to tolerate enteral supply.

It has been shown that it is not necessary to remove an orogastric feeding tube in order to assess the state of dysphagia since an objective swallowing evaluation can be performed with such a tube in place (Leder et al. 2011).

The cells of the intestinal mucosa (the enterocytes and colonocytes) receive around 70% of their nourishment from the intestinal lumen and only a minor part, around 20–30%, from the circulation (Fig. 1). The inner epithelial cell layer has a high cell turnover, the cells being exchanged every 2–3 days, thus requiring sufficient nutritional supply for this high metabolism. The presence of nutrients in the intestinal lumen is the most potent stimulus for proliferation of mucosal cells as well as for other functions such as hormonal release and production of intestinal juices involved in the absorption of nutritional components. The daily endogenous gastrointestinal fluid production is about 8000–9000 mL, of which the small intestine itself accounts for around 3500 mL.

Dietary fibers are fermented by bacteria in the colon to short-chain fatty acids (SCFAs) that are absorbed by the liver and included in the energy metabolism. SCFAs have been shown to have a beneficial effect on the microcirculation of the intestinal mucosa, as well as a trophic effect since they constitute energy substrates for the colonic mucosa, stimulating fluid and electrolyte absorption (Schneider et al. 2006). The amino acid glutamine is the preferred source of fuel for the enterocytes.

Intake of nutrients per se may be at any rate as essential as body mass and structure to preserve normal function and its effects on the intestinal structure are closely linked to loss of luminal nutrition rather than to the metabolic consequences itself. In healthy volunteers it has been observed that if the gastrointestinal tract is not used or there is a short-term loss of nutrients in the intestinal lumen, the absorptive capacity of the small intestine is reduced within 36 h. A sustained total parenteral nutrition leads to atrophy of enterocytes of the small intestine as well as changes in the enteric nerve system, which may explain difficulties encountered during transition from total parenteral nutrition to oral feeding.

Many studies have shown that the concept of "minimal enteral nutrition," meaning a supply of small amounts of enteral nutrition to provide the intestinal mucosa with necessary nutrients and then completing the rest of the patient's nutri-

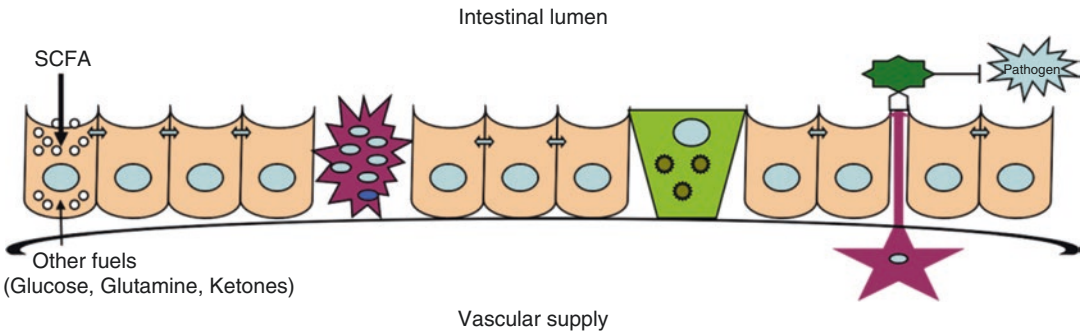

Fig. 1 Immunocompetent cells of different characters are located between the intestinal mucosal cells. The main part of nourishment for enterocytes and colonocytes is received from the intestinal lumen and only a minor part is received from the circulation

tional demands by the intravenous route, is a useful way of preserving gut integrity.

The gut absorptive function is dependent on gut motility, and therefore stimulation of gastrointestinal motility is an important part of nutritional support. Enteral nutrition also enhances biliary and pancreatic secretions, which are important for maintenance of gut integrity and reduction of the risk of gallbladder sludge or gallstone formation.

Many factors seem to be of great importance with regard to wound healing, but nutritional status and especially lately nutritional intake seem to be a crucial aspect to bear in mind when dealing with patients.

2 The Importance of Gut Function

2.1 Surface

The intestinal mucosa, constituting the innermost layer of the intestinal wall, is made up of three layers (epithelium, connective tissue, and smooth muscle) and is responsible for the important functions of the gastrointestinal tract: absorption, digestion, and secretion. The structure of the mucosa is very specialized depending on in which part of the gastrointestinal tract it is exerting its function. It is folded (constituting villi), resulting in an increased surface area.

The intestinal surface is considered to cover a very large area; the exact size is difficult to establish and differs between individuals, extending to around 250 m^2 (equivalent to a doubles tennis court). It is in fact the body's largest surface area, considering all the food that is passing through it. Its main function is absorption of nutrients. The small intestine has a length of about 3.5 m. The minimal length required to ensure significant absorption of nutrients is about 1 m.

When blood flow to the gastrointestinal mucosa ceases, the absorptive surface area is reduced, a fact attributed to changes within villi comprising among other changes decreased villus height, reduction of cell proliferation and cell migration, and augmented apoptosis and cell death. Restoration of blood circulation providing nutritional supply leads to restored absorptive cell mass and the rates of nutrient absorption may be enhanced.

2.2 Bacteria

The gut microbiota fulfills several tasks, among which the most important are protective, immunoregulatory, and metabolic functions. All humans are intimately associated with an extensive population of microbial organisms existing in a symbiotic relationship (Fukatsu and Kudsk 2011). We host more bacterial cells than eukaryotic cells in the gut. The gut constitutes a reservoir of bacteria, considering that every healthy human harbors 1–2 kg of bacteria, made up of up to 1000 different species. This is beneficial as long as the balance between health-enhancing bacteria and potential pathogens is maintained. However, when the balance between commensal bacteria and potentially pathogenic bacteria is altered, the situation may rapidly become detrimental. Since the intestinal microbiota contribute considerably to the production of amino acids and the gut microbes are also involved in the production of fatty acids and in the synthesis of vitamins, e.g., the essential nutrient vitamin B_{12}, alterations in gut function will have wide implications.

Bacteria are, as previously mentioned, highly involved in the process of degrading dietary fibers, thus contributing to a large extent to the intestinal mucosal cells' nourishment and the energy metabolism. Critically ill patients often have a pathologic colonization of the gastrointestinal tract, which is a key factor in the development of multiple-organ failure. The colonization may cause infection by the patient's endogenous flora. This development is the result of a combination of an impaired local defense, the lack of enteral stimulation, and the presence of invasive measures, e.g., the use of broad-spectrum antibiotics that causes a change in the endogenous flora. An alteration of the intestinal microbiota caused by even short-term antibiotic treatment may persist for several years (Jernberg et al. 2007).

Potential pathogens are prevented from colonizing and interacting with epithelial and immunological cells by the microbiota occupying intestinal surfaces (Fig. 2).

2.3 Barrier Function: Translocation

Besides its task to absorb nutrients, the gut constitutes a barrier between the outer surface and the internal milieu of the body.

Under normal circumstances, several barriers, in collaboration with the adaptive immune system, effectively prevent the entry of bacteria into the systemic circulation (Fukatsu and Kudsk 2011). An impaired mucosal barrier may lead to passage of bacteria and/or endotoxins through the mucosal wall to the blood and further to other organs, a process termed "translocation." A subsequent activation of the immune response may enhance a septic reaction in a critically ill patient.

The absence of nutrients in the intestinal lumen, as well as total parenteral nutrition, leads to gut starvation with mucosal atrophy and risk of translocation. The presence of food in the gut lumen stimulates the mucosa mechanically as well as increases blood flow. There is always an advantage in trying to nourish the patient through the gastrointestinal tract to achieve a normal barrier function.

2.4 Immune Function

The gastrointestinal tract constitutes one of the body's largest immunocompetent organs and is considered to harbor around 40% of the immune defense. Between the mucosal cells, various types of immunocompetent cells with different purposes are located, some capable of producing secretory antibodies, mucins, and macrophages, thus keeping the symbiotic microflora alert.

Enteral nutrition has positive effects on intestinal immunity and a local trophic effect on the gastrointestinal mucosa. A connection between the intestinal immune system in gut mucosa and the airway system has been described, with positive effects when enteral nutrition is provided.

Changes in immune function result in a reduced ability to prevent, fight, and recover from infection. Increased immune system activity increases the need for amino acids such as glutamine and alanine to facilitate protein synthesis in muscles and liver in order to prevent breakdown of endogenous proteins.

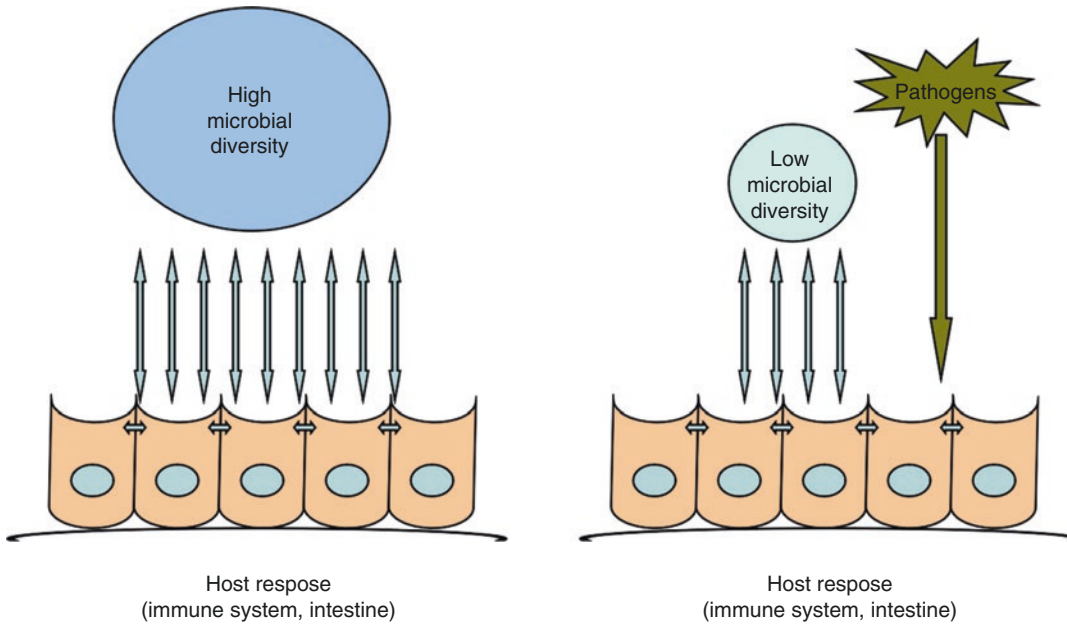

Fig. 2 A balanced intestinal microbial flora under normal conditions and during disorder (e.g., in patients undergoing antibiotic therapy, total parenteral nutrition, starvation, or any other condition leading to altered composition of the luminal microbial content resulting in increased susceptibility to pathogenic attacks)

3 Metabolism

3.1 Starvation

The body is well prepared to withstand starvation (Fig. 3).

During a short period of starvation (12–24 h) glucose is released from breakdown of glycogen through glycogenolysis (giving around 4000 kJ) to maintain blood glucose levels relatively invariable and to provide vital organs with a substrate. Degradation of fat occurs to a small extent as does degradation of amino acids. When starvation is prolonged, the situation will be altered, as in Fig. 4.

The glycogenolysis is now modest since the glycogen supply is ended after 24-h fasting. The large energy store is the fat depot (210,000–250,000 kJ) and a continuous degradation of triglycerides to free fatty acids (FFAs) and glycerol takes place. FFAs and glycerol form ketone bodies in the liver and are used in the glyconeogenesis. FFAs may also be used directly by muscles as an energy source. The vital organs of the body, i.e., the brain, heart, and red blood cells, have now adapted their energy consumption in a way to use mainly ketone bodies and much less glucose. In this situation, the body avoids degradation of endogenous protein to save the muscles and other parts of body protein.

On condition that adequate fluid supply is provided, a human may survive a long-term fasting period of up to 2 months.

3.2 Starvation and Trauma/Sepsis

The situation is completely altered if during fasting the body is exposed to a metabolic trauma, e.g., either a planned or an acute operation, an accident, or a complication such as septicemia. Degradation of fat continues, but fat utilization in muscles and also in the liver with production of ketone bodies is strongly reduced. The body thereafter again uses glucose as an energy source, mainly obtaining glucose through glyconeogenesis from amino acids. A considerable degradation of muscle protein and release of amino acids occurs, and these are converted to glucose in the liver. At the same time, the amount of circulating amino acids increases and they are used as material for wound healing as well as for production of acute-phase reactant proteins. The most important difference from the condition of long-term fasting is the imperfect fat use and the increasing proteolysis. These changes are to a great extent ruled by the neuroendocrine response with an increased release of stress hormones such as cathecholamines, cortisol, and glucagon. Simultaneously, this is also induced by some cyto-

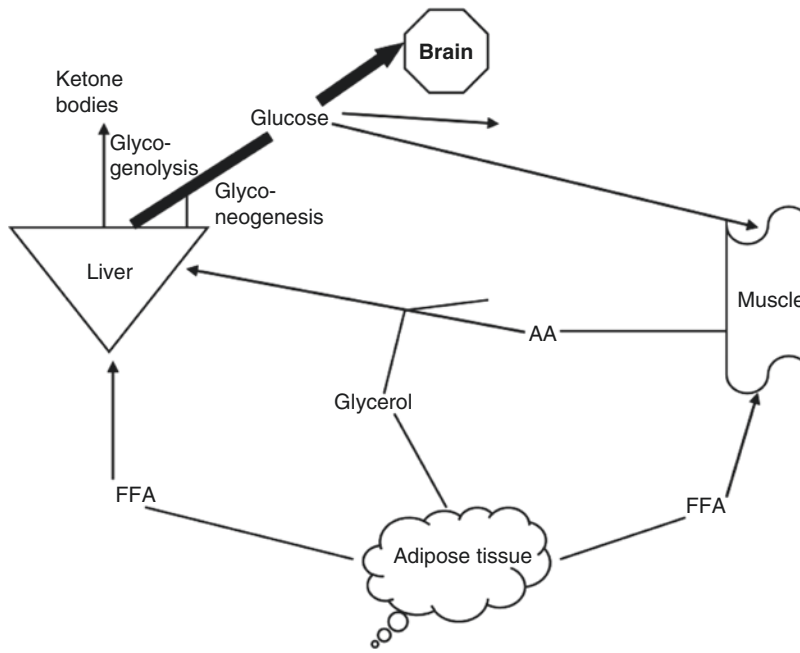

Fig. 3 Metabolic changes during short-term fasting. *AA* amino acid, *FFA* free fatty acid

kines, released from activated macrophages and lymphocytes. Among these interleukin-1 is considered to play a crucial role.

The pathophysiological processes behind the body's response to trauma as described above are not fully known, but inflammation seems to play a vital role.

Starving in combination with trauma reduces the survival time to 20–30 days (Fig. 5).

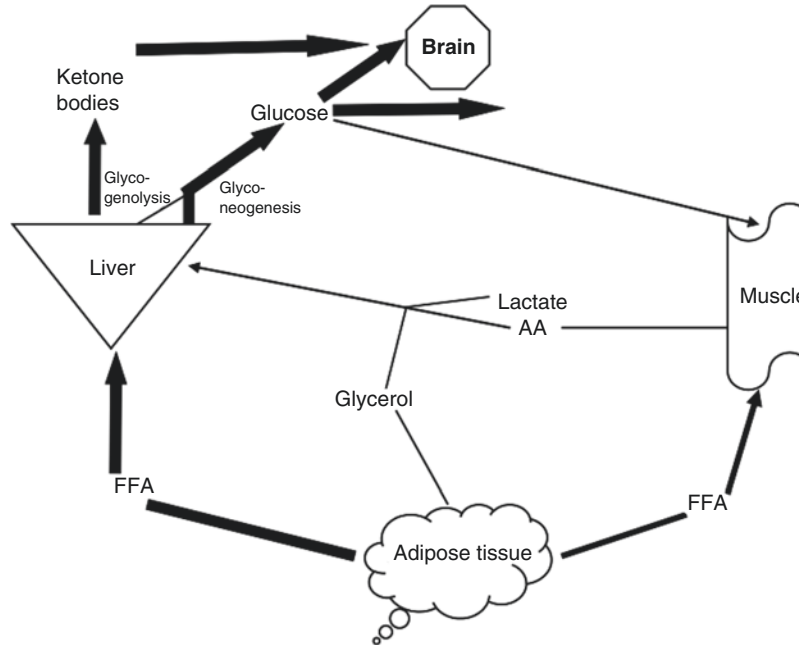

Fig. 4 Metabolic changes during long-term fasting

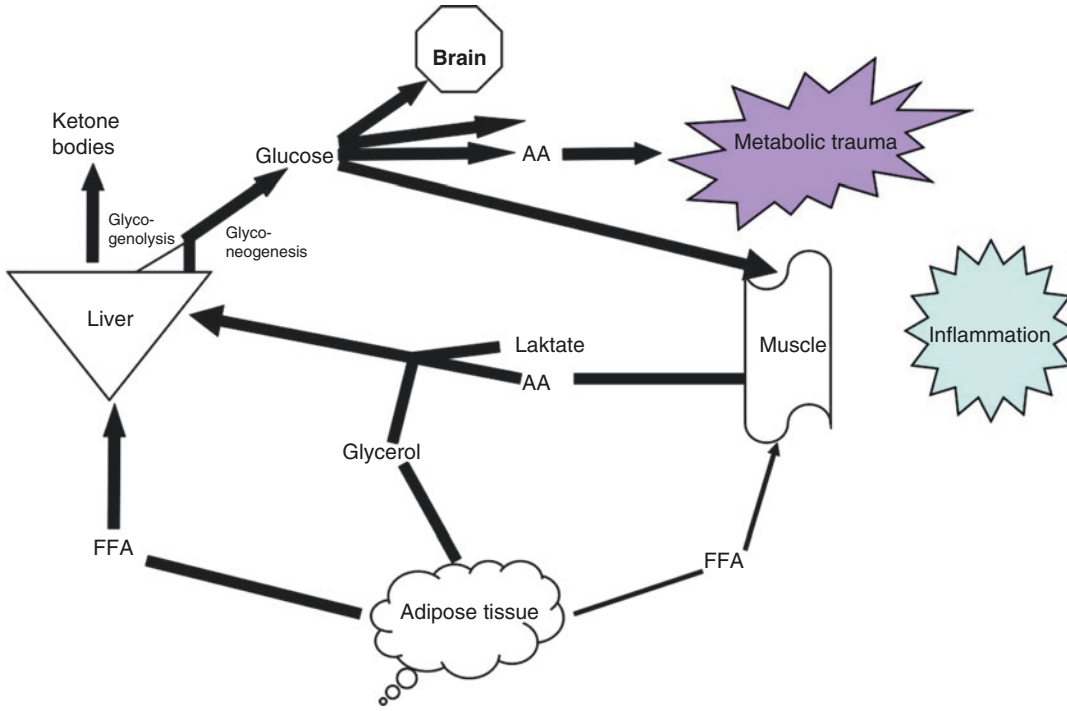

Fig. 5 Metabolic changes in trauma, sepsis, etc.

3.3 Starvation and Cancer

The same pattern of reaction is seen in a patient with a malignant disease. The presence of a tumor involves some metabolic changes similar to those occurring in trauma. Around 50% of all cancer patients are expected to die of starvation. The tumor cells have an imperative need for glucose, and by incomplete combustion of glucose a huge amount of lactate is produced. Lactate is converted into glucose in the liver, and there is an exchange of glucose and lactate between the liver and tumor cells. In this process the body loses a great amount of energy when converting lactate to glucose. The degradation of fat depots continues unaltered as the production of ketone bodies seems to be normal. Simultaneously, a potent proteolysis occurs to keep the glyconeogenesis ongoing as well as to synthesize acute-phase proteins and also to meet the tumor cells' need for amino acids. It seems this proteolytic effect of the tumor is also mediated by cytokines, especially interleukin-1 and tumor necrosis factor. These substances also have a direct effect on the saturation center in the brain, resulting in loss of appetite (anorexia), which further deteriorates the nutritional status of the patient.

In tumor patients, inflammation also plays an important role and thus decreasing inflammation is of value in the short term to reduce metabolic complications of starvation and in the long term in playing a role in cancer survival.

The patient is put into a catabolic condition not only by the tumor but also by the surgical/metabolic trauma. The stores of glucose in the liver and muscles as glycogen contain approximately 1000 kcal (4186 kJ) of energy. The total energy in fat in the form of triglycerides is approximately 50,000–60,000 kcal (209,340–251,208 kJ). If the body's muscle mass is converted into energy, this will result in about 10,000 kcal (41,868 kJ). Thus, it is evident that if these processes with strongly increased proteolysis cannot be broken down, the body's muscle mass will decrease rapidly, and since this will affect the respiratory muscles, the patient will be ruined (Fig. 6).

What can be done to cease this course of events? We know that adequate pain relief is important to reduce the stress response contributing to the inflammatory state. Epidural anes-

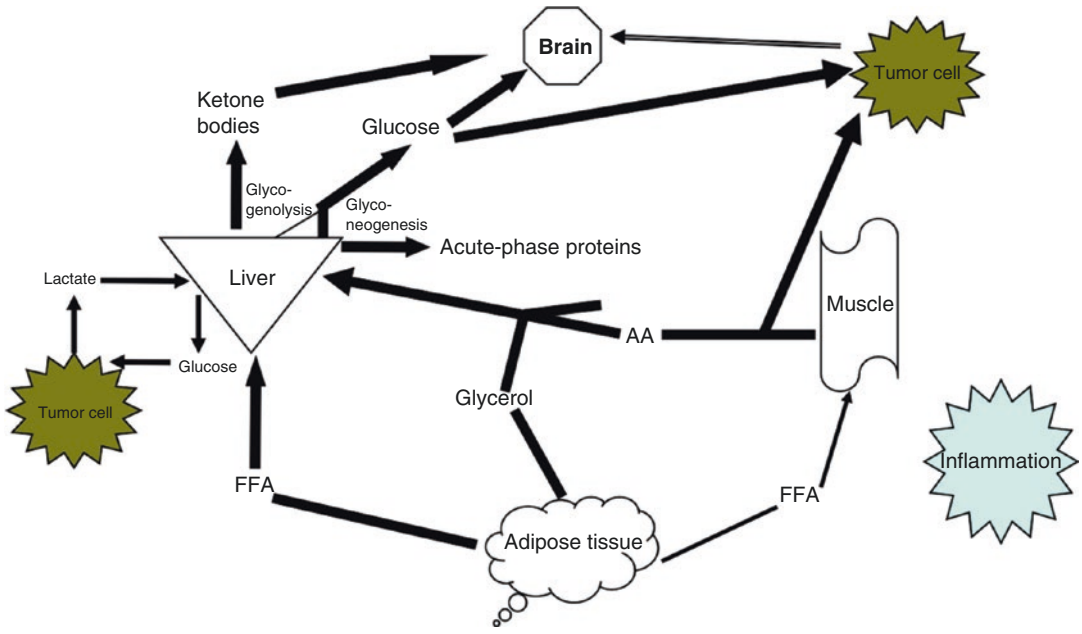

Fig. 6 Metabolic changes in cancer

thesia is especially effective in this aspect. Providing anabolic hormones (androgens, growth hormone) reduces the proteolysis in muscle. It will also be hampered by muscular activity. Energy consumption may be reduced to a certain extent by increasing the indoor temperature. The most important thing is to ensure that the patient has an adequate nutritional supply.

4 Malnutrition

Malnutrition, described more specifically in the chapter "Complications of Oropharyngeal Dysphagia: Malnutrition and Aspiration Pneumonia" by Carrión et al. in this volume, is a condition arising as a result of too little, too much, or unbalanced intake of energy, protein, or other nutrients leading to measurable unfavorable effects on tissue, organs, body constitution, and body functions that will affect the outcome of clinical treatment. "Malnutrition" means "wrong alimentation" but is commonly used to describe insufficient nutrition, a state where intake during a long period is lower than the need of nutrients (Johansen et al. 2004). Preexisting malnutrition occurs frequently, and is often seen upon admission to hospital in a variety of disease states, but malnutrition may also develop during the hospital stay. It has been estimated that over 50 million Europeans are at risk of disease-related malnutrition and up to 40% of hospital inpatients are expected to suffer from malnutrition.

The Council of Europe issued a resolution in November 2003 (Council of Europe, Committee of Ministers 2003) stating that screening for nutritional status must be performed on all admitted patients, that a plan for nutritional care must be made upon diagnosis of malnutrition, and that nutritional support must be an integral part of all therapies (McWirtrer and Pennington 1994).

Nutritional screening is a rapid and simple process conducted by admission staff or community health-care teams, whereas *nutritional assessment* is a detailed examination of metabolic, nutritional, or functional variables by an expert clinician, dietician, or nutrition nurse (Howard et al. 2006).

4.1 Consequences

Malnutrition is a risk factor for complications to hospital care and leads to an unfavorable outcome of treatment comprising infections, extended bed rest resulting in prolonged length of hospital stay, increased costs, and a delayed recovery, as well as a higher (up to eight times higher) mortality rate.

4.2 Diagnostics

All patients should undergo nutritional screening, and in the case of malnutrition, an assessment should be conducted regularly during the hospital stay. A patient at risk of malnutrition is defined as fulfilling one or more of the following criteria:

Involuntary weight loss.

Eating difficulties (e.g., loss of appetite, swallowing or chewing disabilities, problems of getting food into the mouth, problems concerning the oral cavity or teeth, nausea/vomiting).

Underweight (body mass index below 20 kg/m^{-2} if under 70 years and below 22 kg/m^{-2} if over 70 years).

The presence of concomitant diseases/infections should also be taken into consideration.

5 Treatment of Insufficient Nutritional Intake

Oral nutrition is the first choice. Hospital food in adequate amounts should be energy dense, contain balanced nutriments, and be palatable. If food intake is not sufficient, oral nutritional supplements (ONS; also denominated "sip feeds") as nutritional drinks and/or protein drinks are to be given. Mechanical alteration of food, as well as altered consistency of beverages, to achieve various textures might be one way of retaining some degree of oral intake. The possibility of fortification of food, or enriching food, should also be taken into consideration.

Mortality, morbidity, and complication rates are significantly reduced by using ONS compared with routine clinical care in patients at risk

of disease-related malnutrition. Reduction of hospital length of stay has also been observed (Stratton et al. 2003).

ONS can:

- Improve energy and nutrient intake
- Improve body weight or attenuate weight loss
- Improve functional outcomes
- Improve clinical outcomes

The next step, if the above measures are not successful, is enteral nutrition by a feeding tube. The needs for each patient concerning energy and protein are determined by age, weight, activity, and degree of illness parameters. The nutritional plan as well as all other medical treatment should be documented in the medical record. If needed, e.g., in conditions of dysphagia, ENT tumors, or radiation injuries of the mouth, throat, or upper gastrointestinal tract, a feeding tube may be placed in the duodenum or in the jejunum. A percutaneous gastrostomy can also be considered.

If most of the patient's nutritional needs cannot be supplied by the above-mentioned measures, parental nutrition must be undertaken as a supplement to enteral nutrition, or exclusively if enteral nutrition fails or if one expects that gastrointestinal function may not allow enteral nutrition.

Nutrition is not a question of whether or not/all or nothing, but is a question of both feeding pathways:

Supplementation with enteral nutrition if complete oral nutrition cannot be achieved.

Supplementation with parenteral nutrition if total oral and enteral nutrition cannot be achieved.

Specialized nutritional teams trained and organized to provide nutritional support and working to standard protocols produce the best results, with fewer complications and better outcomes than those who provide occasional or ad hoc treatment (Howard et al. 2006) (Fig. 7).

The patient's medical/surgical history and actual condition will be decisive for which feeding pathway should be used. This decision ought to be made shortly after hospital admission, to increase the opportunity for the patient to recover without complications. Enteral feeding is the preferred method if the gastrointestinal tract is functioning and no other contraindications exist. Assessing whether assisted feeding will be required short term or long term is the first step in this pathway, as depicted in Fig. 8.

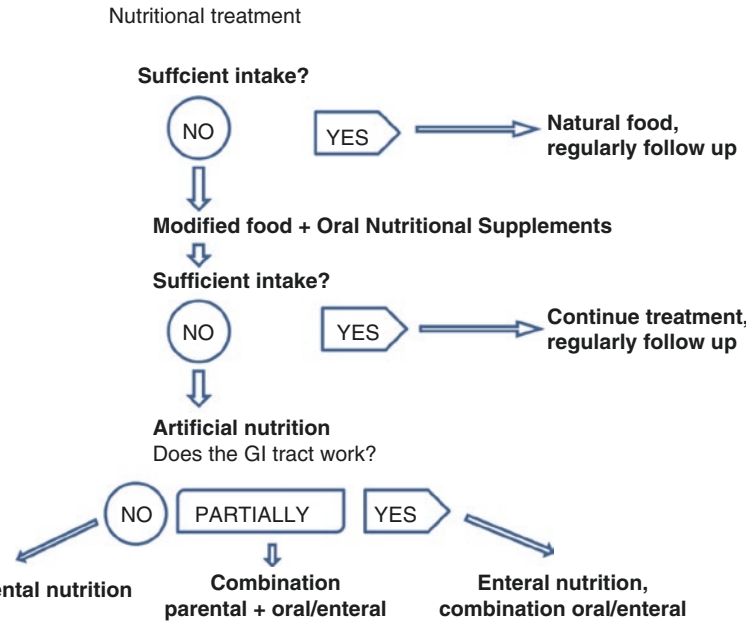

Fig. 7 Stepwise decision tree

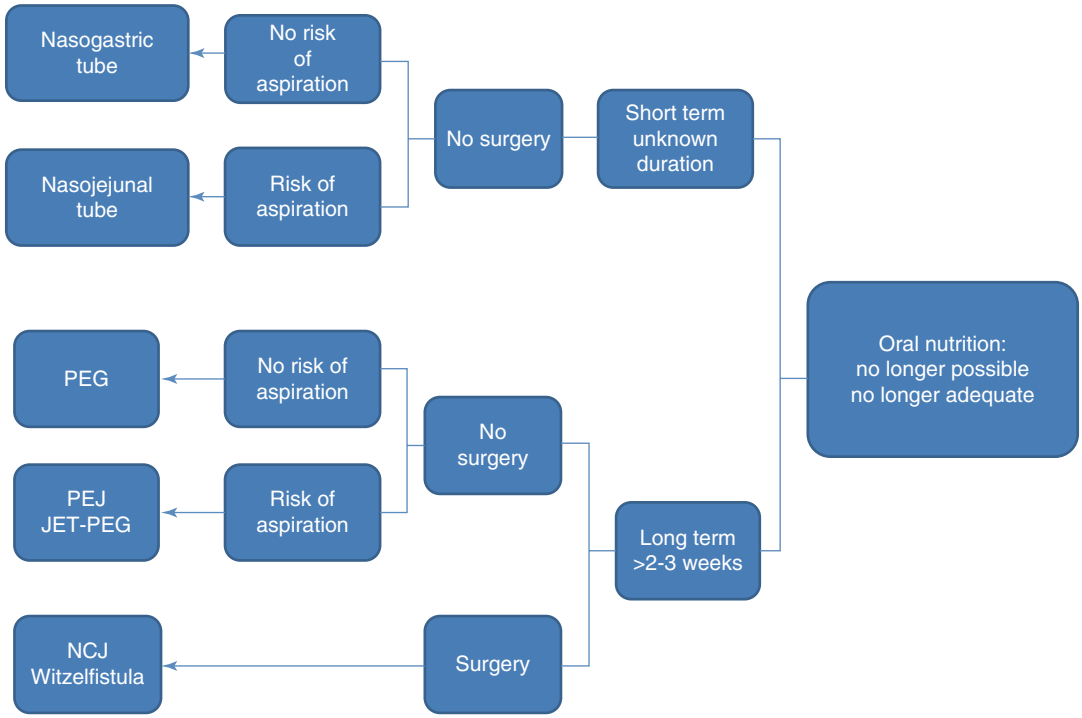

Fig. 8 Tube systems for enteral nutrition. *PEJ* percutaneous endoscopic jejunostomy, *JET-PEG* jejunal tube percutaneous endoscopic gastrostomy (a jejunal catheter placed through the percutaneous endoscopic gastrostomy to the jejunum beyond the ligament of Treitz when there are gastroduodenal motility problems), *NCJ* needle catheter jejunostomy

Since successful nutritional care is built upon multidisciplinary cooperation, a nutritional support team including representatives of different professional groups working together to meet the patient's nutritional demands is fundamental.

Nutritional intervention can prevent or at least ameliorate any deterioration in nutritional status when normal eating is still possible but is inadequate to meet nutritional needs.

5.1 Calculation of Nutritional Needs

At the most, 7–10 days of inadequate oral intake is an indication for considering nutritional support (Arends et al. 2006) (Fig. 9).

To be able to start nutritional support early, it is useful to have some simplified rules to begin with as are outlined here in general terms. To start with, the energy need for most patients is about 25–30 kcal/kg per day, corrected if needed as shown in Fig. 10, especially during recovery and rehabilitation.

Energy and fluid needs should be assessed individually, taking into consideration the actual diagnosis and situation, in that metabolic needs may increase dramatically depending on the medical situation as illustrated in Fig. 11.

The need for fluid should be estimated to around 30 mL/kg per day. The minimal need for protein is 0.8 g/kg per day although it may be 1.0–1.5 g/kg per day for sick patients. Vitamins and trace elements are given if required. If the patient is severely undernourished, a refeeding syndrome has to be avoided (i.e., when more nutrients are given than the tissue can metabolize, a condition that is more common when the supply is provided intravenously).

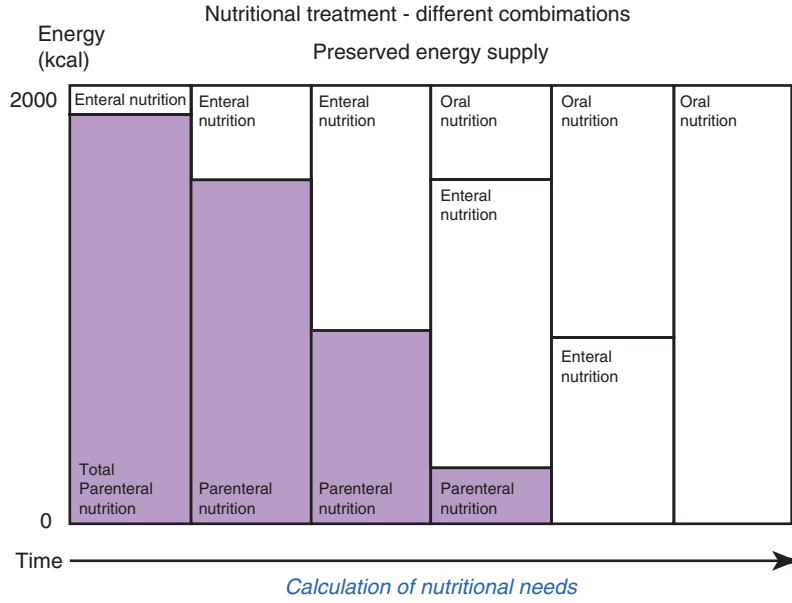

Fig. 9 Oral, enteral, and parenteral nutrition should complement each other to maintain adequate energy supply

Calculation of nutritional needs

Average of energy demands per kg/daily

Basic metabolism (BMB)	= 90 kJ = 22 kcal
Confinement in bed: BMB + 30%	= 120 kJ = 29 kcal
Walking: BMB + 50%	= 140 kJ = 33 kcal
Convalescence: BMB + 80%	= 170 kJ = 40 kcal

Corrections

Thin patient	+ 10%
Obese patient	- 10%
Age between 18 - 30 years	+ 10%
Age 70+ years	- 10%
For each degree of temperature rise	+ 10%

Fig. 10 Estimation of energy demands

Procentual energy increase in different clinical conditions

Increase (%)	Conditions
→ 100	Burn injury
40	Deep infections, sepsis
20	Trauma, multiple fractures
10	Elective surgery
10	Resting condition
0	Basic metabolism

Fig. 11 Increased energy needs in different clinical states

5.2 Enteral Solutions

Essentially two different kinds of enteral solutions are available. Most prevalent are so-called polymeric solutions, composed of whole protein, triglycerides, and glucose polymers along with electrolytes, trace elements, and vitamins. These solutions are available either in standard mode or as solutions with high energy and protein content. As a rule, the standard diet contains 6 g of nitrogen per liter and provides 1 kcal/mL, whereas the concentrated solution comprises 8–10 g of nitrogen per liter and an energy content of 1.5 kcal/mL. More than 90% of all patients needing enteral nutrition can satisfactorily be given these solutions. The second type of enteral solution is referred to as "elementary diet," meaning a split product where the components consist of amino acids, monosaccharides, essential fatty acids, minerals, and vitamins. The advantage of this solution is that it is more easily absorbed than the traditional enteral solution.

The characteristics of some commonly used enteral solutions are listed in Fig. 12.

More than 100 "solutions" including homogenates, emulsions, suspensions, and powders mixed with water for enteral feeding are commercially available. Furthermore, ordinary foods can be modified for use as enteral feedings for infusion into the stomach. Some of these solutions are designed for general nutrition, whereas others are formulated for specific metabolic or clinical conditions and the contents thus differ greatly.

Solutions for enteral feeding can be classified as follows (Dudrick and Palesty 2011):

Type	Content	Application/disadvantages
Caloric content (kcal/ml)	1 1,5 2	 Risk for dehydration
Protein content (energy%)	<20% standard >20% high	 Trauma/septichemia
Osmolality (mOsm/kg)	isotonic < 350 slightly hypertonic 350-550 strongly hypertonic >550	 Diarrhoea, espec at intrajejunal ad min
Fat content (energy%)	Standard >20% Low 5-20% Fat free <5%	Fat free solutions should be used for insufficiency of the pancreas, hyperlipidemia
Type of fat	LCT LCT/MCT ω-3/ω-6	 At malabsorption and trauma With anti-inflam activity
Fiber content	With fiber "Low residue"	Prevents constipation Ameliorate colonic mucosa
Electrolyte content Mineral content	Sodium 400-900 mg/1000 kcal Potassium 16-40 Eq/1000 kcal	NB! Sodium intake at renal failure and malabsorption
Pharmaconutrients	Glutamine, anti-oxidants, arginine, omega-3-fatty acids	Immune enhancing, critically ill
Elementar diets	oligopeptides a/o amino acids	For malabsorption

Fig. 12 Characteristics of enteral solutions

1. Natural foods—modified for providing complete nutrition by various routes.
2. Polymeric solutions—macronutrients in the form of isolates of intact protein, triglycerides, and carbohydrate polymers designed to provide complete nutrition by various routes.
3. Monomeric solutions—mixtures of proteins as peptides and/or amino acids; fat as long-chain triglycerides or a combination of long-chain triglycerides and medium-chain triglycerides; and carbohydrates as partially hydrolyzed starch maltodextrins and glucose oligosaccharides; for patients with disturbances of absorption or digestion.
4. Special metabolic solutions—for patients with unique metabolic requirements, e.g., failure of liver/lungs/kidneys/heart; including immune-modulating solutions (containing, e.g., ω-3 polyunsaturated fat, RNA, arginine, glutamine, taurine, carnitine, *N*-acetylcysteine, antioxidants, vitamins, and trace elements).
5. Modular solutions—nutritional components that may be given individually or mixed together to meet special needs of a patient (e.g., increased number of calories/amount of nitrogen, various minerals).
6. Hydration solutions—provide water, minerals, and small quantities of carbohydrates and/or amino acids as supplementation or as minimal humane support primarily for dehydrated and/or cachectic patients.
7. Medical foods—designed for special dietary purposes or as foods for which health claims have been made and which must be used under medical supervision.
8. Nutritional supplements—intended to supplement/fortify the diet with one or more nutrients otherwise consumed in less than recommended amounts, e.g., vitamins, minerals, amino acids, proteins, enzymes, and metabolites.

Use of the 1–1.5 kcal/mL polymeric high-protein enteral formula is appropriate in most cases.

Elemental or semielemental formulae are rarely needed. Fiber-containing formulations can be used in the rehabilitation setting and in patients requiring long-term enteral feeding. Nutritional support includes food fortification, ONS, tube feeding, and parenteral nutrition and aims for increased intake of macronutrients and/or micronutrients.

Positive biological actions of both fibers and their fermentation products (e.g., SCFAs) and possibility of incorporating different fibers into enteral formulae without increased risk of tube obstruction have changed the enteral feeding approach. Different types of fibers with different biological effects are known. Specific types of fiber are used according to the underlying disease. A formula enriched with a mixture of six fibers has been shown to increase fecal SCFA levels in patients undergoing long-term total enteral nutrition (Schneider et al. 2006).

A high fiber content helps the gut maintain gut physiological function, improve gastrointestinal tolerance (e.g., prevention of diarrhea and constipation), and ameliorate glycemic and lipid control. The recommended fiber intake is 15–30 g/day (Lochs et al. 2006). A high fiber content also stimulates gut microbes.

Since many patients who are in need of nutritional support may also have an imbalance of their gut flora, often secondary to antibiotic use, starvation, and medication, it has been suggested that the addition of "healthy" bacteria such as lactobacilli or bifidobacteria (probiotics) may be of some use. Interesting data are available for this use in intensive care patients and in patients prior to surgery. However, more studies are needed to elucidate the main clinical role of probiotics and prebiotics in improving gut barrier function in this group of patients.

5.3 Immunonutrition

Several different substances have been tested as adjuncts to postoperative nutritional treatment regarding their pharmacological effects in animal models and in vitro experiments. Arginine (improved wound healing), glutamine (improved resistance to infections and a preferred nutrient for enterocytes), ω-3 fatty acids (restraining several inflammatory mediators and cytokines), and nucleotides are among the most used constitutionally essential substrates recommended for patients undergoing major abdominal surgery procedures and have also been shown to improve postoperative outcomes for patients undergoing tumor surgery of the head and neck area (Felekis et al. 2010). These substrates have been shown to upregulate host immune response, control inflammatory response, and modulate nitrogen balance and protein synthesis after metabolic trauma. The substitutes should be given 5–7 days before and after the intervention.

Perioperative immunonutrition aims at modulating altered immunological and metabolic functions in the context of major surgery, which is the most studied setting in this field. Perioperative administration of immunonutrition-supplemented enteral formula significantly reduced postoperative infections, morbidity, costs, and length of hospital stay in patients undergoing surgery for cancer (Braga et al. 1999; Cerantola et al. 2010; Jayarajan and Daly 2011).

5.4 Technique

Improved clinical outcome and a reduction in complication and mortality rates are observed when enteral tube feeding (ETF) is provided, as shown in a systematic review and meta-analysis (Stratton et al. 2003). In this way, an increased total energy supply can be provided as well as a higher volume of nutrient intake, and a more complete nutrient supply is possible at the critical time of recovery.

In cases where oral nutritional support is either unable to increase total nutrient intake sufficiently (e.g., in a patient with poor appetite) or is contraindicated (e.g., cerebrovascular accident, patient with dysphagia and risk of aspiration, or with an upper gastrointestinal tract condition that prevents enteral supply), ETF is the most appropriate way to increase nutritional intake. ETF is clearly indicated in patients with neurological dysphagia and should be initiated as soon as possible (Volkert et al. 2006).

It is important to use the gastrointestinal tract to achieve a trophic effect and activity in the small intestine mucosa, something that probably could be achieved only by a small amount of enteral nutrition. Some studies (Elia et al. 1987) assert that as little as 300 mL/day is required to prevent changes of intestinal permeability caused by total starvation. This implies that two to three teaspoons of the contents to the gastrointestinal lumen per hour may be sufficient to maintain the activity and barrier function of the gut.

Most patients with enteral nutritional supply will receive this via a nasogastric tube. It is important to know where the tube tip is located to avoid the risk of aspiration. If the stomach is atonic or if there is an increased risk of regurgitation, the tip should be placed in the duodenal or jejunal part of the small intestine. Tubes carrying a load, a balloon, or a helical tip are more prone to pass through the pylorus and remain in the duodenum or jejunum. Administration of pharmaceuticals, e.g., metoclopramide, may facilitate passage.

A gastrostomy may be established without an open surgical procedure by using the percutaneous technique for a PEG. The technique to achieve this is outlined in Fig. 13. Compared with nasogastric tube feeding, PEG feeding is well tolerated subjectively by the patient as well as socially, by being less stigmatizing, gives less esophageal reflux and aspiration pneumonia problems, and is superior regarding nutritional efficacy (Löser et al. 2005).

A gastroscope is introduced into the stomach, which is then insufflated. The source of light is identified from the outside and a cannula is introduced through the stomach wall into the insufflated stomach, through which a thread is conducted (Fig. 13a). The thread is captured by the instrument, which then is removed (Fig. 13b). Thereafter, a polyurethane or silicon rubber catheter, with a "disk" at the end, is inserted with the help of the thread (Fig. 13c) and is taken out through the abdominal wall (Fig. 13d). For long-term or permanent use, the catheter may be replaced after approximately 4 weeks when a stable stoma is formed by a so-called gastric button/gastroport (Fig. 13e). This

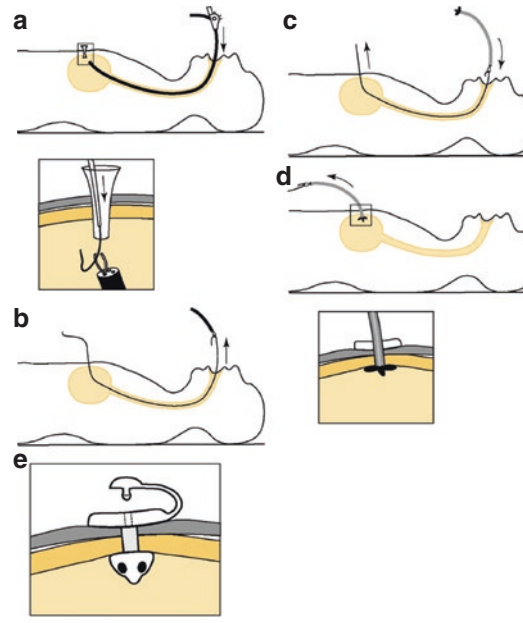

Fig. 13 Principles for establishing a percutaneous endoscopic gastrostomy

procedure has considerably facilitated the establishment of a gastrostomy in a less invasive way.

PEG feeding is easy to establish and to use, with its low risk of complications making it routine practice worldwide and the method of choice for medium-term and long-term enteral feeding, for maintenance and improvement of nutritional status, and for maintenance and improvement of quality of life. Feeding via a PEG is preferred if it is expected that the patient's nutritional intake is likely to be inadequate and supplementary enteral nutrition will be necessary for a period exceeding 2–3 weeks (Löser et al. 2005).

It is important to try supplementary oral nutrition by special drinks and individual nutritional and swallowing advice first; but if this does not stabilize or improve the patient's situation, additional enteral nutrition via a PEG should be considered early in ongoing disease in order to stop the deterioration of the nutritional status and consecutively to stabilize and even improve the patient's quality of life (Löser et al. 2005).

A meta-analysis (Lipp and Lusardi 2009) has shown that prophylactic antibiotics should be routinely administered when establishing a PEG

to reduce the incidence of postoperative infections. One single dose given orally is preferable.

The primary aim of ETF is:

- To avoid further loss of body weight
- To correct significant nutritional deficiencies
- To rehydrate the patient
- To stop the related deterioration of the quality of life of the patient owing to inadequate oral nutritional intake

There are many indications for using a PEG tube. In an oncological setting, a PEG tube may be used either in a palliative situation in patients with inoperable stenosing tumors in the ENT area or in the upper gastrointestinal tract or prior to treatment such as surgery, chemotherapy, or radiotherapy as a temporary measure to be removed after completion of treatment when the patient has recaptured an adequate and lasting oral nutritional intake.

A PEG tube my be used in patients with neurological conditions such as dysphagia after cerebrovascular stroke or craniocerebral trauma, and in patients with, e.g., cerebral tumors, bulbar paralysis, Parkinson's disease, amyotrophic lateral sclerosis, or cerebral palsy. In fact, dysphagic conditions in neurological disorders are the most common and established indications for a PEG. The assessment of safe swallow and adequacy of nutritional supply is crucial in determining which patients with neurological dysphagia should be referred for a PEG. As in stroke patients with dysphagia and inadequate oral food intake, early feeding via a PEG is helpful and highly effective, and in contrast to nasogastric tube feeding allows in parallel adequate training to re-enable swallowing. Most the patients with amyotrophic lateral sclerosis will receive a PEG, and the decision for this should be made early in the course of the disease.

In elderly demented patients, all published data support an individualized but critical and restrictive approach to PEG feeding.

A PEG tube may be used in a variety of other clinical conditions, such as wasting in AIDS, short bowel syndrome, reconstructive facial surgery, prolonged coma, polytrauma, Crohn's disease, cystic fibrosis, chronic renal failure, and congenital abnormalities, e.g., tracheoesophageal fistula, as well as for palliative drainage of gastric juices and secretions in the small intestine in the presence of a chronic gastrointestinal stenosis or ileus.

In a nonselected patient population, less than 40% of patients with a PEG tube have a malignant underlying disorder. The main therapeutic indications are benign neurological disorders (approximately 50% of cases) and ENT disorders, which are usually malignant (approximately 30% of cases).

PEG tubes can be used liberally. Appropriate supplementary enteral nutrition via a PEG system is more effective than oral nutrition alone in those cases in which the patients undergo several weeks of chemotherapy/radiotherapy. PEG should be considered early in order to ensure adequate nutritional support and to prevent the well-known drawbacks of prolonged nasogastric tube feeding. PEG feeding can prevent ongoing weight loss and maintain nutritional status, but full reversal of weight loss is rare even in benign diseases.

Since 1980 when PEG was first introduced, a variety of systems for ETF have been developed especially by endoscopic insertions, making enteral feeding today an efficient and highly effective means of ensuring nutrition when the patient is not able to achieve a sufficient intake orally. The low complication rates for this easy-to-use technique and the high degree of acceptance by patients lead to a pronounced amelioration of nutritional status, general well-being, and quality of life. For ETF purposes, it is recommended to use PEG early in the course of disease.

5.5 Complications

The complication rate is low, and only 1–4% of cases result in serious complications requiring treatment (Löser et al. 2005).

Next to local wound infection, aspiration of gastric content is the most common complication of ETF. This risk may be reduced by placing the tip of the tube quite distant in the small intestine, i.e., in the duodenal or jejunal part. It is also favorable to raise the head and the upper part of the body by approximately 30° with respect to the bed.

Blockage of the tube is not unusual, and it is recommended to flush the tube every 24 h. Diarrhea occurs in one-third of patients, and is caused by several factors, one of which could be the simultaneous administration of antibiotics. Administration of prebiotics and/or probiotics through the tube may improve this condition. In some cases when the patient was earlier receiving long-term total parenteral nutrition, mucosal atrophy and hypoalbuminemia may be noted. Nausea and vomiting is found in 10–20% of patients but may be treated successfully with antiemetic or prokinetic drugs, or with a reduced rate of nutrient supply/infusion. Interactions with simultaneously provided pharmacological treatment may sometimes be a problem, especially when theophylline, warfarin, or digoxin is administered.

Infections may sometimes occur in connection with the PEG wound or be related to contamination of the device. It is recommended that the device be changed every 24 h and that an opened bag of enteral solution not be kept at room temperature for more than 4 h.

5.6 Contraindications

A nonfunctioning gastrointestinal tract is a contraindication to enteral nutrition. In the case of ileus, mechanical obstruction of the gastrointestinal tract, fistulas in the upper part of the gut, or a reduced splanchnic blood flow, nutrition should be provided parenterally.

Contraindications to the establishment of a PEG comprise serious coagulation disorders, interposed organs, marked peritoneal carcinomatosis, severe ascites, peritonitis, anorexia nervosa, severe psychosis, advanced dementia, and a clearly limited life expectancy.

6 Evaluation of the Effect of Nutritional Treatment

ONS and ETF have been shown to improve clinically relevant outcomes such as body weight, mortality, complication rates, length of hospital stay, quality of life, and a number of functional measures, e.g., muscle strength and immune function.

A patient with good nutritional status is better prepared with regard to the outcome of surgery, including rate and degree of complications, morbidity, and survival.

Nourishment per os or via a nasogastric tube leads to:

- Significantly fewer infectious complications and shorter length of hospital stay
- A lower rate of anastomotic leakages
- A lower cost per day
- A more physiologic manner for the body to gather nutriments
- A positive influence concerning immune function and gut barrier function

An adequate nutritional supply is achieved when common parameters are followed over time, such as stabilized/gained body weight, reduction of edemas, decreased inflammation with a declining C-reactive protein level, improved muscle function measured by grip strength or gait ability, a higher degree of mobilization/physical activities, and reduced problems related to constipation.

7 Ethical Aspects

Enteral feeding has a 500-year history in Europe, but findings concerning efforts to provide nutrition enterally have been dated to as early as 3500–1500 BC in Egypt (Dudrick and Palesty 2011). The legislative attitude in Europe differs to some extent between countries and is mainly influenced by ancient Greco-Roman views, religious opinions, and more modern society apprehensions. The Hippocratic tradition is based on beneficence (do good) and nonmaleficence (do no harm) (Körner et al. 2006).

The "four principles" approach to medical ethics, from a "nutritional view," is as follows:

1. Autonomy—the principle of self-determination. Wishes of the patient must be respected.
2. Nonmaleficence—the deliberate avoidance of harm. The expected benefit of nutritional support must outweigh the risks.

3. Beneficence—the providing of "good." Nutritional support therapy in most circumstances will provide benefit.
4. Justice—protection of a patient who is incompetent in understanding or making a decision. Fair and equitable resources for all. Provide cost-effective nutritional support.

Artificial nutrition and hydration constitute medical treatments. Decisions to withhold or withdraw nutritional support are subject to the same ethical considerations as any other therapeutic intervention.

Judgments concerning quality of life are of increasing importance in assessing the efficacy of the treatment. Clinicians must act in the best interests of the patient. It may sometimes be a delicate balance between the patient's legal rights and professional judgment, and medical decisions should be made after consultation with those close to the patient.

Conclusions

A malnourished patient is a high-risk patient and has a higher rate of complications, a prolonged length of hospital stay, and an increased mortality. A good nutritional condition is a prerequisite for avoiding complications and to regain health. Food is part of the medical treatment. An accurate diet is a prerequisite if every other medical treatment is to be effective or enhanced. The sick individual's nutrition should be taken into consideration in the same way as all other medical treatments and should thus be subject to the same requests for investigation, diagnosis, planning of treatment, and investigation/documentation.

The principle of nutritional treatment in hospitals should always be that food or nourishment ought to be provided the natural way if possible. If 7–10 days of care has elapsed without sufficient oral nutritional intake, nutritional support should be considered.

Even if the enteral supply is as low as a volume of 10–15 mL/h, it is of importance for maintaining the integrity and barrier function of the gut. "To nourish the gut enterally—and the rest of the body intravenously …!" If oral and/or enteral nutrition is not satisfactory to complete the patient's nutritional demands, enteral and parenteral nutrition should be used in combination to cover the nutritional needs and to minimize the adverse effects and complications of both regimens when not used in combination. If there is doubt as to whether tube feeding/enteral nutrition will be beneficial or when the prognosis of the underlying condition is uncertain, a trial treatment should be given for a defined period and the goals and criteria for continuing or discontinuing the feeding should be defined in advance.

For patients with neurological diseases, nutritional support should be given at an early stage to prevent malnutrition developing and thereby impair recovery in those whose neurological condition improves.

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Oral Care in the Dysphagic Patient

Jose Nart and Carlos Parra

Contents

Abstract

Biofilms are defined as matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces (Costerton et al. 1995). The mouth is moist and warm, and it can support the growth of several different bacteria, viruses, mycoplasmas, fungi, protozoa, and Archaea (Marsh and Martin 2009). These microorganisms will colonize dental and mucosal surfaces to form three-dimensional, multispecies, well-organized communities (biofilms).

1 The Oral Biofilm

Biofilms are defined as matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces (Costerton et al. 1995). The mouth is moist and warm, and it can support the growth of several different bacteria, viruses, mycoplasmas, fungi, protozoa, and Archaea (Marsh and Martin 2009). These microorganisms will colonize dental and mucosal surfaces to form three-dimensional, multispecies, well-organized communities (biofilms).

It is estimated that more than 700 species and several thousands of phylotypes colonize the oral cavity (Aas et al. 2005; Keijser et al. 2008).

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Nevertheless, under normal circumstances, most oral bacteria are harmless commensals.

Organisms attached in a biofilm behave in a different way than planktonic (single cells that float or swim in a liquid medium) organisms. Gene expression can alter markedly when cells form a biofilm, resulting in many organisms having a radically different phenotype following attachment to a surface (Marsh 2005). Within biofilms, cell-cell communication (*quorum sensing*) is used by some bacteria to coordinate gene expression. These alterations in the genotype allow cells in a biofilm to be up to 1,000 times more resistant to antimicrobials as compared with planktonic cells (Ceri et al. 1999), and organisms that originally were nonpathogenic might become pathogenic.

Dental plaque has been defined as the diverse community of microorganisms found on the tooth surface as a biofilm, embedded in an extracellular matrix of polymers of host and microbial origin (Marsh 2004). It has been shown that there are specific associations among bacteria in dental biofilms. After examining human dental plaque samples, Socransky et al. (1998) used cluster analysis techniques to demonstrate the presence of specific microbial groups within dental plaque (Fig. 1). Moreover, dental plaque can be classified as supragingival or subgingival, based on its location regarding the gingiva (Fig. 2).

- *Supragingival plaque* is found at or above the gingival margin. Usually composed of aerobic or facultative anaerobic gram-positive cocci and short rods as filaments. *Actinomyces* species are the predominant type of bacteria either in health or in disease within the supragingival plaque (Socransky and Haffajee 2002).
- *Subgingival plaque* is found below the gingival margin, between the tooth surface and the periodontal pocket epithelium. Generally, subgingival biofilms are complex, with higher proportion of gram-negative anaerobic bacteria due to the lack of oxygen availability, and so more pathogenic. *Actinomyces* still dominate, but higher proportions of more pathogenic bacteria such as *Tannerella forsythia*, *Porphyromonas gingivalis*, or *Treponema denticola* can be found (Socransky and Haffajee 2002).

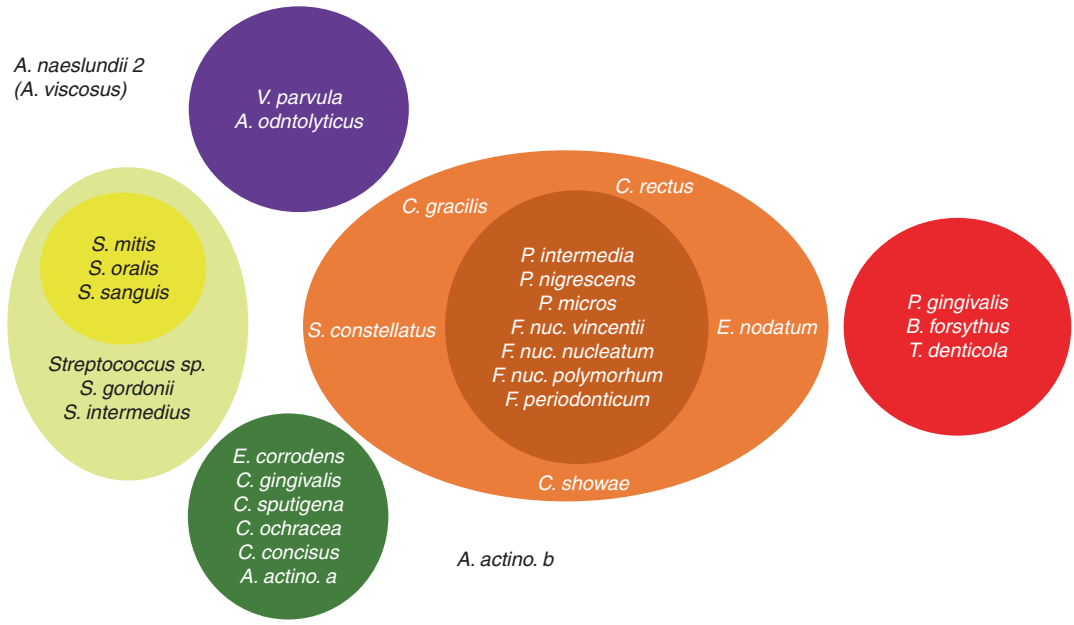

Fig. 1 Diagrammatic representation of the relationships of species within microbial complexes and between the microbial complexes. Bacterial species in the orange and specially the red complexes are the ones related with periodontitis (Adapted from Socransky et al. 1998)

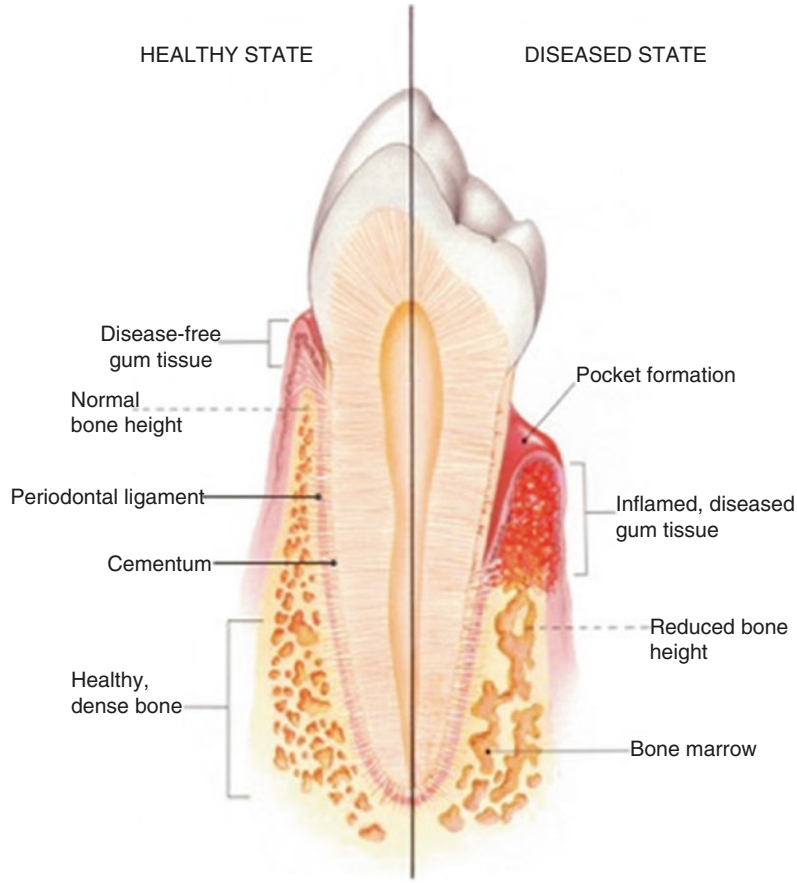

Fig. 2 Diagram describing the different tooth structures on a health and on periodontal disease

Dental calculus consists of mineralized dental plaque which forms both above (supragingival) and below (subgingival) the gumline (White 1997). Calculus does not produce per se gingival inflammation, but it provides a substrate for the accumulation of bacterial plaque and its retention in close proximity to the gingival tissues.

2 Periodontal Disease: Gingivitis and Periodontitis

Periodontal disease is any inherited or acquired disorder of the tissues surrounding and supporting the teeth (periodontium). However, the term periodontal disease usually refers to the common inflammatory disorders of gingivitis and periodontitis that are caused by pathogenic microflora in the biofilm or dental plaque that forms adjacent to the teeth (Pihlstrom et al. 2005).

Gingivitis is the presence of gingival inflammation without loss of connective tissue attachment (Armitage 1995). On the other hand, periodontitis is also an inflammation of the periodontal tissues, but in this case resulting in clinical attachment loss, alveolar bone loss, and periodontal pocketing formation (The American Academy of Periodontology 2001) (Fig. 2). While all periodontitises are preceded by gingivitis, not all gingivitis will progress to periodontitis (Sheiham 1997).

It is estimated that 47.2%, or 64.7 million American adults, have mild, moderate, or severe periodontitis. In adults 65 and older, prevalence rates increase to 70.1% (Eke et al. 2012).

The main diagnostic tools for both periodontitis and gingivitis are clinical and radiographic. Several factors must be assessed to arrive at an accurate periodontal diagnosis (AAP Position Paper 2003): (1) presence or absence of clinical

signs of inflammation (e.g., bleeding upon probing), (2) probing depths (by introducing the periodontal probe in the space between the gingiva and the tooth), (3) extent and pattern of loss of clinical attachment and bone (with the help of radiographs), (4) patient's medical and dental histories, and (5) presence or absence of miscellaneous signs and symptoms, including pain, ulceration, and amount of observable plaque and calculus.

While bacteria are undoubtedly the principal etiologic factor of the initial inflammatory lesion leading to gingivitis, it is mainly the host response, not the type of bacteria, which dictates whether disease progresses (Page and Kornman 1997). In other words, periodontal pathogens will trigger a host immune response that will produce gingival inflammation (gingivitis). If the immune response perpetuates and progresses, the inflammation will further advance and destroy the structural components of the periodontium leading to periodontitis (Fig. 3).

Current evidence supports the major role of host responses, modulated through genetics, immunological and inflammatory responses, stress, smoking, diet, social determinants, and general health as being the major determinants of the outcomes of the classic chronic inflammatory conditions we know as periodontitis (Bartold and Van Dyke 2013).

3 Periodontitis and Systemic Disease

Inflammatory periodontal disease shows a bidirectional association with several systemic conditions. Periodontal disease may worsen already existing systemic conditions, and at the same time, a patient with a systemic condition may have more severe periodontal disease. Results from research suggest that people with periodontal disease have more risk of myocardial infarction, adverse pregnancy outcomes, diabetes

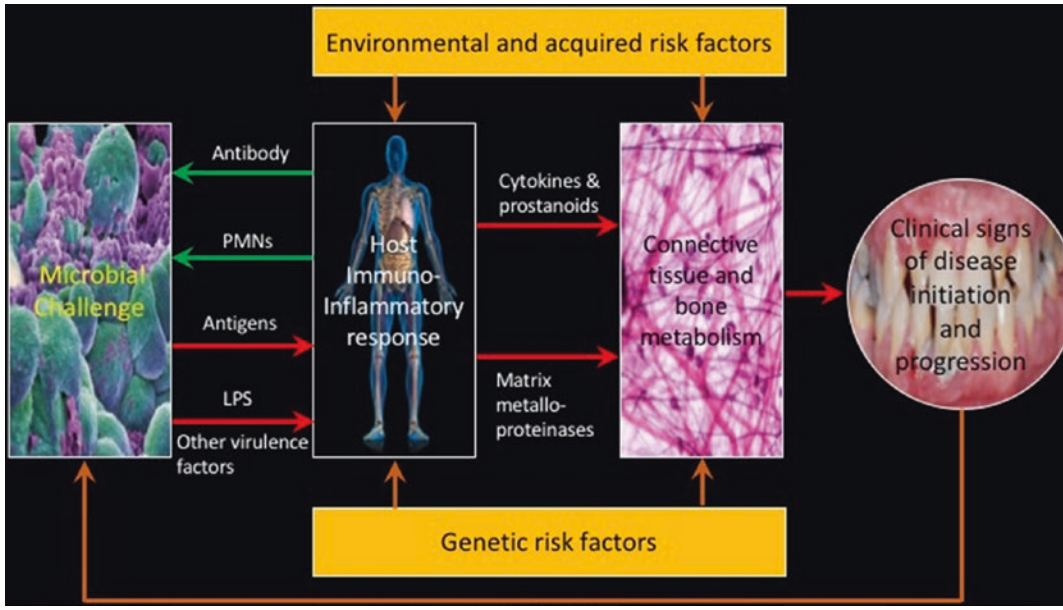

Fig. 3 Diagram of pathogenesis of human periodontitis. The microbial challenge will trigger an immune response that will be at the simultaneously protective and destructive. The host response results in production of cytokines, eicosanoids, other inflammatory mediators such as kinins, complement activation products, and matrix metalloproteinases, which will perpetuate the response and mediate connective tissue and bone destruction. The clinical picture observed is a result of the sum of these events. Genetic and other risk factors will influence the outcomes of the disease. *LPS* lipopolysaccharide, *PMNS* polymorphonuclear lymphocytes (Diagram adapted from Page and Kornman 1997)

mellitus, several lung diseases as pneumonia and chronic obstructive lung disease, and Alzheimer's disease (Scannapieco et al. 2010).

The three major mechanisms by which periodontal infection is thought to affect the rest of the body are (Borgnakke 2015) (Fig. 4):

- *Bacteremia*: Bacteria from deep periodontal pockets can penetrate through ulcerations in the epithelium to the blood stream. These bacteria may travel and land anywhere in the body, for example, atherosclerotic plaques.
- *Inflammation*: Inflammation, manifested by the general acute-phase inflammatory biomarker C-reactive protein (CRP), might be a risk factor for cardiovascular events. Furthermore, the inflammatory biomarkers regulated by the host response will spread through the body, which may explain the links between periodontitis and most of the systemic diseases.
- *Immune response*: The immune system creates antibodies targeting the bacteria and their toxins. Cross-reactive antibodies may be formed and could contribute to systemic disease.

There is evidence that periodontal treatment leads to a decrease blood concentration of periodontal bacteria and inflammatory markers (Borgnakke 2015). This could indicate that periodontal treatment may improve the incidence and severity of systemic diseases. The most evident example available in the literature is related to diabetic patients with periodontitis, where HbA1c levels have been shown to be reduced after periodontal treatment (Chen et al. 2012, Botero et al. 2013; Simpson et al. 2015).

Associations between systemic disease and periodontal disease exist. Nevertheless, no conclusions can be drawn on whether periodontal disease contributes in the initiation of any of the aforementioned systemic diseases; neither there is sufficient evidence that demonstrates that treatment of periodontitis may prevent the incidence or severity of those systemic diseases.

4 Aspiration Pneumonia

Aspiration pneumonia is defined as the inhalation of either oropharyngeal or gastric contents into the lower airways, being the act of taking foreign material into the lungs. The swelling or

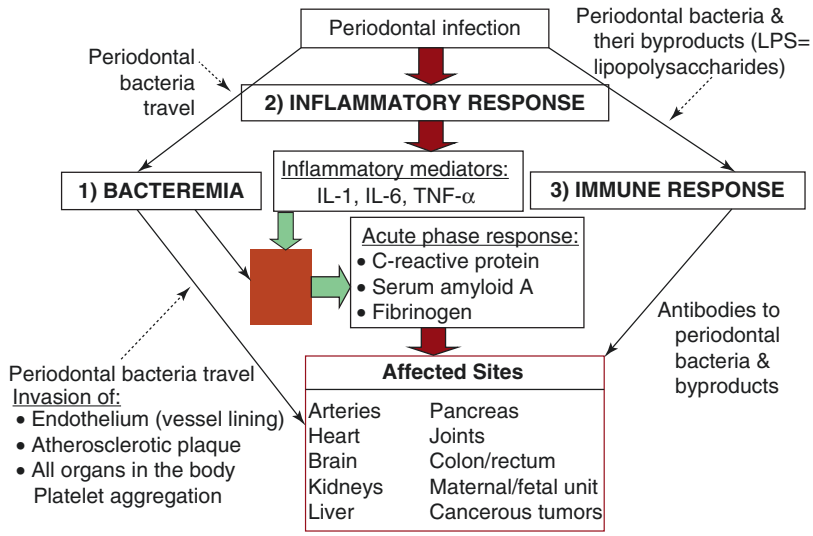

Fig. 4 Conceptual model illustrating the ways in which periodontal infection affects the human body. (1) Bacteremia (direct effect): periodontal bacteria travel in the blood through the entire body. (2) Inflammatory responses (indirect effect): pro-inflammatory mediators (cytokines) cause the liver to produce acute-phase reactants (CRP and others). And (3) immune response (indirect effect): production of antibodies to the bacterial antigens, including their lipopolysaccharides (*LPS*) and various cross-reactive agents (Diagram from Borgnakke 2015)

the infection of the lungs characterizes this condition. Nowadays, aspiration pneumonia is an important cause of morbidity and mortality in people aging 60 or more. Bacterial pneumonia is the most common and treatable form of disease.

Bacterial pneumonia is caused by the colonization of the oropharyngeal region by potential respiratory pathogens. These pathogens can be aspirated into the lower airways and cause pneumonia if the defense mechanisms to eliminate bacteria fail. Aspiration of small quantities of oral secretions occurs in healthy individuals, especially during sleep. Multiple defense mechanisms operate within the respiratory tract to eliminate aspirated bacteria from the lower airway. These mechanisms can be affected by a variety of conditions and circumstances, such as oropharyngeal dysphagia, altering their effectiveness.

Bacteria from the oral biofilms may be aspirated into the respiratory tract to influence the initiation and progression of systemic infectious conditions such as pneumonia. Periodontitis is a risk factor for aspiration pneumonia as the bacterial biofilm resulting from poor oral hygiene and periodontal diseases is increased (Soskolne and Klinger 2003). Improving the oral hygiene can reduce the occurrence of nosocomial pneumonia. Oral colonization by potential respiratory pathogens, possibly adopted by bacteria specific to the oral cavity or to periodontal diseases, contributes to pulmonary infections (Scannapieco and Mylotte 1996). The role of the oral hygiene in high-risk subjects, such as patients in the hospital intensive care and the elderly, is fundamental to avoid these infections. Poor oral health, dependence on conducting daily oral hygiene, and oral colonization of periodontal and respiratory pathogens are related to pneumonia. There is not a direct causal relationship between periodontitis and pneumonia, but the oral colonization by potential respiratory pathogens contributes to pulmonary infections (Cagnami et al. 2016).

5 Periodontal Treatment

Periodontal diseases refer to the infections of the structures around the teeth including the gums, the cementum that covers the root, the periodontal ligament, and the alveolar bone. In early stages of the disease, in gingivitis, the gums are affected, and when it becomes more severe with periodontitis, other structures are affected. Different types of bacteria cause inflammation of the tissues. Our immune system induces the destruction of the connective tissue and the bone provoking dental mobility and the loss of the teeth (Fig. 2).

The main cause of the inflammation is bacteria. Thus, it is very important to avoid plaque formation by means of a good oral hygiene. If plaque is not removed properly, over time it becomes calcified and turns into calculus. This calculus is harder to remove than plaque, and its surface is rougher than the surface of the tooth favoring the adhesion of dental plaque.

As the cause of the disease is the infection caused by bacteria, the main goal of the periodontal treatment is to control the infection by eliminating or decreasing the amount of bacteria in the oral cavity. There are many different treatments depending on the extent of the periodontal disease. All these treatments require a commitment of the patient to maintain high standards of oral hygiene. It is also important to reduce risk factors such as smoking or uncontrolled diabetes to improve treatment outcomes.

The first part of the treatment is about eliminating and controlling the causing agent of the disease to control the infection. The motivation and oral hygiene instructions to the patient are extremely important at this stage. Without the patient's collaboration, the treatment will have no effect. The dentist should explain the patient oral hygiene techniques as well as other auxiliary procedures such as interdental brushing to improve bacterial plaque control.

In most of the cases, periodontitis is treatable and controlled without having to do any surgery. The success of the treatment is based on the control and the elimination of the bacterial plaque through most importantly mechanical and a few chemical procedures. Before starting the periodontal instrumentation, the patient must have controlled the inflammation of the gums.

The dentist removes the plaque and calculus through a deep cleaning method called scaling and root planing. This treatment can be executed

under local anesthesia. The instrumentation is done above and below the gumline. When all the calculus and bacterial plaque have been removed, the dental surface is smoothed to get rid of rough spots on the tooth root where bacteria gather. The gums will then attach themselves again to the dental and root surface. Periodontal instrumentation can be done manually, by ultrasonic instruments or the combination of both.

Scaling and root planing (SRP) allows the dentist to remove the bacteria and calculus of the periodontal pockets. The use of chemical products could also be helpful to reduce inflammation. Some periodontitis may need the use of systemic antibiotics; the most prescribed are metronidazole or the combination of metronidazole and amoxicillin. If by SRP the disease cannot be controlled, these patients might need a surgical intervention after the first hygienic phase of the treatment. There are different types of surgery to treat periodontal disease.

Flap surgery is used when the inflammation and bacterial reservoirs remain after SRP. It is used to remove calculus deposits and/or to reduce the periodontal pocket (reservoirs) and make it easier for the patient to keep the area clean. In this procedure, the gums are lifted back and the calculus is removed. Then, the gums are sutured back in place so that they can adhere around the cleaned root again.

Bone substitutes and/or tissue grafts are used to regenerate lost tissues by periodontitis (American Academy of Periodontology. Periodontal Treatments and Procedures).

6 Periodontal Maintenance

Once the surgical procedure, if needed, has been completed, a restorative treatment can be done. There are different options such as implant therapy where a tooth is missing, orthodontics, prosthesis, dental aesthetics, or others.

The last phase of the periodontal treatment is as important as the initial one. Periodontal maintenance requires the patient's cooperation long life with his/her home care but also attending regularly the recall appointment every 3, 4, or 6 months to prevent bacteria from accumulating again. This phase is important to prevent the chances of the progression of the periodontal disease. Periodontal maintenance increases exponentially the probability of long-term success of the treatment.

Supragingival and subgingival cleaning, root planning, as well as radiographic examination are performed during the maintenance visit. Bacteria formation on the teeth and gums occurs almost immediately after the cleaning. Frequent removal of the bacteria from under the gumline can control the inflammation and can often prevent the further breakdown of the bone and gum supporting the teeth. Periodontal maintenance is essential to control and preserve the periodontal health status obtained by a correct treatment. Moreover, the dentist will be able to perform an early detection of other oral pathologies.

None of the different phases of the periodontal treatment will be successful without the patient's collaboration. Thus, an essential point is to motivate the patient and get his/her commitment. Without the collaboration of the patient and fulfilment with the periodic controls, all the treatment can be in vain, and the periodontal disease can continue progressing (American Academy of Periodontology. Periodontal Treatments and Procedures).

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Complications of Oropharyngeal Dysphagia: Malnutrition and Aspiration Pneumonia

Silvia Carrión, Alicia Costa, Omar Ortega, Eric Verin, Pere Clavé, and Alessandro Laviano

Contents

1 Definition and Prevalence of Dysphagia and Malnutrition

1.1 Dysphagia

Dysphagia is a symptom that refers to difficulty or discomfort during the progression of the alimentary bolus from the mouth to the stomach (Cook and Kahrilas 1999). From an anatomical standpoint, dysphagia may result from oropharyngeal or esophageal dysfunction and from a pathophysiological standpoint, from structure-related or functional causes. The term comes from the Greek and means difficulty (dys) when swallowing (phagia). It is currently possible to

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classify oropharyngeal dysphagia (OD) according to the International Classification of Diseases (ICD), developed by the World Health Organization (WHO), with the codes 787.2 (ICD-9) and R13.1 (ICD-10) (WHO n.d.). In the ICD-10 version it is subdivided into R13.11 dysphagia, oral phase; R13.12 dysphagia, oropharyngeal phase; R13.13 dysphagia, pharyngeal phase; R13.14 dysphagia, pharyngoesophageal phase; and R13.19 other dysphagia.

Any alteration of the swallowing process can be defined as dysphagia. However, ageing causes anatomical, physiological, functional, and neural changes, which in robust patients can cause some alteration of swallowing without compromising safety, and this is known as presbyphagia (Humbert and Robbins 2008; Ney et al. 2009).

Despite being underdiagnosed, the prevalence of OD in the older population is very high and varies according to the study method used (clinical or instrumental), the phenotype of the patient studied (robust elderly, pre-frail, and frail), and the place where the dysphagia was diagnosed (community, hospital, or nursing home). The prevalence of OD and its complications increases with age, for two main reasons, (1) the ageing process itself, which causes alterations in physiology and oropharyngeal motor response (OFMR), and (2) the high prevalence of neurological and neurodegenerative diseases that are directly related to the age of the patient (Rasley et al. 1993). Using instrumental diagnostic methods, OD is present in 57–84% of patients with Alzheimer's or dementia (Horner et al. 1994; Suh et al. 2009), 82% of patients with advanced Parkinson's disease (Kalf et al. 2012), and 64–78% in the acute phase of an ichthus and 40–81% in the chronic phase (Martino et al. 2005). The prevalence of OD measured with screening questionnaires in older persons living in the community ranged from 11.4 to 33.7% (Holland et al. 2011; Roy et al. 2007; Bloem et al. 1990; Kawashima et al. 2004; Yang et al. 2013) and was around 23% when clinical exploration methods were used (volume-viscosity swallow-test (V-VST)) (Serra-Prat et al. 2011). In nursing home residents, the prevalence was 40% using screening questionnaires (Nogueira and Reis 2013), and 38–51% with clinical diagnostic methods (Nogueira and Reis 2013; Lin et al. 2002).

Today, approximately 18.9% of European citizens are older than 65 years and in the last decade this group has increased by 15.24% while the rest of the population has decreased by 3%. An estimated 16.5 million US and more than 40 million European senior citizens required care for dysphagia in the year 2017 (Robbins et al. 2002). Impairment in swallowing efficacy may reduce oral feeding and lead to malnutrition unless nutritional status is monitored and specific strategies are introduced to enhance caloric intake. Up to 30% of neurological patients and up to 55% of frail older patients with dysphagia have or are at risk of malnutrition with a strong relation between severity of dysphagia and incidence of malnutrition (Clavé et al. 2006).

1.2 Malnutrition

There is no universally accepted definition of malnutrition as evidenced by the many attempts to find one. One of the most widely accepted considers malnutrition as that state secondary to a lack of absorption and/or nutrient intake resulting in an altered body composition with a decrease in fat-free mass and total body cell mass which leads to a decrease of physical and mental function (Sobotka 2012). It is also possible to consider malnutrition as a pathological condition resulting from a relative or an absolute absence of one or more essential nutrients. One of the major challenges for clinicians is to assess malnutrition in a sick patient and evaluate its specific effects on patient outcomes. Indeed, the clinical manifestations of the disease may confuse the detection of malnutrition and vice versa due to the interaction between them. It is therefore a challenge to show that malnutrition independently worsens the prognosis of a disease and that nutritional therapy can improve it.

In patients with OD, the decrease in lingual propulsion forces and the increase in residue contribute to a reduction in oral intake leading to MN (Rofes et al. 2010). Sarcopenia and frailty have

also been associated with decreased muscle mass of the cervical swallow muscles and tongue (Robbins et al. 2002; Robbins et al. 2005). Dysphagia associated with sarcopenia (sarcopenic dysphagia) is a new concept recently introduced by Japanese researchers and defined as the difficulty in swallowing caused by sarcopenia of the skeletal musculature including that of the swallowing musculature, the treatment of which requires both swallowing exercises and specific nutritional intake (Wakabayashi 2014a; Wakabayashi and Sakuma 2014; Kuroda and Kuroda 2012).

Dysphagia is very prevalent among older people and in neurological diseases and can further impair the nutritional status of these patients. A study on older patients with dysphagia and pneumonia found that prevalence of malnutrition was 36.8%, with 55.3% at risk of malnutrition, significantly higher than in older patients without dysphagia (Cabre et al. 2010). Similar results were found in another prospective study by the same authors, which showed that in 1662 older patients admitted to a hospital for varying reasons, the prevalence of dysphagia was 47.4 and 45.3% of these patients were malnourished, according to the Mini Nutritional Assessment ((MNA) < 17) ($p < 0.001$), (Carrión et al. 2014). These two studies refer to hospitalized patients. Few articles have been published evaluating the prevalence of dysphagia in independently living older persons and some of them use a variety of nonvalidated instruments based on self-reported symptoms of dysphagia. Only one study used the volume-viscosity swallow test in 254 persons aged ≥70 years who were randomly selected from a primary care center database. The results showed that dysphagia was present in 23% and was associated with the risk of malnutrition (OR = 2.46 (1.10–5.46) (Serra-Prat et al. 2011). A recent review also found a close relation between dysphagia and malnutrition following stroke in 5 of the 8 studies analyzed, with a prevalence of malnutrition ranging from 8.2 to 49% (Foley et al. 2009). The large difference in the prevalence of malnutrition is caused by the methods used for the assessment of malnutrition, the therapy implemented (Chai et al. 2008), and the timing of nutritional assessment during the course of rehabilitation of the patient (Finestone et al. 1995). Dysphagia, 47% on admission, was associated with malnutrition ($p = 0.032$) and significantly declined over time (Finestone et al. 1995) in patients with stroke.

Neurodegenerative diseases such as multiple sclerosis or Parkinson's disease may also be characterized by oropharyngeal dysphagia as a secondary complication and one which may influence their clinical course. In a Japanese study published in 1999, the authors investigated the relation between weight loss and dysphagia in Parkinson's disease. The patients with dysphagia accounted for 31% of the Parkinson's patients and for 7% of the control group ($p < 0.005$), although half of the Parkinson's patients with dysphagia were not aware of their swallowing impairment. Body mass index (BMI) in the dysphagic group (19.1 ± 3.6 kg/m^2) was significantly lower than in the non-dysphagic group (21.6 ± 3.0 kg/m^2) ($p < 0.005$). Patients in the dysphagic group showed significantly lower carbohydrate intake (186 ± 49 g) than those in the non-dysphagic group (215 ± 52 g) ($p < 0.05$). Finally, the biochemical indices of nutritional status were lower in the dysphagic group than in the non-dysphagic group (Nozaki et al. 1999).

2 Pathophysiology and Diagnosis

2.1 Pathophysiology of Dysphagia

Oropharyngeal dysphagia may result from a wide range of *structural alterations* that impair bolus progression. The most common structural abnormalities include esophageal and ear-neck-throat tumors, neck osteophytes, postsurgical esophageal stenosis, and Zenker's diverticulum (Clavé et al. 2004). Dysphagia may also be a side effect in patients with head and neck cancer undergoing radiotherapy (García-Peris et al. 2007). However, oropharyngeal dysphagia is more frequently a functional disorder, affecting the oropharyngeal swallow response and caused by ageing, stroke, or

systemic or neurological diseases. In biomechanical terms, the oropharyngeal swallow response consists of the temporal arrangement of oropharyngeal structures from a respiratory to a digestive pathway, the transfer of the bolus from the mouth to the esophagus, and the recuperation of the respiratory configuration (Kahrilas et al. 1996; Jean et al. 2001) (Fig. 1). Sensory input by physicochemical properties of the bolus is required during bolus preparation, triggering and modulating the swallow response. Taste, pressure, temperature, and nociceptive and general somatic stimuli from the oropharynx and larynx are transported through the V, VII, IX, and X cranial nerves to the central pattern generator (CPG), within the nucleus tractus solitarius (NTS) where they are integrated and organized with information originating from the cortex. Swallowing has a multiregional and asymmetrical cerebral representation in caudal sensorimotor and lateral premotor cortex, insula, temporopolar cortex, amygdala, and cerebellum (Schindler and Kelly 2002). This observation explains why 30–50% of unilateral hemispheric stroke patients will develop dysphagia (Hamdy et al. 1999). Once activated, the CPG triggers a swallow motor response involving motor neurons in the brainstem and axons traveling through the cervical spinal cord (C_1–C_2) and cranial nerves (V, VII, IX, to XII) (Schindler and Kelly 2002) (Fig. 2). Duration of the swallow response in healthy persons is in the range of 0.6–1 s (Jean et al. 2001). Healthy persons present a short reaction time in the submental muscles (Nagaya and Sumi 2002), short swallow response (GPJO-LVO < 740 ms), fast laryngeal vestibule closure (LVC < 160 ms), and fast upper esophageal sphincter opening (UESO < 220 ms) (Clavé et al. 2006). In contrast, the swallow response is impaired in older people, especially in patients with neurogenic dysphagia (Rofes et al. 2010). Older patients have prolonged reaction time in the submental muscles (Nagaya and Sumi 2002), and overall duration of OSR in these subjects is significantly longer than in

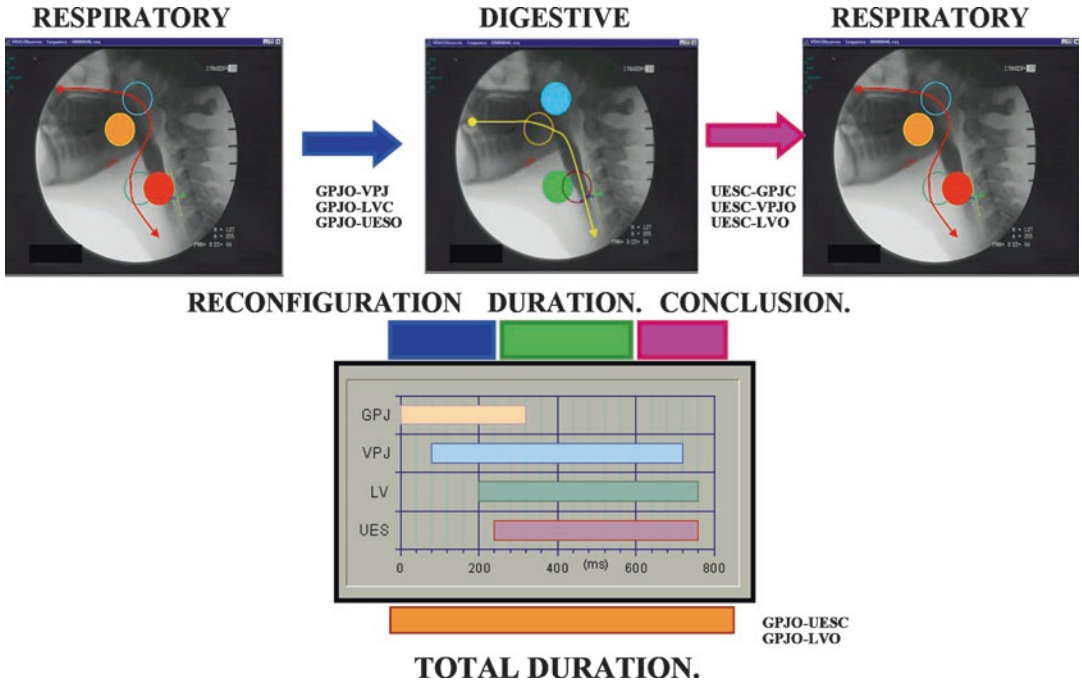

Fig. 1 Configuration of the oropharynx during swallow response**.** Each phase of the response (reconfiguration, duration, and conclusion) is defined by opening (O) or closing (C) events occurring at the glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and upper esophageal sphincter (UES)

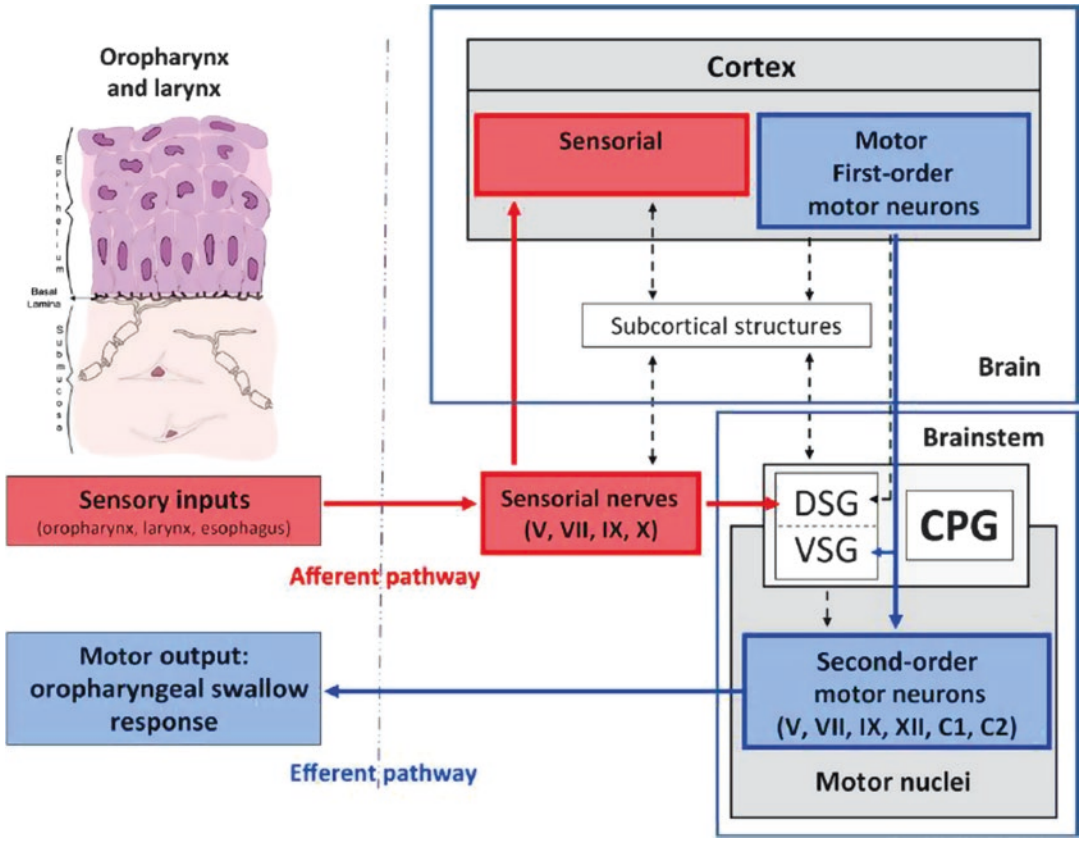

Fig. 2 The oropharyngeal motor response (OMR) is generated through the swallowing center, an interneuronal network located in the medial pattern generator (CPG), which receives inputs from both the cerebral cortex and the peripheral sensory inputs of the pharynx and the larynx. Dorsal swallowing group (DSG), ventral swallowing group (VSG). (Adapted from Cabib et al. 2016)

healthy volunteers due to delay in the early phase of oropharyngeal reconfiguration from a respiratory to a digestive pathway (Rofes et al. 2010). We found that prolonged intervals to LVC and UESO were the key abnormalities of the swallow response, doubling that of healthy persons and leading to unsafe deglutition and aspiration in neurological older patients (Rofes et al. 2010). This delayed swallow response in the elderly and in patients with neurogenic dysphagia can be attributed to impaired sensations (Teismann et al. 2007; Teismann et al. 2009), a decrease in the number of neurons in the brain, and a delay in the synaptic conduction of the afferent inputs to the central nervous system (SNC) caused by ageing (Nagaya and Sumi 2002), and by other risk factors for dysphagia like neurodegenerative diseases or stroke (Nagaya and Sumi 2002; Turley 2009; Clavé et al. 2005a). Other conditions such as delirium, confusion, and dementia, and the effects of sedative, neuroleptic, or antidepressant drugs, can also contribute to impaired swallow response in frail older patients (Wirth et al. 2016) (Fig. 3). Transfer of the bolus from the mouth through the pharynx mainly occurs by the squeezing action of the tongue (Nicosia and Robbins 2001). Older adults present lingual weakness, a finding that has been related to sarcopenia of the head and neck musculature and frailty (Rofes et al. 2010). Tongue propulsion is assessed by direct measurements with oral sensors (Robbins et al. 2005) or by videofluoroscopic studies which measure the

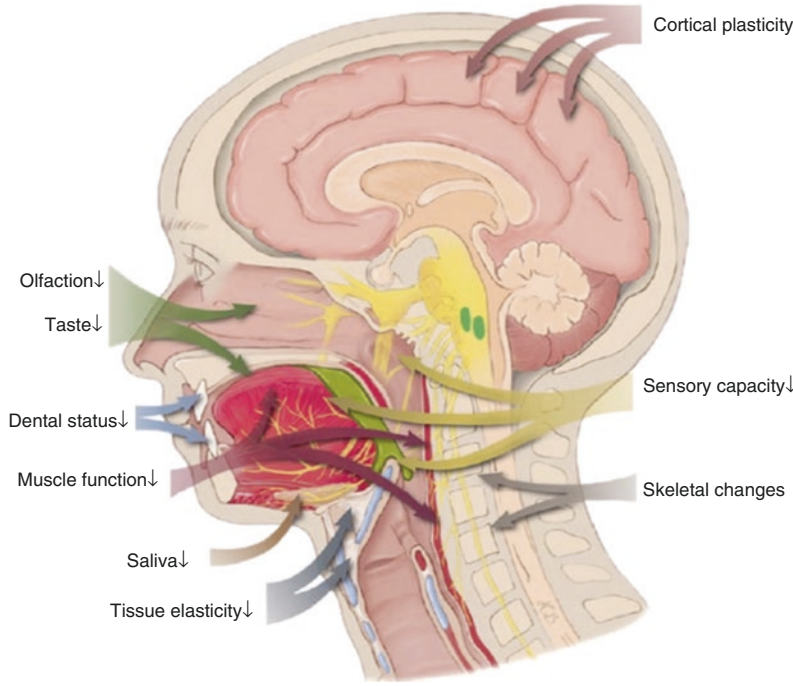

Fig. 3 Factors associated with the risk of OD in older people. Adapted from Wirth et al. (2016)

bolus velocity and kinetic energy during swallow (Clavé et al. 2006). Older adults generate lower maximum isometric pressures than younger adults (Robbins et al. 2005). We showed that young healthy adults present high bolus velocity (>35 cm/s) and strong bolus propulsion forces (>0.33 mJ) (Clavé et al. 2006). In contrast, older people with oropharyngeal dysphagia present impaired tongue propulsion forces (<0.14 mJ) and slower bolus velocity (<10 cm/s) (Clavé et al. 2006). Therefore, functional oropharyngeal dysphagia in older and neurologic patients is associated with impairment in efficacy and safety of swallow caused by weak tongue propulsion and prolonged and delayed swallow response. Pathogenesis of impaired safety is related to a delay in several physiologic protective reflexes in oropharyngeal reconfiguration (mainly laryngeal vestibule closure) caused by a slow neural swallow response and is associated with several risk factors such as ageing, neurodegenerative diseases, confusion, dementia, and drugs. Pathogenesis of impaired efficacy is related to alterations in bolus propulsion caused by a weak muscular tongue squeeze associated with sarcopenia and weakness (Clavé et al. 2005a).

2.2 Screening, Assessment, and Diagnosis of Dysphagia

The goal of the diagnostic program for dysphagia is to evaluate two deglutition-defining characteristics: (a) *efficacy*, the patient's ability to ingest all the calories and water he or she needs to remain adequately nourished and hydrated, and (b) *safety*, the patient's ability to ingest all needed calories and water with no respiratory complications (Clavé et al. 2004). To assess both characteristics of deglutition two groups of diagnostic methods are available: (a) clinical methods such as deglutition-specific medical history and clinical examination, usually used as screening methods, and (b) exploration of deglutition using specific complementary instrumental studies such as videofluoroscopy (Clavé 2011). Figure 4 shows the algorithm for management (screening, diagnosis, and treatment) of oropharyngeal dysphagia at the Hospital de Mataró, Barcelona, Spain (Clavé 2011).

Clinical screening for oropharyngeal dysphagia should be low risk, quick, and low cost and aim at selecting the highest risk patients who require further assessment.

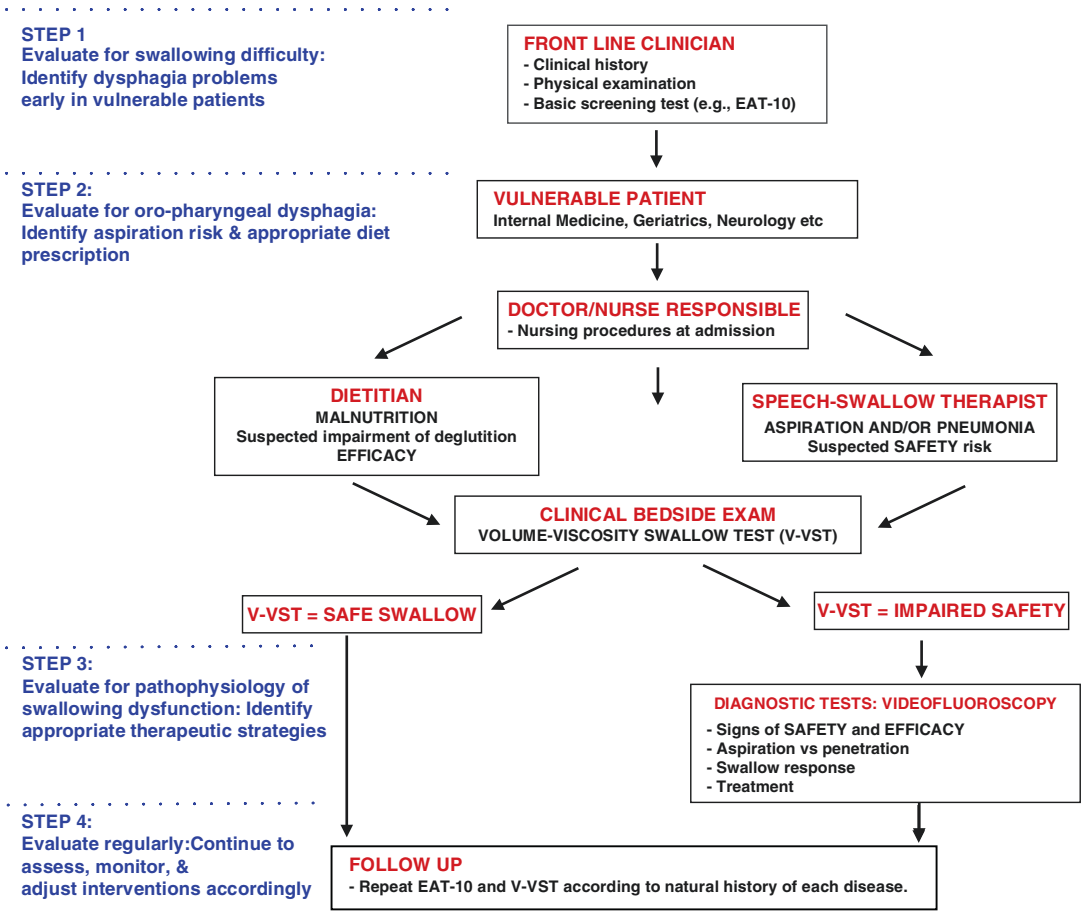

Fig. 4 Algorithm for screening, diagnosis, and treatment of oropharyngeal functional dysphagia at the Hospital de Mataró, Barcelona, Spain. Note the involvement of several professional domains of the dysphagia multidisciplinary team and the vertical and horizontal flows of information. The continuous black lines indicate the diagnostic screening strategy of patients at risk; the broken lines indicate the flow of information on patient status, and broken dotted lines indicate therapeutic interventions. (Adapted Clavé et al. 2008)

2.2.1 Deglutition-Specific Questionnaires

The Eating Assessment Tool (EAT-10) is a self-administered, symptom-specific outcome instrument for dysphagia. The EAT-10 has displayed excellent internal consistency, test-retest reproducibility, and criterion-based validity. The normative data suggest that an EAT-10 score of 3 or higher is abnormal. However, a recent study by our group recommends using a score ≥2 because it improves the sensitivity of the questionnaire to 85% (with a cutoff point of ≥3) to 89%, with no change in specificity (82%) (Rofes et al. 2014a). The instrument may be used to document the initial dysphagia severity in persons with swallowing disorders (Belafsky et al. 2008).

There is also a validated specific symptom inventory to assess the severity of oropharyngeal dysphagia in patients with neuromyogenic dysphagia (Wallace and Middleton 2000). The inventory consists of 17 questions, each answered on a 100 mm visual analogue scale, and shows strong test-retest reliability over 2 weeks. Also, content, construct validity, and score correlated closely with an independent global assessment severity score (Wallace and Middleton 2000). If a patient at risk for OD is present after performing the screening method, an evaluation should be performed

using clinical methods and/or complementary examinations to confirm clinical suspicion.

2.2.2 Clinical Examination

The clinical assessment methods for the diagnosis of OD should be able to establish a first clinical diagnosis, select those patients who need a more complete examination, and establish treatment for those patients who cannot finish the diagnostic process with a videofluoroscopy (VFS) or a swallowing fibroendoscopy (FEES). In this case, the staff performing the clinical assessment will require specific training. The majority of methods that existed until a few years ago were variants of the water test (Speyer 2013), in which patients had to drink a variable amount of water (50 mL, 60 mL, 150 mL, and 3 oz) from a glass without interruption (DePippo et al. 1992; Nathadwarawala et al. 1992; Smithard et al. 1998; Westergren 2006), with the presence of a series of signs (pre- or post-swallow cough, wet voice, or an intake velocity less than 10 mL/s) for the diagnosis of OD. This methodology puts vulnerable patients at risk for aspiration given the high volume of fluid ingested and the fact that the test is performed with the most dangerous viscosity for aspiration. Additionally, these methods do not allow the psychometric properties of swallowing to be measured accurately (Smithard et al. 1998). Two reviews have recently been published using the methodology and quality criteria of the Cochrane Collaboration and recommend the following for clinical assessment tests for the diagnosis of OD: (a) the administration of water or any other liquid must be accompanied by a pulse oximeter in order to detect the occurrence of desaturation during the test and signs of silent aspiration, together with the assessment of the appearance of coughing, choking, and changes in voice, and (b) and have a sensitivity of ≥70% and a specificity ≥60% (Kertscher et al. 2014; Bours et al. 2009). These guidelines recommend two methods that meet these conditions, one of them developed by Clavé et al., the volume-viscosity swallow test, (V-VST), and the second, the Toronto Bedside Swallowing Screening Test (TOR-BSST) (Kertscher et al. 2014; Bours et al. 2009).

The method developed by Clavé et al. is a safer clinical method, which uses a series of 5–20 mL nectar, liquid, and pudding boluses sequentially administered in a progression of increasing difficulty (Fig. 5). Cough, fall in oxygen saturation ≥3%, and changes in voice quality are considered to be clinical signs of impaired safety, whereas piecemeal deglutition and oropharyngeal residue are considered to be signs of impaired efficacy. If the patient shows any sign of impaired safety during the test, it will be continued with a thicker viscosity at the lowest volume (5 mL pudding) and if the patient shows impaired safety with pudding the test will be stopped. The V-VST is a safe, quick, and accurate clinical method with a high sensitivity (94%) and specificity (88%) for OD and for safety alterations (87% sensitivity and 81% specificity, respectively) compared to VFS and using xanthan gum thickeners (Rofes et al. 2014a).

2.2.3 Instrumental Evaluation

Instrumental assessment is used to confirm the diagnosis and/or help in the design of the most useful treatment in those patients in whom the clinical study method is positive for OD. The results obtained in the instrumental assessment will help us understand the pathophysiology of swallowing disorders, to follow the process and to determine the response to treatment in an objective way (Speyer et al. 2010). The VFS and the FEES are the *gold standard* for the diagnosis of OD and they should be performed by experienced staff. There is no consensus on the number of swallows, or the volume and consistency of the bolus to be used. Nowadays, the study of the upper esophageal sphincter is complemented by high-resolution manometry.

2.2.3.1 Videofluoroscopy (VFS)

Videofluoroscopy (VFS) is a dynamic exploration that evaluates the safety and efficacy of deglutition, characterizes the alterations of deglutition in terms of videofluoroscopic symptoms, and helps to select and assess specific therapeutic strategies. Technical requirements for clinical VFS are an X-ray tube with fluoroscopy and a videotape

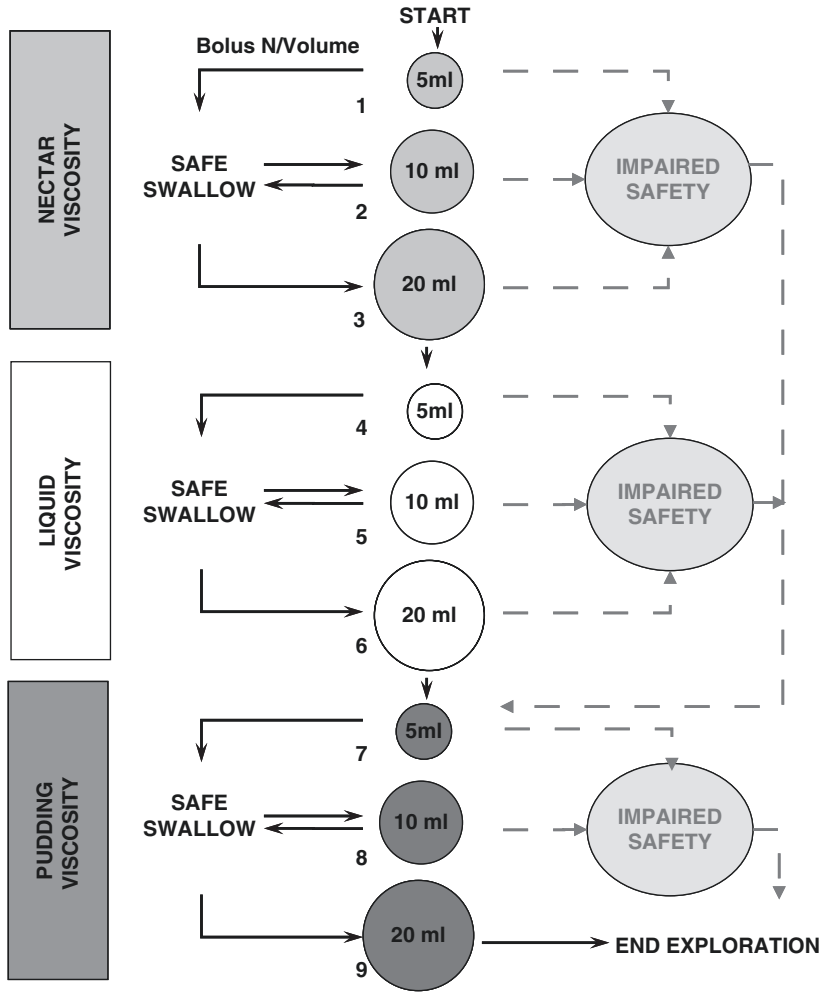

Fig. 5 Algorithms of bolus volume and viscosity administration during V-VST. The strategy of the V-VST aims at protecting patients from aspiration by starting with nectar viscosity and increasing volumes from 5 mL to 10 mL and 20 mL boluses in a progression of increasing difficulty. When patients complete the nectar series without symptoms of aspiration (cough and/or fall in oxygen saturation ≥3%), a less "safe" liquid viscosity series is assessed also with boluses of increasing difficulty (5–20 mL). Finally, a more "safe" pudding viscosity series (5–20 mL) is assessed following the same procedure. If the patient presents a sign of impaired safety at nectar viscosity, the series is interrupted, the liquid series is omitted, and the pudding viscosity series is assessed. If the patient presents a sign of impaired safety at liquid viscosity, the liquid series is interrupted and the pudding series is assessed

recorder; additionally, there are computed-assisted methods of analysis of images allowing quantitative temporal and spatial measurements. Main observations during VFS are done in the lateral plane while swallowing 5–20 mL boluses of at least three consistencies: liquid, nectar, and pudding. Patients can be kept at minimal risk for aspiration by starting the study with low volumes and thick consistencies, introducing liquids and high volumes as tolerated (Clavé et al. 2006). Major signs of impaired efficacy during the oral stage include apraxia and reduced control and bolus propulsion by the tongue. Many older patients present deglutitional apraxia (difficulty, delay, or inability to initiate the oral stage) following a stroke. This symptom is also seen in patients with Alzheimer's,

dementia, and diminished oral sensitivity. Impaired lingual control (inability to form the bolus) or propulsion results in oral or vallecular residue when alterations occur at the base of the tongue. The main sign of impaired safety during the oral stage is glossopalatal (tongue-soft palate) seal insufficiency, a serious dysfunction that results in the bolus falling into the hypopharynx before the triggering of the oropharyngeal swallow response and while the airway is still open, which causes predeglutitive aspiration (Clavé et al. 2004; Logemann 1993). Videofluoroscopic signs of impaired safety during the pharyngeal stage include penetrations and/or aspirations. Penetration refers to the entering of contrast into the laryngeal vestibule within the boundaries of the vocal cords. When aspiration occurs, contrast goes beyond the cords into the tracheobronchial tree (Fig. 6b). The potential of videofluoroscopy regarding image digitalization and quantitative analysis currently allows accurate swallow response measurements in patients with dysphagia (Fig. 6). A slow closure of the laryngeal vestibule and a slow aperture of the upper esophageal sphincter (as seen in Fig. 6b) are the most characteristic aspiration-related parameters (Clavé et al. 2004; Kahrilas et al. 1997). Penetration and aspiration may also be the result of an insufficient or delayed hyoid and laryngeal elevation, which fail to protect the airway. A high, permanent post-swallow residue may lead to post-swallow aspiration, since the hypopharynx is full of contrast when the patient inhales after swallowing, and then contrast passes directly into the airway (Clavé et al. 2004; Logemann 1993). Thereafter, VFS can determine whether aspiration is associated with impaired glossopalatal seal (predeglutitive aspiration), a delay in triggering the pharyngeal swallow or impaired deglutitive airway protection (laryngeal elevation, epiglottic descent, and closure of vocal folds during swallow

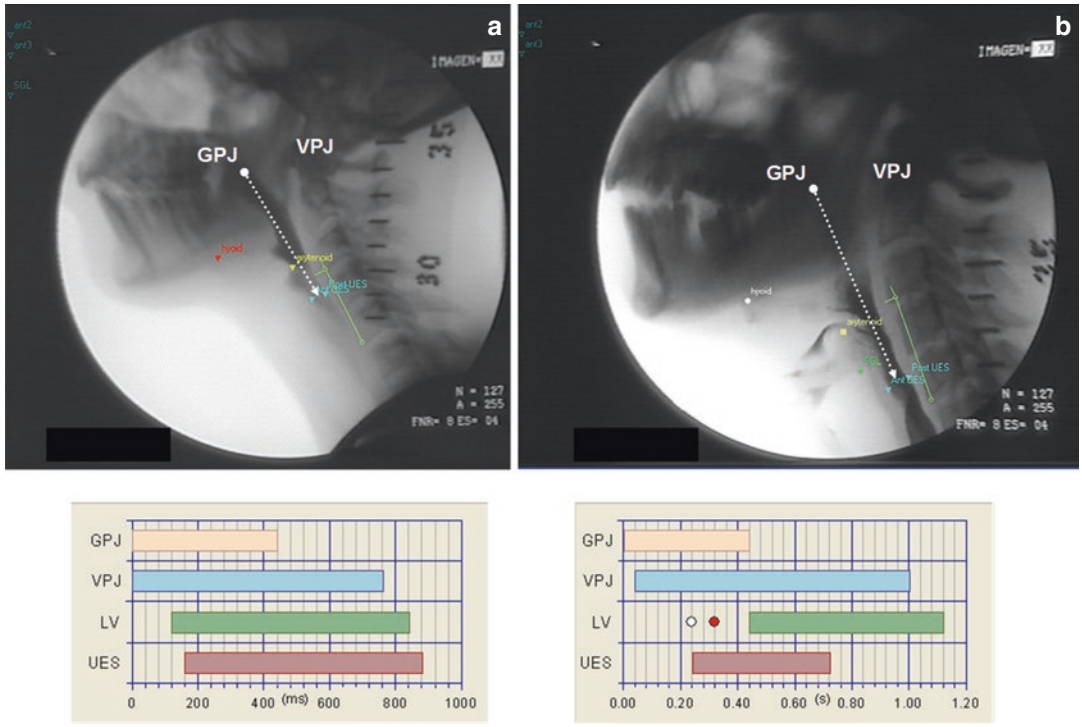

Fig. 6 Videofluoroscopic images and oropharyngeal swallow response during the ingestion of a 5 mL nectar bolus in (**a**) a healthy individual; (**b**) an older patient with neurogenic dysphagia and aspiration associated with stroke. An increase in the total duration of the swallow response can be seen, as well as delayed closure of the laryngeal vestibule and delayed aperture of the upper sphincter. The white dot indicates the time when contrast penetrates into the laryngeal vestibule, and the red dot indicates passage into the tracheobronchial tree (aspiration). *GPJ* glossopalatal junction, *VPJ* velopalatal junction, *LV* laryngeal vestibule, *UES* upper esophageal sphincter

response), or an ineffective pharyngeal clearance (post-swallowing aspiration) (Clavé et al. 2004).

2.2.3.2 Fiber-Optic Endoscopic Evaluation of Swallowing (FEES)

Using a flexible fibroscope connected to a light source and a video recorder, the deglutary sequences are recorded. This is a well-tolerated technique, easy to repeat, and one which can be performed at the patient's bedside. Like VFS, protocols vary with the use of different consistencies and volumes of bolus, administered after adding food coloring. It is a technique that also enables evaluation of the therapeutic measures performed. Some of the limitations of the technique are (a) the inability to assess the oral phase and (b) the restricted visibility during swallowing, as the endoscope comes in contact with the base of the tongue, the epiglottis, and the bolus itself and can prevent direct visualization of penetrations and aspirations (Leder and Murray 2008).

2.2.3.3 High-Resolution Manometry (HRM)

High-resolution esophageal manometry (HRM) is a variation of conventional manometry and uses simultaneous recording points, enabling the evaluation of the pharynx, UES, and esophageal body. The development of this technique was enabled by a series of advances such as the incorporation of a large number of sensors and computer systems that can analyze large amounts of data in real time, complex calculations, and topographic representation by pressure levels (Kahrilas 2010).

Regarding the study of the UES by HRM, the high-pressure zone of the UES is easily identifiable. The swallowing of a bolus produces a wave from the velopharynx and pharynx, a relaxation of the UES, and a contraction of the proximal esophagus. The force of contraction of the pharynx is evaluated by the peak pharyngeal amplitude (mmHg) with a mean value of 140 mmHg (107–194 mmHg) (Omari et al. 2011), affected by the age, characteristics of the bolus (volume and consistency), and position of the subject. The extension of UES relaxation is given by the minimal pressure during relaxation (UES "nadir pressure") which decreases to atmospheric pressure or negative pressures (McCulloch et al. 2010). The duration of UES relaxation is determined by the onset and end of the UES pressure drop. Pharyngeal intrabolus pressure (IBP) is a manometric marker of bolus resistance during the passage through the

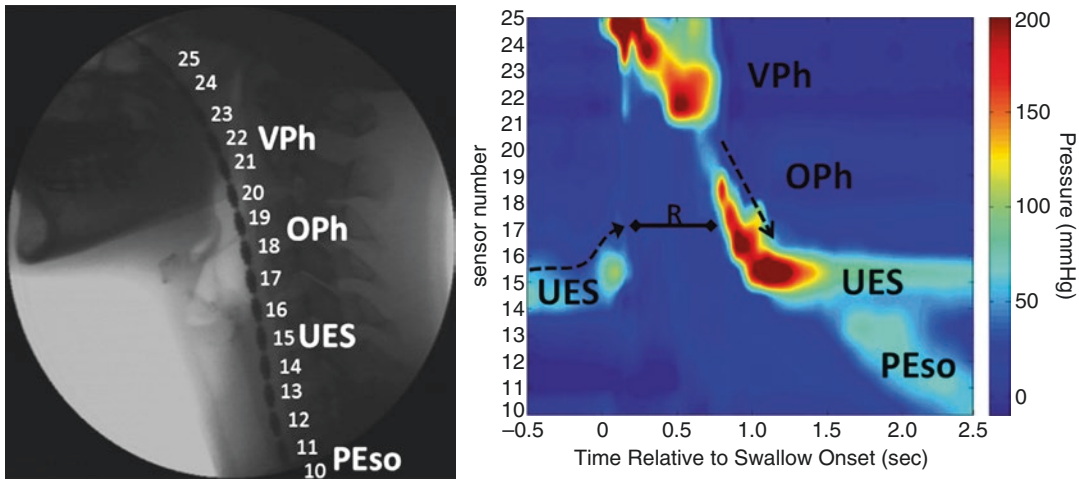

Fig. 7 High-resolution pharyngoesophageal manometry. The image on the left shows by fluoroscopy the situation of the high-resolution manometric catheter at rest. Pressure sensors are shown at the level of the velopharynx, (PVh), oropharynx (OPh), upper esophageal sphincter (UES), and proximal esophagus (PEso). The image on the right corresponding to the high-resolution manometry shows the pressure generated from the swallowing of a bolus. Observe the proximal displacement of the UES with elevation of the larynx (curved line), relaxation of the UES (R), and pharyngeal wave (diagonal arrow) (modified from Sifrim, Vilardell, Clavé) (Sifrim et al. 2014)

UES. Intrabolus pressure gradient (IBPG) reflects the difference in pressure between the UES and the pharynx during the transsphincteric passage of the bolus (Fig. 7).

Pharyngeal contraction is considered hypocontractile when it has a pressure lower than 100 mmHg, and hypercontractile when it is more than 200 mmHg (Omari et al. 2011; McCulloch et al. 2010; Sifrim et al. 2014). High pharyngeal pressure with an increase in intrabolus pressure may represent a compensatory mechanism in patients with obstruction at the level of UES, such as in patients with a cricopharyngeal bar. Patients with Zenker's diverticulum present a decreased compliance of UES which is unable to relax during the opening of ESS (Cook et al. 1992). The HRM of these patients shows an increase in intrabolus pressure when passing through the UES proportional to the increase of the volume of the bolus with normal pressure at rest and an adequate coordination between the pharyngeal contraction and the relaxation of the UES.

Other important factors for an adequate functionality of the UES are the correct relaxation of the UES and the time in which it is performed. A decreased relaxation interval may occur secondary to delayed onset of relaxation or premature contraction of UES. Shortening the duration of the UES relaxation impacts the flow of the bolus, corresponding to alterations in the pressure.

2.3 Pathophysiology of Malnutrition in Patients with Dysphagia

2.3.1 Screening and Assessment of Malnutrition

The assessment of nutritional status is a complex and time-consuming procedure which requires trained personnel. Indeed, the procedure and thus the diagnosis of malnutrition are based on a combination of data extracted from the patient history, physical examination, and specific laboratory parameters.

The patient's history will focus on finding out possible changes in diet and body weight and to explore socioeconomic aspects and symptoms that may influence the patient's nutritional status in the context of the disease. The patient will be asked about his usual weight, to assess weight changes over time, and recorded toxic habits, medication, gastrointestinal symptoms, and presence of known diseases will be examined. It is important to investigate the patient's usual diet and that of recent weeks to estimate intake. The physical examination should detect any loss in muscle and fat and the presence of edema and ascites. Body weight, as an absolute value, has its limitations; however, combined with the individual's height it provides the body mass index (BMI = weight in kg/height in m^2) which can be used to diagnose malnutrition. One of the best indicators of malnutrition or risk of malnutrition is the assessment of weight changes over time. An unintentional weight loss of 5% of previous weight in a month or 10% in 3 months is highly suggestive of malnutrition. The skinfold measurement by a precision caliper provides an estimate of fat mass, the triceps skinfold being the most used. The measurement of body circumferences can estimate the individual's muscle mass, arm circumference being the most used. Like with the triceps skinfold, measurements should be compared with reference values. It is important to note that skinfolds and circumferences have significant interobserver variability, which limits the reproducibility of the data. Among the markers, there is no single ideal biochemical marker for malnutrition, as most laboratory parameters are limited by being insensitive and not very specific or being affected by non-nutritional factors. Of these, the most commonly used is serum albumin, a protein with liver synthesis and relatively long half-life, which is a good marker of nutritional status and prognosis in the absence of overt inflammation. The dosage of proteins synthesized by the liver but having a shorter half-life than albumin, i.e., *prealbumin*, could be of help to monitor changes of the nutritional status during a short period of time (Peña Morant et al. n.d.)

Considering the complexity of assessing nutritional status, simpler tools should be used by untrained personnel to detect the patients at risk of malnutrition, in order to request a more detailed evaluation by specialized personnel, and to start nutritional intervention early. To this end, a number of screening tools for nutritional risk have been developed. The validated nutritional screening method for hospitalized patients is that Nutritional Risk Screening [NRS] 2002 developed by the European Society for Clinical Nutrition and Metabolism—ESPEN and built on a retrospective analysis of 128 controlled trials focusing on nutritional assessment, nutritional support, and patient outcomes. Very simple and fast to complete, it has a low variability between observers, the most subjective assessment being the severity of the disease (Kondrup et al. 2003). The Malnutrition Universal Screening Tool (MUST), developed by the British Society for Parenteral and Enteral Nutrition (BAPEN) in 2003, has been validated to identify adult patients malnourished or at risk. ESPEN recommends the use of MUST test in the community, but it can also be utilized in institutionalized or hospitalized patients. MUST has been shown to predict the duration of hospital stay and mortality. The method is simple and reproducible between observers and is linked to specific protocols and treatment recommendations (Malnutrition Advisory Group (MAG) 2011). The Subjective Global Assessment (SGA), designed by Baker in 1982 and validated for the majority of the population, is a dynamic process of nutritional assessment, structured and simple with high predictive power and a high rate of interobserver agreement. However, it requires training and is more appropriate for the detection of established malnutrition rather than acute changes in nutritional status or nutritional risk (Detsky et al. 1987). The method validated for the geriatric population is the Mini-Nutritional Assessment (MNA), with a high positive predictive value and high specificity and sensitivity, recommended by the ESPEN for the screening of older patients. The MNA identifies patients at risk before any other visible changes occur. The first part consists of a screening (MNA-Short Form) and the second considers food habits, social status, functional ability, and physical examination (Vellas et al. 1999).

2.4 Types and Mechanisms of Malnutrition in Dysphagia

There is a close relation between prevalence and severity of dysphagia and incidence of malnutrition. Up to 50% of nursing home residents and up to 70% of hospitalized geriatric patients show signs of malnutrition. However, the true prevalence of malnutrition among patients with dysphagia, the pathophysiology of malnutrition associated with OD, the relevance of OD as a cause of malnutrition, and the type of malnutrition associated with diseases also causing OD have not been fully determined.

Three types of malnutrition have been described: starvation-related malnutrition, chronic disease-related malnutrition, and acute disease- or injury-related malnutrition (Jensen et al. 2010). **Starvation-related malnutrition** develops in situations of chronic energy and protein deficiency while maintaining a ratio between the amount of energy and protein. It is characterized by *absence of inflammation*, and loss of the body's muscle mass and subcutaneous fat, eventually leading to emaciation. **Chronic disease-related malnutrition** is characterized by the *presence of mild-to-moderate chronic inflammation*, and by a variable degree of reduced food intake because of disease-associated anorexia. Cancer, liver cirrhosis, chronic obstructive pulmonary disease, and chronic renal failure are clinical conditions frequently characterized by this type of malnutrition. **Acute disease- or injury-related malnutrition** is characterized by acute and severe inflammation, which impairs the ability to use nutrients introduced by the diet or infused by artificial nutrition. Critically ill patients frequently develop this type of malnutrition. Chronic disease-related malnutrition is the most common form of malnutrition in hospital (Jensen et al. 2010). The existence of disease-associated malnutrition is very common and the

prevalence may range from 20 to 50% of patients, depending on the variability of the diagnostic criteria used (Norman et al. 2008). In developed countries, the main cause of malnutrition is disease. Any disorder, whether chronic or acute, may result in or aggravate malnutrition in various ways: response to trauma, infection, or inflammation may alter metabolism, appetite, absorption, or assimilation of nutrients (Campbell 1999). The catabolic effects of several mediators such as cytokines (interleukin 1, interleukin 6, and tumor necrosis factor alpha), glucocorticoids, catecholamines, and lack of insulin growth factor-1 have been extensively studied in recent years, though their relevance is still not entirely understood (Tisdale 2005). Drug-related side effects (e.g., chemotherapy, morphine derivatives, antibiotics, sedatives, neuroleptics, digoxin, antihistamines, captopril) can cause anorexia or interfere with the ingestion of food. In geriatric patients, further factors such as dementia, immobilization, anorexia, and poor dentition can worsen the situation (Markson 1997; Morley 1997) Apart from the pathological causes of malnutrition, socioeconomic factors such as low income and isolation may contribute to the development of malnutrition (Pirlich et al. 2005). The situation can be further aggravated in hospital due to adverse hospital routines that lead to insufficient nutrient intake (Serra-Prat et al. 2012). Several studies have suggested that hospitalized patients often receive less than an optimal level of nutritional care due to lack of training and awareness of hospital staff (Kondrup et al. 2002). Patients are frequently ordered nil by mouth without being fed by another route or are called for an examination immediately prior to food being served, multiple episodes of fasting before an examination occur, and meals are often considered unpalatable. Depression, dementia, and lack of feeding assistance also lead to decreased nutrient intake.

We studied the prevalence of malnutrition among inpatients with chronic dysphagia caused by nonprogressive brain disorders (NPBD, e.g., stroke, brain injury) or by neurodegenerative diseases (NDGD patients, e.g., amyotrophic lateral sclerosis, multiple sclerosis). Prevalence and type of malnutrition were studied using the Subjective Global Assessment (**SGA**) (Clavé et al. 2006). **Anthropometric measures** (triceps skin fold thickness, arm circumference, and arm muscle circumference), **body mass index, % weight loss, plasma albumin, and lymphocyte count** were also recorded. Prevalence and type of malnutrition were similar between NPDB and NDGD patients with neurogenic dysphagia. Malnutrition was found in 16% of NPBD patients according to SGA (SGA B or C), in 24.1% according to body mass index and in 20% according to weight loss >10%. In NDGD patients, malnutrition was found in 22% of patients according to SGA, in 21.9% according to body mass index, and in 23.5% according to weight loss >10%. The study found a **strong correlation between dysphagia and malnutrition as the clinical severity** (Clavé et al. 2006) of dysphagia scored 325.6 ± 12.3 points in patients with normal nutritional status and 529 ± 34.5 points in patients with or at risk of malnutrition ($p < 0.05$). The type of malnutrition in both groups of patients with neurogenic dysphagia was uniformly of the chronic type. Significant differences were found in relation to anthropometric parameters between well-nourished patients and malnourished patients in (a) skeletal muscle measured as upper arm muscle circumference 28.4 ± 0.4 vs. 24.8 ± 0.5 cm ($p < 0.05$) and (b) fat mass measured as triceps skin fold 15.5 ± 0.6 vs. 10.9 ± 1.0 mm ($p < 0.05$). In contrast, measurements of visceral protein were found to be within the normal range in most patients with neurogenic dysphagia and malnutrition as plasma albumin was 40.2 ± 0.7 vs. 40.9 ± 1.9 g/L and lymphocyte counts were similar among patients with SGA A vs. patients with SGA B or C (Clavé et al. 2006). A recent study has been published, the main objective of which was to describe the nutritional characteristics of older patients with OD without an acute condition and during an acute process. A total of 133 patients were studied with OD secondary to neurological processes or to ageing, 23 with pneumonia, 95 without an acute condition, and 15 older patients without OD. The results show that 51.1% patients with OD and in a chronic situation presented a MNA® ≤ 23.5, with reduced vis-

ceral and muscular protein compartments and fat compartment and reduced body weight. A total of 69.5% of patients with OD and pneumonia presented an MNA® ≤ 23.5, the inflammatory response of the pneumonia further depleting visceral protein and muscular mass. Chronic patients at risk of malnutrition or malnourished had poorer swallowing function with greater need for thickeners to adapt liquids to nectar viscosity for safe swallowing, and more residue at pudding viscosity (Carrión et al. 2017).

2.4.1 Sarcopenia and Dysphagia

The tongue plays a key role in bolus propulsion. We and others found that older patients with dysphagia showed impaired tongue propulsion (Rofes et al. 2010) and decreased tongue volume due to sarcopenia (Robbins et al. 2005). Older adults present lingual weakness, a finding that has been related to sarcopenia of the head and neck musculature and frailty (Robbins et al. 2005) and one of the major causes for dysphagia in older people, associated with impairment in efficacy and safety of swallow (Clavé et al. 2011). Sarcopenic dysphagia is a new concept, describing dysphagia caused by sarcopenia affecting tongue and swallow musculature, the treatment of which involves both rehabilitation therapies and nutritional intervention (Wakabayashi 2014b).

Depending on the literature definition used for sarcopenia, the prevalence in 60–70-year-olds is reported as 5–13%, while the prevalence ranges from 11 to 50% in people >80 years (Morley 2017). Even with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million in the next 40 years. The impact of sarcopenia on older people is far reaching; its substantial toll is measured in terms of morbidity, disability, high costs of health care, and mortality. The European Working Group on Sarcopenia in Older People (EWGSOP) has recently developed a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia (Cruz-Jentoft et al. 2010). They define sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death (Cruz-Jentoft et al. 2010). They recommend using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. The rationale for the use of two criteria is that muscle strength does not depend solely on muscle mass, and the relationship between strength and mass is not linear (Goodpaster et al. 2006; Janssen 2004). There are several mechanisms that may be involved in the onset and progression of sarcopenia. These mechanisms involve, among others, protein synthesis, proteolysis, neuromuscular integrity, and muscle fat content (Fig. 8). Sarcopenia can be considered "primary" (or age related) when no other cause is evident but ageing itself, and "secondary" when one or more other causes are evident. Sarcopenia staging, which reflects the severity of the condition, is a concept that can help guide clinical management of the condition. EWGSOP suggests a conceptual staging as "presarcopenia," "sarcopenia," and "severe sarcopenia" (Cruz-Jentoft et al. 2010). The parameters of sarcopenia are the amount of muscle and its function. The measurable variables are mass, strength, and physical performance. The following sections briefly review measurement techniques that can be used and discuss their suitability for research and clinical practice settings. A wide range of techniques can be used to assess muscle mass (Markson 1997). We present here the proposals of EWGSOP:

(a) *Body imaging techniques.* Three imaging techniques are used to estimate muscle mass

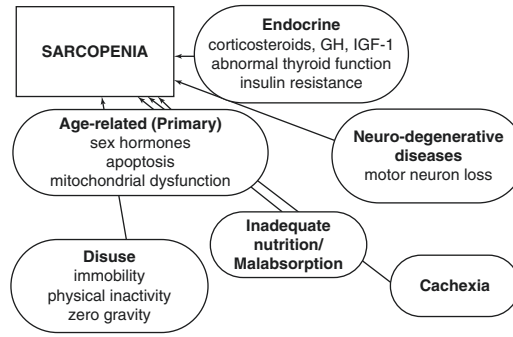

Fig. 8 Mechanisms of sarcopenia (Jensen et al. 2010)

or lean body mass—computed tomography (CT scan), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DXA). CT and MRI are considered to be very precise imaging systems that can separate fat from other soft tissues of the body, making these methods gold standards for estimating muscle mass in research. High cost, limited access to equipment at some sites, and concerns about radiation exposure limit the use of these whole-body imaging methods for routine clinical practice (Chien et al. 2008). DXA is an attractive alternative method both for research and for clinical use to distinguish fat, bone mineral, and lean tissues. This whole-body scan exposes the patient to minimal radiation. The main drawback is that the equipment is not portable, which may preclude its use in large-scale epidemiological studies (Chien et al. 2008).

(b) *Bioimpedance analysis*. Bioimpedance analysis (BIA) estimates the volume of fat and lean body mass. The test itself is inexpensive, easy to use, reproducible, and appropriate for both ambulatory and bedridden patients. BIA measurement techniques, under standard conditions, have been used for over 10 years (ANON 1996), and BIA results under standard conditions have been found to correlate well with MRI predictions (Janssen et al. 2000). Prediction equations have been validated for multiethnic adults (Sullivan et al. 2002) and reference values established for adult white men and women, including older persons (Kyle et al. 2001a, b; Roubenoff et al. 1997). Thus, BIA might be a good portable alternative to DXA.

(c) *Total or partial body potassium per fat-free soft tissue*. As skeletal muscle contains >50% of the total body potassium (TBK), TBK is the classic method for estimation of skeletal muscle. More recently, partial body potassium (PBK) of the arm has been proposed as a simpler, safe, and inexpensive alternative (Wielopolski et al. 2006). TBK is the classic method for the estimation of skeletal muscle, but this method is not used routinely.

(d) *Anthropometric measurement*s. Calculations based on mid-upper arm circumference and skin fold thickness have been used to estimate muscle mass in ambulatory settings. However, age-related changes in fat deposits and loss of skin elasticity contribute to errors of estimation in older people. There are relatively few studies validating anthropometric measures in older and obese people; these and other confounders make anthropometric measures vulnerable to error and questionable for individual use (Rolland et al. 2008).

(e) *Muscle strength.* There are fewer well-validated techniques to measure muscle strength. Although lower limbs are more relevant than upper limbs for gait and physical function, handgrip strength has been widely used and is well correlated with most relevant outcomes. Again, cost, availability, and ease of use can determine whether the techniques are better suited to clinical practice or are useful for research. It must be remembered that factors unrelated to muscle, e.g., motivation or cognition, may hamper the correct assessment of muscle strength (Cruz-Jentoft et al. 2010).

(f) *Physical performance.* A wide range of tests of physical performance are available, including the Short Physical Performance Battery (SPPB), which includes usual gait speed, 6-min walk test, and stair climb power test (Working Group on Functional Outcome Measures for Clinical Trials 2008). Tongue strength can be assessed by several standardized instruments for lingual pressure measurements, air-filled bulbs between the tongue and hard palate, manometric devices, or assessing the bolus velocity and kinetic energy during videofluoroscopic studies.

3 Complications of Dysphagia: Aspiration Pneumonia and Malnutrition

The severity of OD varies from moderate difficulty to complete inability to swallow. OD may give rise to two groups of clinically relevant com-

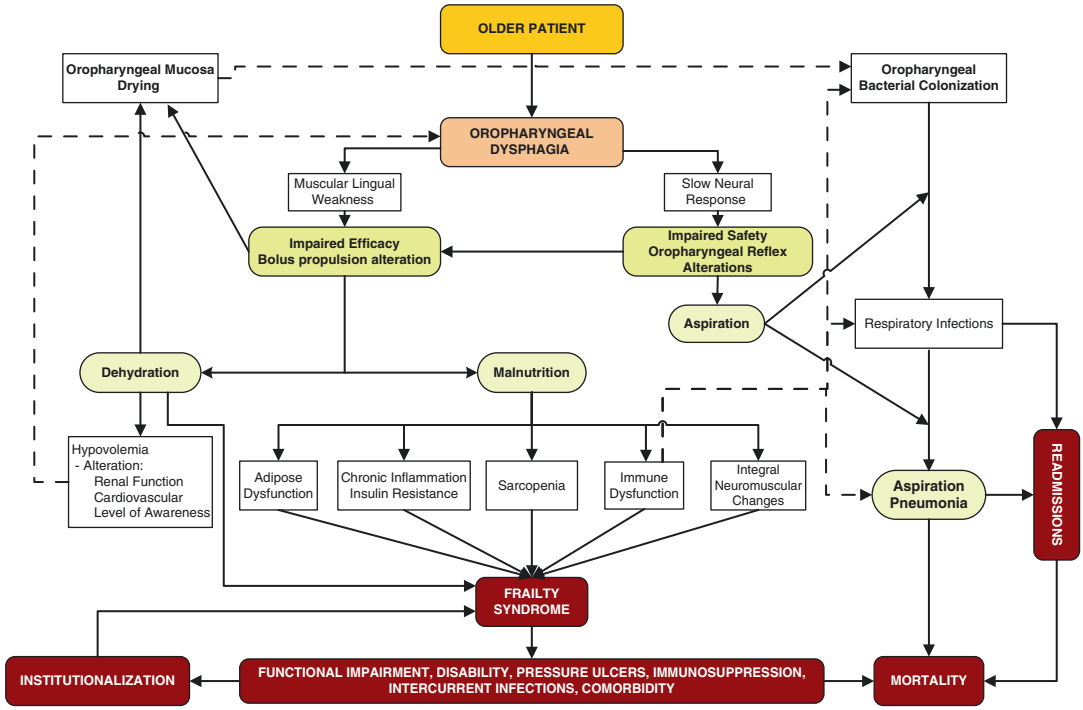

Fig. 9 Pathophysiology of nutritional and respiratory complications associated with oropharyngeal dysphagia in older patients (Ortega et al. 2014b)

plications: (a) malnutrition and/or dehydration caused by an impairment in the efficacy of deglutition, present in 25–75% patients with dysphagia, and (b) choking and tracheobronchial aspiration caused by an impairment in the safety of swallow (impaired airway protection) that can lead to respiratory infections and aspiration pneumonia (AP) in up to 50% of cases, with an associated mortality of up to 50% (Cook and Kahrilas 1999; WHO n.d.). Figure 9 summarizes the pathophysiology of complications related to OD in older and neurological patients.

3.1 Respiratory Complications: Aspiration Pneumonia

AP has been defined as a respiratory infection with radiological evidence of condensation that occurs when contents of the oral cavity (liquid, saliva, food) colonized with respiratory pathogens are aspirated into the lungs. AP is the most severe complication of OD and is the main cause of death in patients with OD associated with neurological disorders (Mikasa et al. 2016; Ortega Fernández and Clavé 2013; Ortega et al. 2013; Marik and Kaplan 2003). The incidence and prevalence of AP in the community are poorly defined. They increase in direct relation with age and underlying diseases with a prevalence of around 0% in patients younger than 50 years to as high as 90% in patients older than 90 years (Teramoto et al. 2008). The risk of AP is higher in older patients because of the high incidence of dysphagia (Loeb et al. 2003). Up to 10% of older community-living patients admitted to a general hospital for pneumonia are diagnosed with AP and this prevalence increases to 30–50% in institutionalized older patients with an associated mortality of 45% (Cook and Kahrilas 1999; Reza Shariatzadeh et al. 2006). In older patients (>70 years) with CAP, prevalence of AP has been found to be 60.1% (Teramoto et al. 2008). In patients with stroke, up to 20% will develop AP during the first days of stroke and AP is the first cause of death during the first year after stroke

(Cook and Kahrilas 1999; Ickenstein 2011). We recently studied 134 older patients (>70 years) consecutively admitted with pneumonia to an acute geriatric unit in a general hospital. Of the 134 patients, 53% were over 84 years old and 55% presented clinical signs of OD; the mean Barthel score was 61 points, indicating a frail population. Patients with dysphagia were older, and showed lower functional status, higher prevalence of malnutrition and comorbidities, higher Fine's pneumonia severity scores, and higher mortality at 30 days (22.9% vs. 8.3%, $p = 0.033$) and at 1 year of follow-up (55.4% vs. 26.7%, $p = 0.001$) (Fig. 10). OD is therefore a highly prevalent clinical finding and an indicator of disease severity in older patients with pneumonia (Cabre et al. 2010). Nevertheless, aspiration is not usually considered the etiological factor for pneumonia in a patient at risk of aspiration and therefore AP is underdiagnosed in most medical centers (Ortega Fernández and Clavé 2013; Ortega et al. 2013; Marik and Kaplan 2003; Committee for the Japanese Respiratory Society Guidelines in Management of Respiratory 2004). A revision of the literature described AP as a common complication of OD associated with the following risk factors: advanced age, poor oral hygiene (colonization), malnutrition, smoking, use of antibiotics and inhalers (COPD patients), dehydration, and reduced immunity (Almirall et al. 2007) (Fig. 11). A meta-analysis found a positive correlation between OD and AP in post-stroke older patients and concluded that proper oral hygiene significantly reduced the risk of developing AP (Van et al. 2011). The pathogenesis of aspiration pneumonia has been recently revised and includes three main risk factors: (a) OD with impaired safety of swallow and aspirations; (b) vulnerability with MN and impaired immunity; and (c) poor oral health and hygiene with colonization by respiratory pathogens (Ortega Fernández and Clavé 2013; Ortega et al. 2013).

Aspiration observed with VFS is associated with a 5.6–7-fold increase in risk of pneumonia (Schmidt et al. 1994). Up to 45% of older patients with dysphagia presented penetration into the laryngeal vestibule and 30%, aspiration, half of them without cough (silent aspiration), and 45%, oropharyngeal residue (Clavé et al. 2005a). Detection of aspiration by VFS is an accepted predictor of pneumonia risk and/or probability of rehospitalization (Cook and Kahrilas 1999). It is also well known that not all patients who aspirate during VFS develop pneumonia. Impairment in host defenses such as abnormal cough reflex (Marik and Kaplan 2003; Addington et al. 1999), impaired pharyngeal clearance, amount and bacterial concentration of aspirate, and weakened immune system also strongly contributes to the development of AP (Almirall et al. 2007). Impairment of cough reflex has been shown to increase the risk of AP in stroke patients (Addington et al. 1999). Several risk factors contribute to oropharyngeal colonization such as the following: (1) older age, as swallow response, cough reflex, and breathing coordination are impaired in older people; (2) malnutrition: poor nutritional status is a marker of a population highly susceptible to acquire pneumonia in older people as malnutrition depresses the immune system; (3) smoking status, number of cigarettes smoked per day, and lifetime smoking; (4) poor oral hygiene: AP is probably the most common infectious sequelae of poor oral health in seniors, particularly those who reside in nursing homes. A study on older people with dysphagia in Spain found that oral health and hygiene in those patients were very poor with a high accumulation of microbial biofilm (dental plaque and calculus) in more than 70% of patients, and high prevalence of periodontitis (>90%) and caries (59%) (Ortega et al. 2013). A study from the same group of researchers found a high percentage and amount of respiratory pathogens (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Escherichia coli*) in the oral cavity of patients with OD that was higher than in non-dysphagic patients (Teramoto et al. 2008). In addition, the oral bacterial load was found to be higher in the oral cavity than in the nasal cavity, suggesting that the etiological route of pneumonia in these kind of patients was aspiration instead of inhalation (Teramoto et al. 2008). Likewise, several publications have found a decrease in the inci-

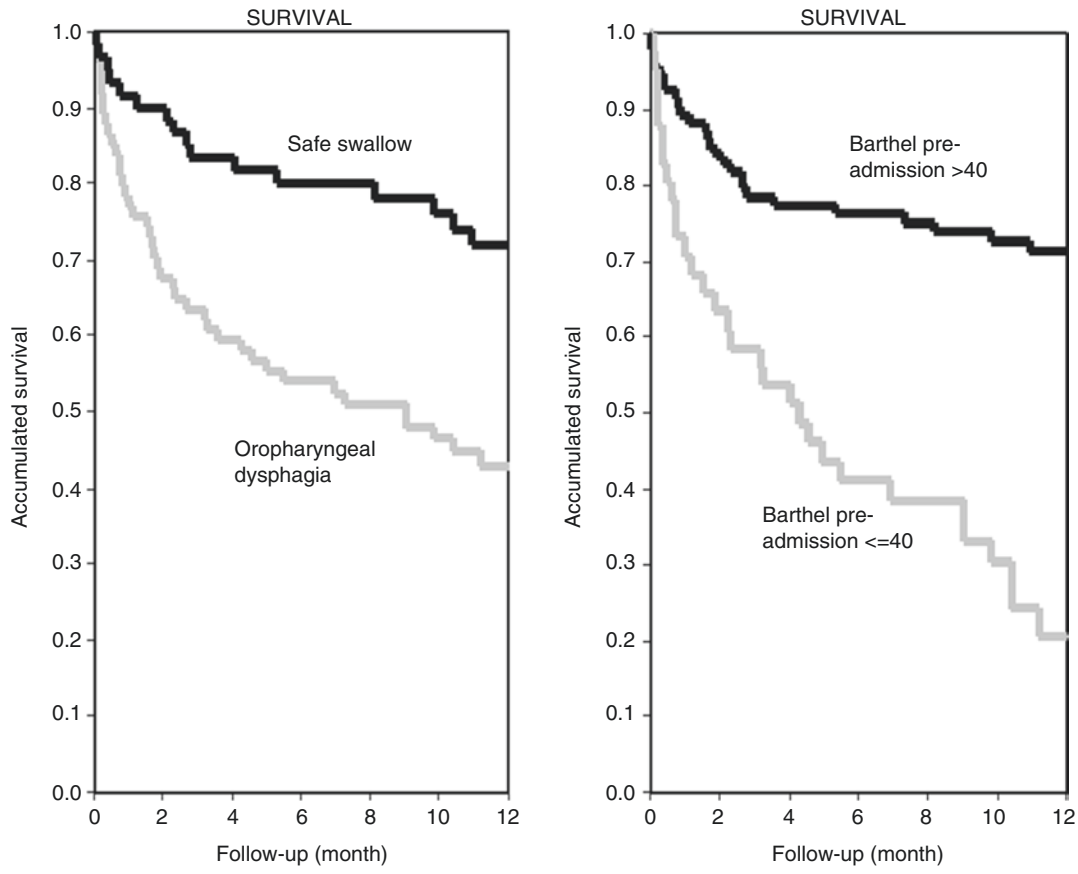

Fig. 10 Accumulated survival at 1 year according to the presence of clinical signs of oropharyngeal dysphagia and functional status (preadmission Barthel score) (Cabre et al. 2010)

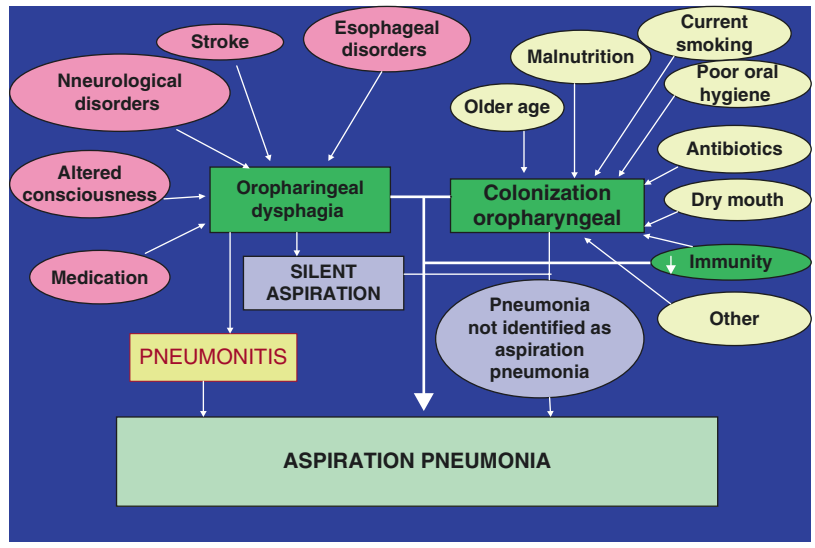

Fig. 11 Pathophysiology of aspiration pneumonia and oropharyngeal dysphagia

dence of pneumonia and respiratory tract infections after the evaluation and treatment of oral health and hygiene (Sjögren et al. 2008; Sørensen et al. 2013; Van et al. 2013), indicating a simple but effective measure to avoid respiratory complications of OD. A systematic review concluded that oral hygiene had a preventive effect in the development of pneumonia and respiratory infections and, specifically, that mechanical toothbrushing had a preventive effect on nonfatal pneumonia and reduced the mortality risk of pneumonia by 10% in dependent older persons (Sjögren et al. 2008). (5) Antibiotics: it has been suggested that inappropriate antibiotic treatment could be a risk factor for pneumonia. In some patients who are smokers or have chronic bronchitis, the use of antibiotics in the previous 3 months may provoke a variety of respiratory flora, predisposing to opportunistic infection with colonization of more aggressive organisms, which could be causative pathogens of AP. (6) Dry mouth: many medications reduce salivary flow or create xerostomia as a side effect. This creates a favorable environment for bacteria that are pathogenic to the lungs if aspirated. (7) Immunity: older adults can have reduced oropharyngeal clearance, reduced numbers of T cells, reduced helper T-cell activity and response to antigens, reduced numbers of B cells and B-cell response to antigens, reduced antibody response, reduced phagocytosis, and reduced Toll-like receptors on phagocytic cells. (8) Feeding tubes: these reduce salivary flow and subsequently alter oropharyngeal colonization in tube-fed patients, but gastroesophageal reflux disease is also more prevalent in tube-fed patients and predisposes them to pneumonia (Fig. 11). Increased incidence of oropharyngeal colonization with respiratory pathogens is also caused by impairment in salivary clearance (Palmer et al. 2001). The microbial etiology of AP involves *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* for community-acquired AP and gram-negative aerobic bacilli in nosocomial pneumonia (Palmer et al. 2001). It is worth bearing in mind the relative unimportance of anaerobic bacteria in AP (Palmer et al. 2001). Surprisingly, in the clinical setting, OD and aspiration are not usually considered etiologic factors in older patients with pneumonia (Marik and Kaplan 2003; Almirall et al. 2007).

There are many unanswered questions about the monitoring and treatment of aspiration pneumonia. In an editorial, Martin J. Connolly raised the following points: (a) Should we be instituting a policy of universal screening for dysphagia in older people presenting with pneumonia (or indeed in frail, hospitalized older patients in general)? (b) Should we modify our treatment of pneumonia in older people to "cover" gram-negatives and staphylococci? (c) What evidence is there that mouth colonization by potentially unpleasant bacteria is of any clinical significance? (d) Should we screen for mouth colonization? (e) Can we eradicate such colonization, and if so does this affect the incidence or prevalence of morbidity and/or mortality from lower respiratory tract infection? (f) If eradication attempts are deemed useful and feasible, what methods should we use? (g) What are the possible side effects of such policies and what will be the costs (Connolly 2010)? These and other questions must be answered in the next years if we want to reduce the incidence of this important complication.

3.2 Complications of Malnutrition

Consequences of malnutrition for patients with oropharyngeal dysphagia can be very serious: impaired ventilatory drive and immune function, delayed wound healing, and convalescence from illness and decreased functional status are the main contributors to enhanced morbidity in malnutrition (Norman et al. 2008).

Impaired nutritional status results in impaired ventilatory drive and decreased respiratory muscle function. Malnutrition and protein depletion reduce muscle mass and impair the strength of the respiratory muscles. This leads to decreased vital capacity, increased airflow resistance and residual volume (Arora and Rochester 1982), and lower strength of cough. The weight of the diaphragm is related directly and significantly to body weight and lung function tests have correlated with body mass index and lean mass in sev-

eral patient groups, including those with COPD or cystic fibrosis (Dureuil and Matuszczak 1998). The reduction of contractile force present in starvation-related malnutrition can be reversed completely with nutritional replenishment (Luís 2010). Malnutrition may also influence the clinical outcome of patients with dysphagia by depressing the immune response. Epidemiological observations confirm that infection and malnutrition aggravate each other. However, nutrition does not influence all infections equally (Scrimshaw and Suskind 1976; Chandra 1990; Chandra 1996). For some infections (e.g., pneumonia, bacterial and viral diarrhea, measles, tuberculosis), there is overwhelming evidence that the clinical course and final outcome are negatively affected by nutritional deficiency. For other infections (e.g., viral encephalitis, tetanus), the permissive role of impaired nutritional status is limited. It is now established that nutritional deficiency is commonly associated with impaired immune responses, particularly cell-mediated immunity, phagocyte function, cytokine production, secretory antibody response, antibody affinity, and complement system (Chandra 2002). In fact, malnutrition is the most common cause of immunodeficiency worldwide. Another important fact is age: it is recognized that the immune system in many older people cannot defend against microorganisms, malignant cells, and other "foreign" agents. Ageing is associated with a reduction in many immune responses. Changes in immunity associated with ageing include decreased delayed hypersensitivity, reduced interleukin-2 production, decreased lymphocyte response to mitogens and antigens, low rate of seroconversion, and decreased antibody titer after vaccination. Immune dysfunction as assessed by the prevalence of autoantibodies also increases in older people (Chandra 2002).

4 Treatment

Treatment of dysphagia and malnutrition in older patients varies greatly among centers. This variability can contribute to some controversy on the effect of swallowing therapy in preventing malnutrition and AP. In addition, there are a limited number of studies addressing these—unresolved—questions. A recent review found that there is insufficient data to determine the effectiveness of treatments for dysphagia prevention in older adults (Working Group on Functional Outcome Measures for Clinical Trials 2008). In contrast, other authors found that treatment of dysphagia is cost effective and the use of dysphagia prevention programs correlates with a reduction in AP rates (Mikasa et al. 2016).

4.1 Treatment of Oropharyngeal Dysphagia

The current treatment of patients with OD is based on two basic interventions: (a) adaptation of fluid viscosity and volume that reduce the risk of aspiration (Cook and Kahrilas 1999; Logemann 1995; Clavé et al. 2005b) along with the adaptation of the texture of solids taking into account the masticatory and deglutory capacity of the patient and their caloric-protein needs in order to maintain a correct nutritional status and to avoid aspiration and (b) rehabilitation treatment with the aim of improving the biomechanical deglutory function through postural strategies, sensorial enhancement, neuromuscular praxis, and specific maneuvers. The improvement of oral hygiene and reduction of bacterial colonization are also important elements in the treatment of these patients (Ortega et al. 2013). Following videofluoroscopy, a combination of strategies may be selected to compensate each patient's specific deficiency. Swallow therapy aims at improving the speed, strength, and range of movement of muscles involved in the swallow response and at modifying the mechanics of swallow to improve bolus transfer and avoid or minimize aspiration. It should be remarked that the largest body of literature concerns swallow therapy in older patients after strokes (Cook and Kahrilas 1999). Furthermore, a recent systematic review on the effects of therapy in OD by speech and language therapists indicated that many questions remain about the actual therapeutic effects, even though some positive significant

outcome studies have been published (Speyer et al. 2010). Nutritional and respiratory status should always be monitored in dysphagic patients in order to assess the efficacy of treatments.

1. *Postural strategies, body and head positions.* Verticality and symmetry should be sought during patient's ingestion. Attention must be paid to controlling breathing and muscle tone. Postural strategies are easy to adopt—they cause no fatigue—and allow modification of oropharyngeal and bolus path dimensions. Anterior neck flexion (chin tuck) protects the airway (Bülow et al. 2001; Logemann et al. 1989; Lewin et al. 2001); posterior flexion (head extension or chin raise) facilitates gravitational pharyngeal drainage and improves oral transit velocity; head rotation (head turn maneuver) toward the paralyzed pharyngeal side directs food to the healthy side, increases pharyngeal transit efficacy, and facilitates UES aperture (Robbins et al. 2005; Turley 2009; Nicosia and Robbins 2001) whereas head tilt to the stronger side prior to the swallow directs the bolus down to the stronger side by utilizing the effects of gravity; deglutition in the lateral or supine decubitus protects against aspirating hypopharyngeal residues.
2. *Change in bolus volume and viscosity.* Reductions in bolus volume and enhancement of bolus viscosity significantly improve safety signs, particularly regarding penetration and aspiration in patients with neurogenic dysphagia and in older patients (Clavé et al. 2006; Rofes et al. 2010). Viscosity is a physical property that can be measured and expressed in international system units by the name of Pa.s. The prevalence of penetrations and aspirations is maximal with water and thin fluids (20 mPa.s) and decreases with nectar (270 mPa.s) and pudding (3900 mPa.s) viscosity boluses (Clavé et al. 2006). Multiple studies have shown how thickeners reduce penetrations in the laryngeal vestibule as well as tracheobronchial aspirations (Clavé et al. 2006; Rofes et al. 2010), but adherence to these treatments is very low, between 48 and 56% due to their poor organoleptic characteristics (taste and texture) (Rosenvinge and Starke 2005). A recent review by the European Society for Swallowing Disorders concludes that (a) the use of thickeners increases the risk of dehydration due to the poor palatability of thickened liquids, (b) causes an increase in oral and/or pharyngeal residue and may increase the risk of post-deglutary aspiration, and (c) affects swallowing physiology with an increase in lingual pressure patterns without significant changes in the airway-protective mechanisms which has contradictory effects on oral and pharyngeal transit, hyoid displacement, opening of the upper esophageal sphincter (UES), and bolus velocity; several studies suggest that the therapeutic effect of the thickeners is due to the intrinsic properties of the bolus (Newman et al. 2016).While the review concludes that there is enough evidence to continue recommending the use of thickeners given their proven benefits, it recommends the development of new products to solve the palatability problems that exist nowadays (Newman et al. 2016).
3. ***Specific swallowing maneuvers***. These are maneuvers the patient must learn and perform in an automated way. Each maneuver is specifically directed to compensate a particular biomechanical alteration (Clavé et al. 2005b):
   (a) *Supraglottic and super supraglottic swallow:* This aims at closing the vocal folds before and during deglutition in order to protect the airway from aspiration, and by coughing immediately after the swallow to clear any residue. The difference between these related maneuvers is the degree of effort in the preswallow breath-hold. The super supraglottic swallow requires an effortful breath-hold, whereas the supraglottic swallow requires a breath-hold with no extra effort. It is useful in patients with penetrations or aspirations during the pharyngeal stage or a slow pharyngeal motor pattern.

(b) *Effortful, forceful, or hard swallow:* This aims at increasing the posterior motion of the tongue base during deglutition in order to improve bolus propulsion. It is useful in patients with low bolus propulsion (Clavé et al. 2005b).

(c) *Double deglutition:* This aims at minimizing post-swallow residue before a new inspiration. It is useful in patients with post-swallow residue (Clavé et al. 2005b).

(d) *Mendelsohn* maneuver*:* This enables increased extent and duration of laryngeal elevation and therefore increased duration and amplitude of UES aperture (Clavé et al. 2005b).

4. ***Neuromuscular praxis****:* It aims at improving the physiology of deglutition (the tonicity, sensitivity, and motility of oral structures, particularly the lips and tongue, and pharyngeal structures) (Clavé et al. 2005b). Lingual control and propulsion may be improved by using rehabilitation and biofeedback techniques (Robbins et al. 2005). Improved isometric strength after 2 months of progressive resistance lingual exercises has proved to correspond with spontaneous increased pressure generation during swallowing in stroke patients, thus showing significant improvement in swallowing function and dietary intake (Robbins et al. 2005). Of late, the rehabilitation of hyoid muscles with cervical flexion exercises (Shaker exercise) has been shown to improve hyoid and laryngeal elevation, increase UES aperture, reduce pharyngeal residue, and improve dysphagia symptoms in patients with neurogenic dysphagia (Shaker et al. 2002). The management of patients with impaired UES aperture as a consequence of propulsive deficiencies should be basically oriented to increasing bolus propulsion force and to rehabilitating the extrinsic mechanisms of UES aperture, particularly the activity of hyoid muscles (Shaker et al. 2002). The tongue-holding or Masako maneuver is presumed to compensate for the reduction in tongue base-pharyngeal wall contact in swallowing, thus contributing to an increased anterior movement of the posterior pharyngeal wall during swallowing. However, the use of the maneuver per se, which inhibits posterior retraction of the base of tongue, results in increased pharyngeal residue after swallow.

5. ***Oral sensory strategies***, useful in patients with apraxia or alterations in oral sensitivity, include mechanical stimulation of the tongue, bolus modifications (volume, temperature, and taste), and mechanical stimulation of the pharyngeal pillars. These techniques are based on the fact that sensory stimuli, such as piperine (main component of *Piper nigrum*) (Okumura et al. 2010) or capsaicin (a component of several species of capsicum sp.) (Ebihara et al. 2005), can reduce the time of the swallowing response in older patients with OD and improve both the speed and the amplitude of the peristalsis of the esophageal body (Gonzalez et al. 1998). Other TRPV1 agonists (Logemann et al. 1995) as well as high temperatures (Watando et al. 2004) have also been shown to improve swallowing in patients with OD. Results from our group show how adding capsaicin to food boluses shortened laryngeal vestibule closure and UES opening times and improved hyoid movement, improving safety by decreasing the number of penetration to 50% and increasing effectiveness (Rofes et al. 2012). Likewise, adding piperine to food bolus reduced the prevalence of unsafe swallowing by decreasing the severity of aspiration and penetration and shortening the time of laryngeal vestibule closure (Rofes et al. 2014b). In our studies, we found a significant therapeutic effect with 150 μM for piperine (maximal effect at 1 mM) (Rofes et al. 2014b) and 150 μM for natural capsaicinoids (Rofes et al. 2012). Both molecules may be pharmacological therapeutic alternatives for patients with OD. Our group has recently shown how TRPV1/A1 receptors are expressed in the human oropharynx, confirming that these receptors may be future therapeutic targets for the development of pharmacological

treatments for patients with OD (Alvarez-Berdugo et al. 2016).

6. ***Neuromuscular electrostimulation (NMES)***: Neuromuscular electrical stimulation (NMES) stimulates nerves and swallowing muscles with the aim of improving oropharyngeal motor response (OMR). To perform NMES, the innervation of the musculature must be intact and produce a muscular contraction on stimulation. Its effectiveness and safety are still under discussion as studies have inconsistent results (Cabib et al. 2016). However, studies have shown that stimulation of the sensory areas innervated by the glossopharyngeal nerve (IX) and the vagus (X) nerve improve swallowing (Kitagawa et al. 2002, 2009). The electrical stimulation can be applied in two ways, transcutaneously, where electrodes are placed in specific positions in the patient's neck and intrapharyngeal, applied by a tube inserted in the pharynx. In patients with neurogenic dysphagia (post-stroke), electrical stimulation of the suprahyoid musculature during swallowing can produce a laryngeal rise which protects against aspirations (Burnett et al. 2005), and is related to better clinical prognosis, with improved nutritional status and reduced hospital stay during the acute episode (Jayasekeran et al. 2010). Rofes et al. have observed how transcutaneous sensory and motor stimulation in patients with a previous stroke reduced unsafe swallows, decreased laryngeal vestibule closure time and hyoid extension and motor stimulation, reduced residue at the level of the laryngeal vestibule, decreased the opening time of the UES, and increased the force of propulsion of the bolus (Rofes et al. 2013). In a study conducted by our group on subacute stroke patients with OD, intrapharyngeal electrostimulation showed no effect on OD, probably due to the use of low doses (Bath et al. 2016), although studies with doses of 10 min/days, 5 Hz for 3 days, had observed an increase in safety, reduced aspiration, and improved nutritional status with decreased hospital stay after 2 weeks of intervention (Jayasekeran et al. 2010).
7. ***Central stimulation*** is based on inducing cortical neuroplasticity by central stimulation of the pharyngeal motor cortex based on the principles of electromagnetism. The main noninvasive central stimulation techniques are repetitive transcranial magnetic stimulation (rTMS) and direct transcranial stimulation (tDCS). High frequencies of rTMS (>1 Hz) increase cortical excitability, while low frequencies (<1 Hz) decrease it (Cabib et al. 2016). The first studies carried out on patients with OD secondary to stroke have positive results regarding the improvement of the RMOF (Kumar et al. 2011; Michou et al. 2013; Momosaki et al. 2014; Shigematsu et al. 2013). Although the current targets of central stimulation focus on the motor cortex, neuroimaging studies show strong activation of cortical sensorimotor areas along with other areas during swallowing that could be focal points for treatment of OD (Cabib et al. 2016).
8. ***Pharmacology of swallow response***. Several drugs, most of them centrally acting, can elicit OD in older people. Neural activity in the nucleus tractus solitarius (NTS) is inhibited by γ-aminobutyric acid (GABA) (Wang and Bieger 1991; Hockman et al. 1996), and benzodiazepine administration can potentiate GABA system at CNS and cause dysphagia (Dantas and Nobre Souza 1997). Ethanol also acts in the CNS binding to the $GABA_A$ receptor and alcohol ingestion can predispose to oropharyngeal aspiration (Dua et al. 2009). Neuroleptics are widely used in the older demented population for control of aggressive or disruptive behavior, and dopamine antagonists like phenothiazines and haloperidol can impair swallow function. Despite the suspected effect on swallowing function of drugs that have their therapeutic targets in the central nervous system, current scientific evidence is scarce and relies largely on clinical cases (Bieger and Neuhuber 2006; Sokoloff and Pavlakovic 1997; Stewart 2003). A recent study carried out by our

group on older patients admitted to an acute geriatric unit showed a higher prevalence of neuroleptic drugs and antidepressants, with a negative effect on the swallowing function, without significant association with benzodiazepines. With regard to antidepressant drugs, those with anticholinergic action increased the risk of xerostomia, worsening the transport of the bolus. With regard to neuroleptic drugs, an increased risk of OD was observed but this was probably also influenced by other factors such as age, functional status, or underlying pathologies (Palomera et al. 2016). Studies using pharmacological stimulants also show some promising positive effects. Several types of pharmacological and mechanical stimulation increase the concentration of substance P (SP) in saliva and improve the swallowing reflex and cough-reflex sensitivity. The increase in serum SP with volatile black pepper oil or capsaicin may improve the swallow response (Ebihara et al. 2005; Ebihara et al. 2006). Capsaicin and piperine (active substance from black pepper) act as transient receptor potential channel vanilloid 1 (TRPV1) agonists. TRPV1 is widely expressed on sensory neurons innervating pharynx and larynx, projecting to NTS and co-localizes with SP (Hamamoto et al. 2009). Other stimulants of TRPV1, like heat and acid, have also been reported to improve swallowing (Logemann et al. 1995; Watando et al. 2004; Hamdy et al. 2003). Moreover, intervention with an angiotensin-converting enzyme inhibitor also resulted in an increase in serum SP, and reduced the incidence of AP (Nakayama et al. 1998). Use of a dopamine agonist such as amantadine and a folic acid supplement known to activate dopaminergic neurons also prevented AP (Nakagawa et al. 1999). The development of physical or drug-based strategies to accelerate the swallow response is a relevant field of research for the management of neurogenic dysphagia and ageing-associated dysphagia.

9. ***Surgical/drug-based management of UES disorders***: Identifying an obstructive pattern at the UES allows patient management using a surgical cricopharyngeal section (Shaw et al. 1996) or an injection of botulin toxin (Ravich 2001). Impaired neural UES relaxation observed in spastic neurological diseases such as Parkinson disease or brain injury is characterized by delayed or absent swallow response, short hyoid motion, weak bolus propulsion, and reduced or even absent neuromuscular relaxation and reduced sphincter compliance on manometry (Williams et al. 2002). Treatment must combine treatment of neurogenic dysphagia and improvement of neuromuscular relaxation of the sphincter. Efficacy of cricopharyngeal myotomy in patients with impaired swallow response is fair to poor and injection of botox in the sphincter could be a therapeutic alternative for these patients. Patients with impaired UES opening associated with Zenker's diverticulum or isolated cricopharyngeal bars show normal swallow response, wide hyoid motion, and strong bolus propulsion and reduced sphincter compliance caused by sphincter fibrosis (Kuhn and Belafsky 2013). Treatment of this group of patients is surgical and combines cricopharyngeal myotomy and resection of the diverticulum. Surgical results in older patients with Zenker's diverticulum and preserved swallow response are excellent (Kuhn and Belafsky 2013).
10. ***Percutaneous endoscopic gastrostomy***: Videofluoroscopy will help in *treatment selection* depending upon the severity of efficacy or safety impairment in each patient: (a) patients with mild efficacy alterations and correct safety may have a family-supervised restriction-free diet; (b) in patients with moderate alterations, dietary changes will be introduced aiming at decreasing the volume and increasing the viscosity of the alimentary bolus; (c) patients with severe alterations will require additional strategies based upon increased viscosity and introduction of postural techniques, active maneuvers, and oral sensorial enhancement; and (d) there is a group of patients with alterations so severe

that they cannot be treated despite using rehabilitation techniques; in these patients, VFS objectively demonstrates the inability of the oral route and the need to perform a percutaneous endoscopic gastrostomy (PEG). However, there is little evidence that nonoral feeding reduces the risk of aspiration (Cook and Kahrilas 1999). Even though no absolute criteria exist, a number of dysphagia teams have indicated gastrostomy in (a) patients with severe alterations of efficacy during the oral or pharyngeal stages, or with malnutrition; (b) patients with safety alterations during the pharyngeal stage that do not respond to rehabilitation; and (c) patients with significant silent aspirations, particularly in neurodegenerative conditions. For long-term nutritional support, PEG should be preferred to nasogastric tubes since it is associated with less treatment failure and better nutritional status, and may also be more convenient for the copatient (Löser et al. 2005). In patients with severe neurological dysphagia, tube feeding has to be initiated as early as possible (Finestone et al. 1995). For most patients requiring gastrostomy, a small amount of food may still be safely administered through the oral route (Löser et al. 2005). Figure 12 presents an algorithm of indication of PEG in patients with OD and impaired safety of swallow.

4.2 Treatment of Malnutrition

A recent resolution of the Council of Europe on food and nutritional care in hospitals claimed that undernutrition among hospital patients leads to extended hospital stays, prolonged rehabilitation, diminished quality of life, and unnecessary healthcare costs, and identified functional OD as a major contributor to malnutrition (Milne et al. 2009). Robinson et al. showed that patients with impaired nutritional status on hospital admission had 30% longer hospital stay (Robinson et al. 1987) and this was associated with a doubling of the costs, even though the patients had the same disease-related group (DRG) and therefore the same reimbursement. A recent study from South America reported an increase of treatment costs by 300% (Correia and Waitzberg 2003). Trials have also showed that the prevalence of malnutrition can be reduced by proper nutritional care (O'Flynn et al. 2005) and that nutritional therapy in malnourished patients resulted in a significant reduction of length of stay by an average of approximately 2.5 days and in treatment costs (Kruizenga et al. 2005). Recommendations from

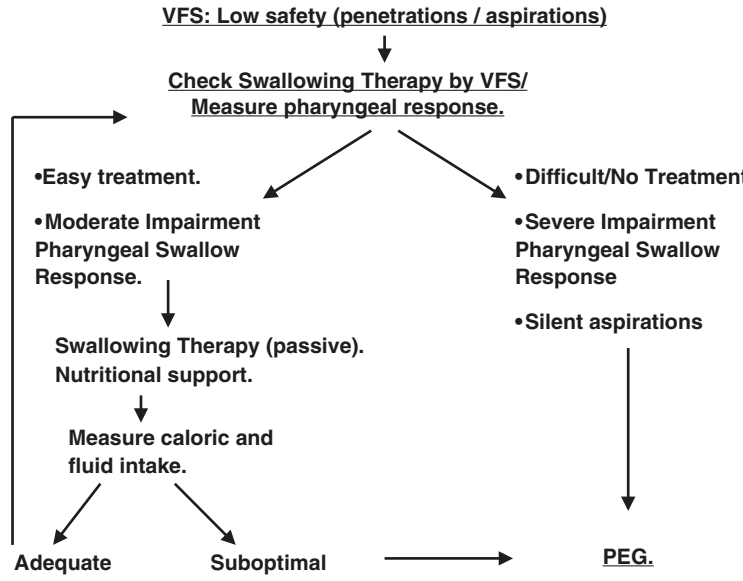

Fig. 12 Algorithm of indication of PEG in patients with oropharyngeal dysphagia and impaired safety of swallow

this resolution (Milne et al. 2006) which are related to dysphagia include (a) the development of dietary management at national levels as well as national descriptors for texture modification, (b) documentation and assessment of food intake, (c) detailed food service contracts to include texture-modified menus, (d) meal serving system adjusted to patients, and (e) informing and involving patients/families in the process by giving them help and guidance in ordering and consuming food. If a patient is at nutritional risk or malnourished, nutritional counselling will be given to improve oral feeding. This is the first nutritional intervention previous to any nutritional support. In some circumstances, nutritional counselling is not enough to maintain or recover proper nutritional status, and oral nutritional supplements (ONS) are indicated. Milne (Milne et al. 2006) reviewed 55 randomized control trials that studied the clinical and nutritional benefits of ONS in older patients on hospital admission, at home, and in nursing homes. The authors concluded that ONS can improve nutritional status and reduce morbidity and mortality in malnourished patients during hospital admission. The scientific evidence does not support ordinary supplementation in older people at home or older well-nourished patients in any clinical setting (hospital, home, or nursing home). However, in patients with stroke and dysphagia, the FOOD study (Dennis et al. 2006) evaluated the effect of systematically adding an oral supplement to the hospital diet. These data did not support indiscriminate use of ONS in patients with stroke and it must be prescribed only in malnourished patients on admission or those in whom nutritional status was impaired.

The usual diet of patients with OD must be adapted to the patient's intake and the severity of the swallow disorder. The texture of traditional dishes can be modified into purees, creams, or puddings or special adapted foods offered by the industry can be used. Various dietitian and speech therapist societies have developed specific nomenclatures to define the characteristics of the different textures of solid food and the same for liquids that can be used in the diet of patients with dysphagia according to the severity of swallow (Tables 1 and 2) (Irish Nutrition and Dieteic Institute 2009; The British Dietetic Association et al. 2011; Australian 2007; Risks 2007). Currently there is an attempt to standardize the nomenclature between the different scientific organizations (Cichero et al. 2013).

Food plays a very important role in preventing malnutrition and dehydration in patients with dysphagia. When designing the diet, the recommendations for a balanced diet should be followed and, if necessary, be adapted to the specific therapeutic prescriptions, taking care that all the alimentary groups are provided in the recommended rations and qualitatively and quantitatively sufficient. The presentation should be appetizing, combining colors in an attractive way and adapting to the needs of older people. One of the authors of this manuscript has designed a nutritional intervention based on the traditional Mediterranean diet specifically for the nutritional treatment of the older population with OD that involves a triple adaptation: (a) caloric-proteic based on the nutritional status of the patient; (b) textural according to the descriptors proposed by the British Dietetic Association; and (c) palatable according to the characteristics of the Mediterranean diet (Gallegos et al. 2016).

4.3 Other Treatments: Oral Hygiene

One of the main complications of patients with OD is respiratory infection. Multiple risk factors related to oral health, such as the presence of dental cavities, the number of functional dental pieces, presence of periodontal disease, and dental plaque, have been associated with the appearance, severity, and mortality of AP in older patients (Awano et al. 2008; Terpenning et al. 2001). The study of the microbiota composition and colonization by respiratory pathogens of the oropharyngeal and nasal cavities using molecular biology techniques in older people with OD compared to a control group shows that older people with OD have high oropharyngeal colonization by respiratory pathogens (*S. pneumoniae*, *S. aureus, P. aeruginosa*, *H. influenzae*, and *E. coli*) (91% vs.

Table 1 International terminology for thickened liquids (Cichero et al. 2013)

Country	< "Water-like"				"Pudding-like" >
USA (NDD)[45]	Thin (1-50 cP[a])		Nectar-Like (51-350 cP[a])	Honey-like (351-1750 cP[a])	Spoon-thick (>1750cP[a])
United Kingdom[44]	Thin	Naturally thick fluid	Thickened fluid – stage 1	Thickened fluid - stage 2	Thickened fluid – Stage 3
Australia[6]	Regular	-	Level 150 – Mildly thick	Level 400 – moderately thick	Level 900 – Extremely thick
Ireland[40]	Regular	Grade 1 – Very mildly thick	Grade 2 – Mildly thick	Grade 3 – Moderately thick	Grade 4 – Extremely thick
Japan (JSDR; scheme)[41]	Less mildly thick (< 50 mPa.s[a])	Mildly thick (50-150 mPa.s[a])	Moderately thick (150-300 mPa.s[a])	Extremely thick (300-500 mPa.s[a])	Over Extremely thick (> 500 mPa.s[a])
Canada	Regular/ Thin/ Clear		Nectar / Stage 1 / Level 1/ >250cP / 51-350 cP	Honey / Stage 2 / Level 2/ > 800 cP / 351-1750cP / Default Thick	Pudding / Spoon thick / Stage 3 / level 3 / > 2000 cP / > 1750 cP
Denmark[46]	Normal	Chocolate milk	Syrup	Jelly	
Spain	Thin			Medium	Full protection/thick/pudding
Netherlands	Thin		'Thickened'		Pudding-like
Brazil	Normal or thin	Thicker liquid		Nectar or Honey	Paste or Creamy (Homogenous or Heterogenous)
Sweden[43]	Liquids	Thickened liquids			

Table 2 International terminology for texture-modified food (Cichero et al. 2013)

Country	< Regular food					Extensively texture modified food >
USA (NDD)[45]	Regular	Dysphagia Advanced (bite sized, < 2.5cm)	Dysphagia mechanically altered (0.6cm)	Dysphagia pureed		
United Kingdom[44]		Texture E – Fork mashable dysphagia diet (1.5cm)	Texture D – Pre-mashed dysphagia diet (0.2cm)	Texture C – Thick Puree Dysphagia Diet	Texture B – Thin Puree dysphagia diet	
Australia[6]	Regular	Texture A – Soft (1.5cm)	Texture B- Minced + Moist (0.5cm)	Texture C – Smooth pureed		
Ireland[40]		Texture A - Soft	Texture B - Minced and Moist	Texture C – Smooth Pureed	Texture D - Liquidised	
Japan (Hardness, cohesiveness and adhesiveness ranges available)[41]	Level 5 Normal diet	Level 4 Soft food	Level 3 (Dysphagia Diet) Paste containing meat/fish	Level 2 (Dysphagia Diet) Jelly food with protein [Rough jelly surface]	Level 1 (Dysphagia Diet) Smooth Jelly food with protein, except for meat and fish	Level 0 (Test Food) Smooth Jelly food without protein
Canada	Easy to chew or Regular / General / Dysphagia General	Chopped or diced / Dysphagia Soft/ Dysphagia soft + minced / stage 3 / Level 3 / Dental soft / Easy to chew with minced meat / cut up	Advanced Minced / Minced with finger foods / Diced / Chopped / Soft minced	Minced / Mashed / Modified minced / Dysphagia Fully totally minced / Level 2 mechanical / minced moist / minced meat modified vegetables	Pureed / Thin Pureed / Dysphagia Pureed / Stage 1 / Level 1/ Semi-pureed	Blenderized / liquidized
Denmark[46]	Normal	Soft		Puree		
Spain	Normal	Easy mastication		Puree		
Netherlands	Normal	Normal with soft meat/fish/chicken – no particulates (e.g peas, rice)	Mashed	Puree		
Brazil	Solid					Soft Solid or Puree
Sweden[43]	Regular or Cut	Coarse Paté	Timbales	Jellied products	High viscosity fluids	Low viscosity fluids

67% control; $p < 0.05$), a higher microbial load in the oral cavity than in the nasal cavity ($p < 0.0001$), and a distinct distribution of the bacterial population between both locations. These results show that these patients are at high risk of contracting respiratory infections and AP (Ortega et al.

2015). Recent studies in our group also show a higher incidence of periodontitis, greater accumulation of dental plaque and calculus (66.6% toothed patients), and a high prevalence of periodontitis (93.3%) and cavities (53.3%) compared to patients without OD (Ortega et al. 2014a). Strategies based on improved oral hygiene significantly reduce the incidence of pneumonia (Scannapieco et al. 2003).

These strategies consist of dental brushing after each meal or a dental prosthesis cleaning once a day and dental hygiene on a regular basis, along with chlorhexidine mouthwash without ethanol for no more than 15 days and phenolic derivatives for maintenance (Van et al. 2013). Studies that evaluated the outcome of the intervention showed a decrease in pneumonia mortality in patients (Sjögren et al. 2008).

4.4 Combination of Therapeutic Strategies

The best current clinical practice is to select the best treatment based on the efficacy and safety alterations identified during clinical exploration and/or videofluoroscopic study: (a) patients with minor alterations in efficacy and correct safety could follow a free diet supervised by their family or caregivers; (b) patients with a moderate alteration should introduce dietary changes, decreasing the volume and increasing the viscosity of the alimentary bolus; (c) patients with a severe alteration will also require the introduction of postural techniques, active maneuvers, and oral sensorial increase; and (d) for patients with a severe alteration that cannot be treated with rehabilitation techniques and where the oral route is no longer possible, a percutaneous endoscopic gastrostomy will be necessary (Cook and Kahrilas 1999; Clavé et al. 2004, 2005a; Mazzini et al. 1995).

Changes in volume and viscosity of the bolus are the most effective therapeutic strategy in terms of efficacy, and which do not produce fatigue, require cognitive integrity, or involve learning (Clavé et al. 2006). Most patients need treatment to be continued after hospital discharge to avoid nutritional and respiratory complications as well as dietary strategies to concentrate their caloric and protein requirements into the small volume of food they can ingest.

A study was performed by our group on 62 older patients (≥70 years old) discharged from the hospital following an acute process and diagnosed with OD during admission. The study measured patient prognosis and nutritional status after a nutritional intervention (liquid and solid adaptation according to severity of swallowing impairment) and recommendations for oral hygiene in all patients. Compared with a control group, this strategy was shown to decrease hospital readmission for respiratory complications with an increase in the surveillance at the end of the follow-up (Martín et al. 2016).

Conclusions

Identification of functional OD as a major neurological and geriatric syndrome will cause many changes in the provision of medical and social services in the near future. Education of health professionals in diagnosis and treatment of dysphagia and its complications, early diagnosis, development of specific complementary explorations in the clinical setting, improvement in therapeutic strategies to avoid aspirations and malnutrition, and research into its pathophysiology are the cornerstones to allow maximal recovery potential for older patients with functional OD. In many hospitals there is a big discrepancy between the high prevalence, morbidity, mortality, and costs caused by nutritional and respiratory complications of functional OD and the restricted availability of human and material resources dedicated to dysphagic patients. Dysphagia with oropharyngeal aspiration is not usually considered an etiologic factor in older patients with community-acquired pneumonia (Cabib et al. 2016; Kitagawa et al. 2002) or with malnutrition (Kuroda and Kuroda 2012).

Therefore, diagnosis and management of OD need a **multidisciplinary approach**. A *dysphagia multidisciplinary team* should include several professional domains: nurses, speech-swallow therapists, gastroenterologists, ENT specialists, neurologists, surgeons,

rehabilitation physicians, dietitians, radiologists, geriatricians, etc. The goals of a multidisciplinary dysphagia team include (a) early identification of older patients with dysphagia; (b) diagnosis of any medical or surgical etiology for dysphagia that may respond to specific treatment; (c) characterization of specific biomechanical events responsible for functional dysphagia in each patient; and (d) design of a set of therapeutic strategies to provide patients with safe and effective deglutition, or provision of an alternative route to oral feeding based on objective and reproducible data (WHO n.d.; Kuroda and Kuroda 2012). The involvement of patient's family in the diagnostic and therapeutic process is of capital importance.

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Dehydration in Dysphagia

Zeno Stanga and Emilie Aubry

Contents

Abstract

Dehydration—loss of water from intracellular space—is a major problem, especially in the elderly. In patients with dysphagia, this imbalance of body fluids is often accelerated due to restricted fluid intake, leading to increased medical costs, morbidity, and mortality in hospitalized older adults. As a result, the hydration status of patients with swallowing difficulties must be closely monitored and rapidly corrected.

In the following, dehydration and fluid balance, as well as their pathophysiology and disorders, will be discussed in detail. Furthermore, risk factors for and signs and symptoms of dehydration in the elderly in general and in dysphagic patients in particular will be outlined. In addition, management of dehydration with oral, enteral, and parenteral replacement of fluids will be explained. Parenteral hypodermoclysis, for example, has been shown to be as safe and effective as intravenous replacement, with a similar or better adverse event profile in a number of systematic reviews.

1 Learning Points

- To be aware of dysphagia-related dehydration.
- To be familiar with the pathophysiology of dehydration.
- To recognize signs, symptoms, and laboratory values of dehydration.
- To know treatment strategies of dehydration.

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2 Introduction

Fluid balance and electrolytes are vital to all life and are involved in countless regulatory mechanisms such as cell shape, body temperature, signal transduction, and transport systems. Dehydration is a large problem among elderly people in long-term care facilities, in acute care hospitals, as well as in the community. (Allison and Lobo 2004) Dysphagia—a frequent consequence of neuromuscular or obstructive disease—is directly related to dehydration (Vivanti et al. 2009). An assessment of total water intake from food, beverages, and enteral and parenteral sources among dysphagic adult patients receiving thickened fluids showed that none of the patients achieved their calculated fluid requirements unless they received enteral or parenteral fluids (Vivanti et al. 2009). Therefore, it is important to be aware of the risk of dehydration, especially in patients with dysphagia. Special attention should be paid to signs and symptoms of dehydration in such patients. Treatment should be initialized promptly because consequences of dehydration can be severe since increased medical costs, morbidity, and mortality among hospitalized older adults are all associated with dehydration (Warren et al. 1994; Cowen et al. 2013).

3 Definition of Dehydration

Different suggestions for the definition of dehydration exist. Clinical observation based on a combination of history, physical assessment, and laboratory tests is the best approach to the diagnosis of dehydration (Armstrong et al. 2016). From a clinical point of view, the rapid weight loss of greater than 3% of body weight has been proposed (Weinberg and Minaker 1995). From a pathophysiological standpoint however, dehydration is a loss of water which results in a relative deficit of body water in relation to sodium. With consequently increased sodium values, plasma osmolality increases, resulting in a loss of intracellular volume, often referred as hypertonic dehydration or hypovolemic hypernatremia. Although the terms "hypotonic dehydration" and "isotonic dehydration" are widely used, pathophysiologically they rather characterize a condition of volume depletion, indicated as loss of sodium from the extracellular volume, than dehydration. This distinction is important for therapeutic considerations (Armstrong et al. 2016).

4 Prevalence of Dehydration

The true prevalence of dehydration is difficult to assess. It depends on the indicators used to define dehydration. It can be up to 60% among community-dwelling adults when defined as either plasma sodium ≥145 mmol/L, blood urea nitrogen (BUN) to creatinine ratio >20, plasma osmolality >295 mOsm/kg, or hypotonic hypovolemia (Stookey et al. 2005). Another study found that 48% of older adults visiting an emergency department had laboratory values indicating dehydration. Physicians documented assessment for signs of dehydration in only 26% of them (Bennett et al. 2004). In older adults, dehydration is one of the ten most frequent diagnoses for hospitalization (Xiao et al. 2004) and dehydration has been reported to be the most common fluid and electrolyte imbalance in older adults (Martin and Larsen 1994). In an American study from Warren et al., dehydration was diagnosed in 6.7% of hospitalized patients age 65 and over and 1.4% had dehydration as the principal diagnosis (Warren et al. 1994).

5 Risk Factors

5.1 Impact of Dysphagia

Dysphagia has been shown to be directly related to dehydration (Vivanti et al. 2009). In one study, daily fluid intake of thickened liquids was only 22% of the recommended amount of 1500 mL/day (Whelan 2001).

5.2 Other Risk Factors

The sensitivity to antidiuretic hormone (ADH) decreases and the sense of thirst appears to diminish in older adults (Phillips et al. 1993). Several studies showed that otherwise healthy older people maintain adequate hydration status under normal conditions. However, physical or emotional illness, surgery, trauma or higher physiologic demands increase the risk of dehydration (Luckey and Parsa 2003).

A study following nursing home residents for 6 months found that 31% were dehydrated during that period and 1/3 of those had prior episodes of dehydration (Mentes 2006). Dehydration in nursing homes has been linked to inadequately trained nurses. Residents with moderate to severe dysphagia, severe cognitive and functional impairment, aphasia or inability to speak the official country language, and a lack of family or friends to assist them at mealtime are at great risk for dehydration (Kayser-Jones et al. 1999).

Female gender and polypharmacy has also been shown to increase the risk of dehydration in nursing home residents (Lavizzo-Mourey et al. 1988). Dehydration occurs more frequently in older adults with diabetes, cancer, cardiac disease, or acute infections (Xiao et al. 2004; Warren et al. 1994) or especially in patients having multiple comorbidities (Bennett et al. 2004; Lavizzo-Mourey et al. 1988).

6 Pathophysiology of Dehydration

6.1 Fluid Compartments

Figure 1 illustrates water distribution in the body. Depending on age and gender, about 50–60% of body weight consists of water. Since women generally have a higher percentage of body fat and a smaller muscle mass than men, they have somewhat less body fluid. Two different compartments are functionally separated by cell membranes. About 2/3 of body water or 40% of total body

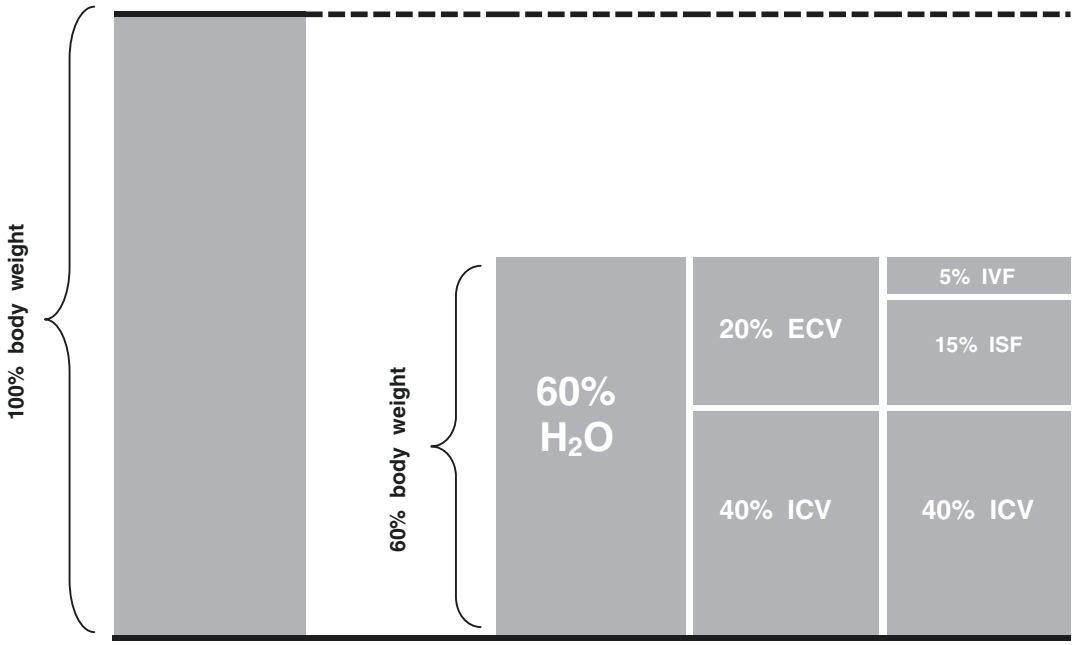

Fig. 1 Fluids compartments. H_2O water, *ECV* extracellular volume, *ICV* intracellular volume, *IVF* intravascular fluid, *ISF* interstitial fluid

weight is found in the intracellular space, the remaining 1/3 of body water, counting 20% of total body weight, in the extracellular space (i.e., for an adult weighing 70 kg: about 60% ≈ 42 L is water; the extracellular volume is about 14 L and the intracellular volume is about 28 L).

Extracellular water can further be subdivided into extravascular and intravascular fluid, functionally separated by the capillary wall. Extravascular fluid counts for approximately 3/4 of extracellular fluid or 15% of total body weight. Only 1/12 of total body water is found intravascular, counting 5% of total body weight.

The extravascular component again can be subdivided into the interstitial fluids, the transcellular fluids, such as water in the gastrointestinal tract, and fluids in cartilages, connective tissues, and bones.

6.2 External Fluid Balance

The skin, the respiratory tract, the endocrine system, the kidneys, and the gastrointestinal tract are involved in fluid balance. The average total fluid intake and output is about 2600 mL/day (30–40 mL/kg body weight). Liquids account for about 1500 mL of daily input; 800 mL come from liquids within solid food and the remaining 300 mL from oxidation water (Fig. 2).

The main water output of 1500 mL/day passes via the kidneys. A considerable amount is lost via the skin (600 mL) and the lungs (400 mL), together also referred to as insensible perspiration (Fig. 2). Only 100–150 mL/day is lost with the feces.

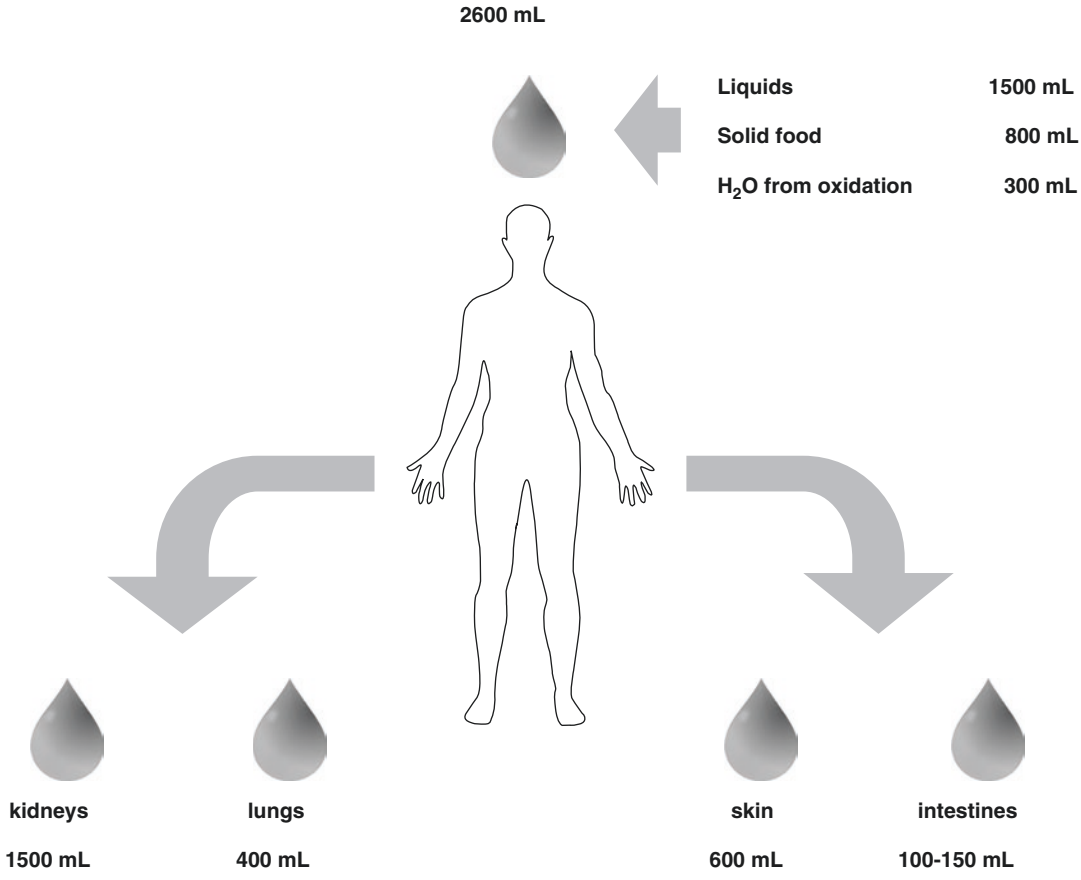

Fig. 2 Fluid balance: sites involved in fluid loss

To understand the mechanisms of fluid balance it is important to understand that maintenance of effective arterial blood volume is primarily related to the regulation of sodium balance. In contrast, maintenance of osmolality is related to the regulation of water balance. Maintenance of volume always overrides maintenance of osmolality. The ability of the kidney to excrete urine with an osmolality different from plasma plays a central role in the regulation of water balance. The kidney can conserve sodium very efficiently but its capacity to excrete excess sodium is limited.

6.3 Internal Fluid Balance

The distribution of fluid between the different compartments is kept constant within close limits. The membranes separating the two main compartments, the intracellular and extracellular space are semipermeable, meaning that they allow only selected solutes to pass through. Water, however, can freely pass. The membranes with their Na^+-K^+-ATPase pump therefore maintain the different solute composition within each compartment.

Osmolality is defined as the amount of solute particles per kilogram of solution. Plasma osmolality can directly be measured or calculated as 2× serum sodium [mmol/L] + BUN [mg/dL]/2.8 + plasma glucose [mg/dL]/18. It normally ranges from 275 to 290 mOsm/kg.

Tonicity is determined by those solutes which determine the transcellular distribution of water, called effective osmoles. Urea, for example, is an inactive osmole since it can pass freely through the membrane and its elevation in serum does not lead to movement of water out of the cell, still urea contributes to plasma osmolality.

Sodium, with normal serum concentrations of 135–145 mmol/L, is the major extracellular cation determining plasma osmolality, whereas potassium is the key determinant for intracellular osmolality (Table 1). Only 2% of the body's potassium is found in the extracellular fluid; the normal serum concentration range is from 3.5 to 4.5 mmol/L. The intracellular concentration is much higher with approximately 150 mmol/L (Table 1). Electroneutrality is granted by the anions chloride and bicarbonate as well as proteins.

Osmotic forces are the primary determinant of water distribution in the body. A change in osmolality in one compartment makes the fluid hypertonic compared to the other compartments and triggers water movement across the cell membrane from lower to higher osmolality. Since water can freely cross the cell membrane, the osmolality of the intracellular and the extracellular space is the same.

Table 1 Electrolyte balance

Electrolyte	Plasma (mmol/L)	ECV (mmol/L)	ICV (mmol/L)
Na^+	142	144	10
K^+	4	4	150
Ca^{2+}	2.5	2.5	1.5
Cl^-	102	114	2
Mg^{2+}	1.0	0.5	13
PO_4^{2-}	1.0	1.0	57
HCO_3^-	26	30	8

ECV extracellular volume, *ICV* intracellular volume

6.4 Disorders of Fluid Balance

6.4.1 Isotonic and Hypotonic Dehydration

"Isotonic dehydration" is a somewhat confusing term, in fact referring to a state of volume depletion rather than dehydration. It occurs when there is a balanced loss of solutes and water. The extracellular fluid volume decreases, when severe isotonic dehydration occurs, leading to tissue hypoperfusion, whereas the plasma osmolality and consequently the intracellular fluid volume remains normal (Fig. 3).

It happens during vomiting, diarrhea, fistulae, diuretics, third space sequestration, burns, sedative and carbon monoxide intoxication, sunstroke, blood loss, or complete fast. Volume depletion results in a decreased blood flow to the kidneys and triggers the renin-angiotensin-

Fig. 3 Disorders of water balance: isotonic dehydration

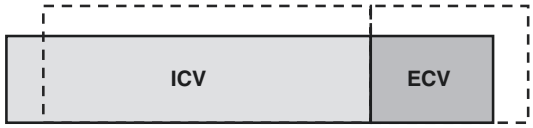

Fig. 4 Disorders of water balance: hypotonic dehydration

aldosterone system which results in increased sodium and water reabsorption. ADH secretion triggers water retention in order to correct volume depletion.

Hypotonic dehydration occurs when sodium is lost at a greater rate than water, resulting in serum osmolality less than 270 mOsm/kg and serum sodium concentration of less than 135 mmol/L. The low serum osmolality results in a reduction of the extracellular space (Fig. 4). It can occur when salt and fluid losses are partly replaced by hypotonic fluids.

These forms of dehydration should be treated with isotonic fluids.

6.4.2 Hypertonic Dehydration

Pathophysiologically, "hypertonic dehydration" is the literal form of dehydration. It results when water losses exceed those of sodium. Serum sodium concentrations exceed ≥150 mmol/L and BUN to creatinine ratio is ≥20. The elevation in serum sodium concentration and therefore osmolality pulls water out of the cells into the extracellular fluid (Fig. 5).

Acute hypernatremia causes water movement out of the brain. The decrease in brain volume can cause rupture of veins, causing intracerebral or subarachnoidal hemorrhage.

Fig. 5 Disorders of water balance: hypertonic dehydration

As a compensatory mechanism, the cells of the brain begin to accumulate solutes, initially sodium and potassium, in order to pull water back to the cell and restore cell volume. Later, the accumulation of osmolytes occurs. These consist primarily of myoinositol and the amino acids glutamine and glutamate (Heilig et al. 1989; Lien et al. 1990).

Hypertonic dehydration occurs, as in dysphagia, due to decreased water intake or during either renal or extrarenal excessive water losses. Renal water losses occur with loop diuretics or osmotic diuretics, in postobstructive disease, in polyuric phase of acute renal failure, or in renal or central diabetes insipidus. Extrarenal water losses occur transcutaneously by sweating, as in the condition of fever, burns, or via the respiratory tract in hyperventilation. The increasing plasma osmolality triggers ADH release and thirst (Fig. 6). But also nonosmolar, volume-dependent receptors exist which trigger ADH secretion. Secretion of ADH from the supraoptic and paraventricular nuclei of the thalamus results in decreased excretion of free water. In humans the threshold for ADH secretion is 280–285 mOsm/kg. Above this threshold there is a relatively linear rise of ADH secretion with rising plasma osmolality (Fig. 7). The trigger value for the sense of thirst, which is the major protective mechanism against hypernatremia, is somewhat higher than for ADH secretion (Robertson 1987). This form of dehydration must be treated with hypotonic fluids (see Sect. 8.3.2).

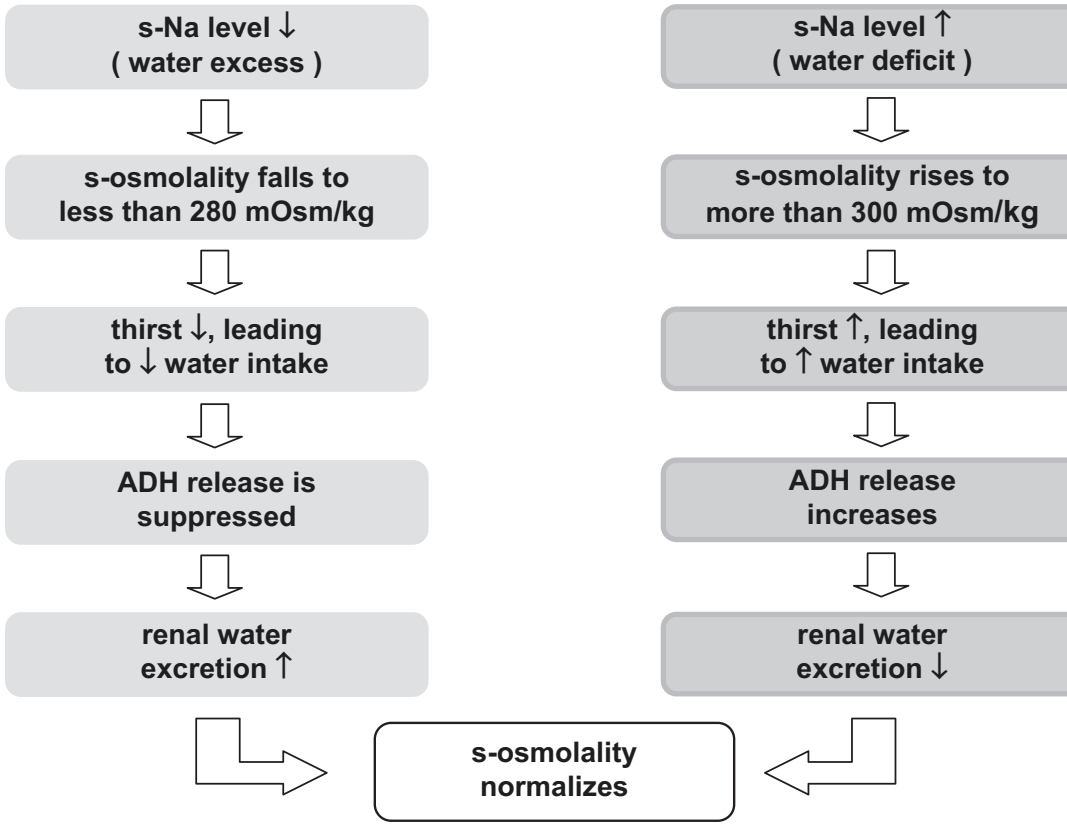

Fig. 6 Compensatory mechanism of the regulation of sodium and water

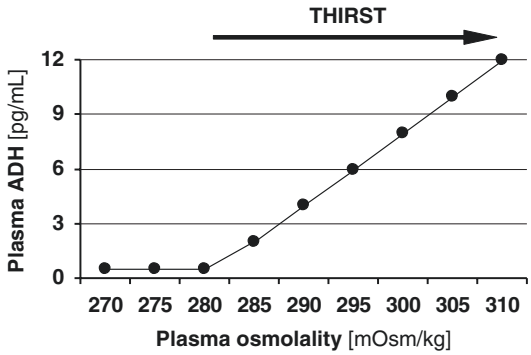

Fig. 7 Osmotic regulation of ADH release and thirst (Robertson et al. 1982)

7 Symptoms, Clinical Signs, and Laboratory Tests (Table 2)

Symptoms of dehydration can be very subtle and include mainly dry mucous membranes, dry axilla, absence of tears, and thirst (Armstrong et al. 2016; Fortes et al. 2015; Hooper et al. 2015). With rising sodium levels, especially in the setting of acute development, vomiting can occur and consciousness levels can become distinctively depressed up to irritability, delirium, or coma. In general, central nervous system symptoms occur when dehydration results in a 1% loss of body weight and

Table 2 Single signs, symptoms, and laboratory tests to identify dehydration (Armstrong et al. 2016; Fortes et al. 2015; Hooper et al. 2015; Mentes et al. 2006)

Assessment of hydration status	Feasibility of test	Scientific value
Signs and symptoms		
– Seated systolic blood pressure ≤100 mmHg	H	H
– Blood pressure change supine/standing ≥20 mmHg	H	H
– Thirst sensation	H	M
– Dark urine color	H	M
– Heart rate ≥100 bpm	H	L
– Absence of tears	H	L
– Sunken eyes	H	L
– Palpated intraocular pressure	H	L
– Body weight	H	L
– Dry axilla	H	L
– Respiratory rate >20 breaths pm	H	L
– Nail bed refill time >2 s	M	L
– Dry mucous membrane	M	L
– Skin turgor	L	L
Laboratory tests		
– Urine specific gravity ≥1.025	H	H
– Urine osmolality ≥800 mmol/kg	H	H
– Salivary osmolality	H	H
– Blood urea nitrogen/creatinine ratio ≥20	M	H
– Blood osmolality ≥300 mmol/kg	L	H
– Hematocrit/hemoglobin ratio	M	M
– Mean corpuscular volume	M	M
– Serum sodium concentration >150 mmol/L	L	M

H high, *M* medium, *L* low

are very prominent at 5% loss (Lieberman 2007; Thomas et al. 2008). Chronic hypernatremia is less likely to cause neurologic effects than acute hypernatremia, defined as development in less than 48 h.

Common clinical findings in dehydrated patients are dry skin and mucous membranes, sunken eyes, poor skin turgor, weight loss, decreased jugular venous pressure, oliguria, orthostatic hypotension with a greater risk of collapse, and tachycardia. In a prospective trial only low systolic blood pressure (<100 mmHg), out of many other physical signs (tachycardia, dry mucous membrane, dry axilla, poor skin turgor, and sunken eyes), showed high utility in diagnosing dehydration (OR = 14.7) (Fortes et al. 2015). While physical examination may suggest the presence of dehydration, physicians should not rely only on symptoms and clinical signs to indicate that dehydration is present. To aid the diagnosis dehydration, the final evaluation should be based on the clinical observations in combination with laboratory findings indeed.

Reliable laboratory values are listed in Table 2 (Armstrong et al. 2016; Fortes et al. 2015; Hooper et al. 2015). Blood osmolality ≥300 mOsm/kg has been proposed in several studies as a suitable index of dehydration (Chevront et al. 2013; Sollanek et al. 2012). Chevront et al. considered following indices as accurate: plasma osmolality, plasma sodium, urine specific gravity, and tear osmolality (Chevront et al. 2013). In another prospective study, Fortes et al. demonstrated that saliva osmolality shows a superior diagnostic accuracy compared to physical signs and urine markers (OR = 5.0) (Fortes et al. 2015).

7.1 Complications

Complications include hypotension, risk of falls related to hypotension, decreased cardiac output, and perfusion of organs and tissues. Severe dehydration can progress to hypovolemic shock. When left chronically untreated, moderate to severe dehydration increases chronic kidney disease, morbidity, and mortality (Armstrong 2012; Cowen et al. 2013).

8 Management

8.1 General Management

As first step, it is important to identify acute situations that may lead to dehydration such as episodes of vomiting, diarrhea, fever or certain medication. Symptoms and vital dehydration signs should be carefully monitored and fluid intake as well output should be accurately observed and recorded. Useful laboratory tests should also be performed (Table 2). Skin and mouth care must be provided to maintain the integrity of the skin surface and oral mucous membranes. Medications, particularly diuretics, can interfere with the biochemical parameters by varying the renal clearance of water and electrolyte (Armstrong et al. 2016). The same goes for chronic kidney disease, heart failure, and other diseases which may affect renal blood flow (Clark et al. 2016; Sontrop et al. 2013).

Rehydration and prevention can be achieved by maintaining fluid and electrolyte balance. The minimum administration of fluid from food or liquids to adults weighing from 50 to 80 kg is 1500–2500 mL/day (Smith and Cotter 2012). The route of fluid administration depends on the acuteness and severity of clinical signs. Caution should be paid for signs of overhydration, especially in patients with congestive heart failure.

The most appropriate method of fluid administration should be the simplest, safest, most effective one. The best suitable fluid to use is the one that matches most closely any previous or ongoing losses. The oral route should be used whenever possible. In acute situations and in the presence of gastrointestinal dysfunction or large deficits, the intravenous route is the most appropriate. This, however, should be discontinued at the earliest opportunity. Subcutaneous infusions should be considered, particularly in the elderly, for the management of chronic or recurrent problems (Lobo et al. 2013).

Maintenance prescriptions should aim to restore insensible loss (500–1000 mL), provide sufficient water and electrolyte to maintain normal status of body fluid compartments, and sufficient water for an optimal perfusion of the kidney. The average person requires 25–35 mL/kg water, 1 mmol/kg Na^+, and 1 mmol/kg K^+/day (Lobo et al. 2013). Any fluid prescription should not only incorporate daily maintenance requirements, but also replacement of any ongoing abnormal losses. Chidester et al. demonstrated another effective standard to calculate fluid requirement for normal weight, underweight, and overweight patients using the following scheme: 100 mL/kg for the first 10 kg of body weight, 50 mL/kg for the next 10 kg of body weight, and 15 mL/kg for the remaining body weight (Chidester and Spangler 1997). In the case of fever, additional 100–150 mL/°C higher than 37 °C will be needed.

8.2 Oral/Enteral Replacement

To replace missing fluids in a patient with dysphagia, thickened liquids, frozen juice bars, or food with high fluids (e.g., pureed fruits and vegetables) should be offered first. Enteral tube administration may be appropriate where dysphagia is severe. Sodium-containing solutions and food should be avoided. Water boluses given via feeding tube (e.g., percutaneous endoscopic gastrostomy) may be necessary if hydration cannot be maintained. Although a mild dehydration of 1.5–2% body weight loss alters mood and results in reduced cognitive and physical performance, it can easily be corrected with oral or enteral fluid administration (Armstrong et al. 2012; Watson et al. 2015; Bardis et al. 2013).

8.3 Parenteral Replacement

8.3.1 Hypodermoclysis (HDC)

With HDC, fluid is infused into the subcutaneous space trough a fine cannula. Several studies and reviews showed that HDC is a safe and effective alternative to intravenous fluid administration in order to rehydrate older adults with mild to moderate dehydration who are unable to take adequate fluids orally (Remington and Hultman 2007; Slesak et al. 2003; Dasgupta et al. 2000). Favored sites for HDC are the thighs, abdomen, back, and arms as shown in Fig. 8.

Fluid can be infused using gravity at a rate of 20–80 mL/h. Over 24 h, up to 1500 mL can be delivered at one site or 3000 mL using two sites (Thomas et al. 2008; Walsh 2005; Sasson and Shvartzman 2001; Jain et al. 1999). Other authors recommend an infusion rate of 82–148 mL/h (Baxter, Inc. data on file, 2007). Our experience in the outpatient clinic shows that the infusion of 1 L solution within 2 h is safe. Commonly, normal saline, isotonic dextrose-saline, dextrose 5%, or Ringer's solutions are used accordingly to the clinical situation. In a study of 60 residents with dementia and mild to moderate dehydration in a long-term care facility, more subjects were agitated (80%) receiving intravenous fluids compared with subjects receiving subcutaneous fluids (37%). No difference was found in amount of fluid administered or in improvement of dehydration parameters (O'Keefe and Lavan 1996). Lipshitz et al. demonstrated that radioactive technetium injected at the site of the infusion is absorbed into the blood supply within 60 min (Lipschitz et al. 1991).

Subcutaneous infusions with hyaluronidase (enzyme that is very useful in breaking down hyaluronic acid, resulting in an opening of the interstitial space) usually allow a faster infusion rate, a lower rate of moderate edema, and less discomfort.

The administration of up to 20 mmol potassium chloride per liter seems to be uncomplicated, but there are no systematic studies. Local adverse effects occurred rarely and were similar in the HDC and IV groups. They included edema, erythema, and cellulitis. There was also no difference in the incidence of systemic adverse effects like cardiac failure or hyponatremia (Slesak et al. 2003). Both methods showed the same effectiveness. HDC requires less nursing time and the cost for IV supplies was reported to be approximately four times greater than for HDC (O'Keefe and

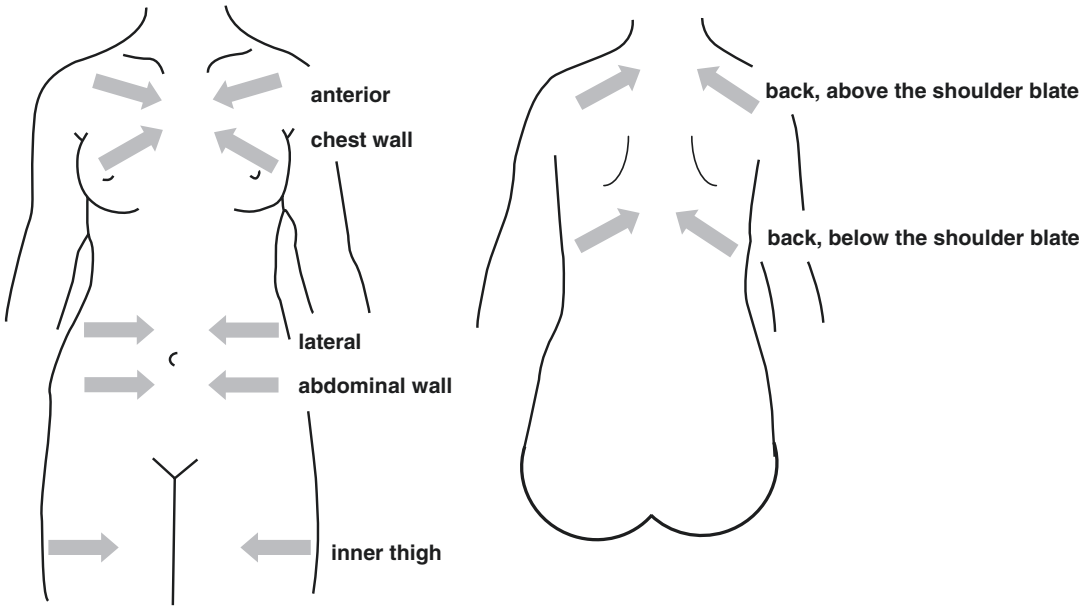

Fig. 8 Hypodermoclysis: selection of sites

Lavan 1996). HDC seem to be particularly well suited for use in the nursing home, because it can be sited out of the reach of the patient, making it less likely to become dislodged (Remington and Hultman 2007). Patients or their caretakers may also easily be taught to manage this technique at home. It is appropriate for treatment of mild to moderate dehydration or for the prevention of dehydration. However, it is not an alternative for intravenous hydration in the condition of severe dehydration or hypovolemic shock.

8.3.2 Intravenous Rehydration

Severe dehydration usually requires the application of intravenous fluids. Published data favor the use of balanced electrolyte solutions rather than 0.9% to replace salt and water deficits, except in the case of losses of gastric juice (high chloride) (Lobo et al. 2013). Therefore, the solutions should be hypotonic with a low-sodium content. Rapid administration of the intravenous solutions should be avoided, because this will cause fluid to move from the intravascular space to the extracellular volume and results in edema. Fluids should be administered gradually, over a period of 12–48 h.

Although there is no exact definition for severe dehydration, a serum sodium concentration ≥150 mmol/L, serum osmolality ≥300 mOsm/kg, or BUN to creatinine ratio ≥20 indicates a distinctive lack of water. The free water deficit in patients with hypernatremia can be calculated as follows:

$$\text{Free water deficit}\left[\text{L}\right] = 0.6 \times \text{body weight}\left[\text{kg}\right] \times \left[\left(\text{plasma sodium}\left[\text{mmol}/\text{L}\right]/140\right) - 1\right]$$

As an example: For a patient with a body weight of 60 kg and a serum sodium of 150 mmol/L, the free water deficit is 0.6 × 60 × [(150/140) − 1] = 2.5 L. The deficit can be replaced with an isotonic dextrose solution. In the case of hypovolemia, dextrose-saline (2.5% glucose, 0.45% sodium chloride) should be preferred. The doubled total volume is approximately needed to achieve the same serum sodium level as with isotonic dextrose solution. One should be aware that the addition of potassium chloride or bicarbonate reduces the amount of free water in the same proportion as the addition of sodium chloride. Figure 9 demonstrates the distribution of infused fluids in the different departments of the body.

In the setting of acute hypernatremia, lasting less than 48 h, the free water deficit should be replaced rapidly. However, rapid application of hypotonic solutions will cause fluids to move

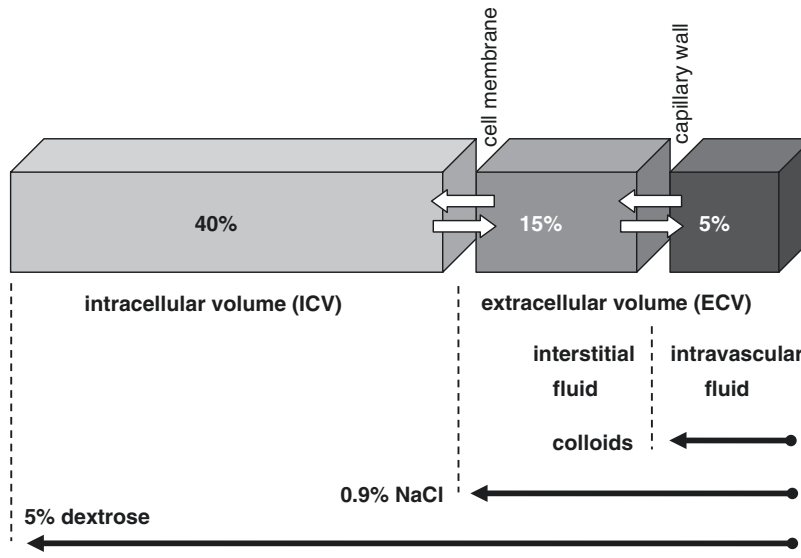

Fig. 9 Distribution of infused fluids

quickly from the intravascular space to the extravascular space and then into the cells. Especially in the brain, where osmolytes have been accumulated in the cells in order to maintain normal cell volume (see Sect. 6.4.2), the rapid application of hypotonic solutes can cause brain oedema. A slow correction is therefore mandatory for patients with hypernatremia lasting longer than 48 h. In the first 24 h maximally 50% of the replacement should be completed and special attention should be paid for signs for cerebral oedema like headache or seizures. The remaining deficit can be corrected in the next 48–72 h. Ongoing water and sodium losses through the urine and insensible perspiration should be taken into account. In a patient with hypernatremia, a urine sodium concentration of less than 25 mmol/L indicates an inadequately low fluid replacement.

Take Home Messages

- Dehydration is a large, probably underestimated problem in dysphagic patients.
- Special attention must be paid on signs and symptoms of dehydration in this population.
- It is important to distinguish between dehydration and volume depletion, since treatment approaches are different.
- Dehydration should be treated with hypotonic fluids according to the calculated water deficit.
- Volume depletion should be treated with isotonic fluids.
- Whenever possible oral or enteral (severe dysphagia) rehydration should be favored in order to treat mild dehydration.
- Hypodermoclysis is a safe and effective alternative to intravenous fluid administration in order to treat mild to moderate dehydration in patients with contraindications for oral/enteral rehydration, particularly in dysphagic patients.

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Social and Psychologic Impact of Dysphagia

Nicole Pizzorni

Contents

Abstract

Complications of oropharyngeal dysphagia include aspiration pneumonia, malnutrition, dehydration, and impact on psychosocial well-being. However, patients, caregivers, and clinicians perceive the importance of these complications differently, with patients addressing psychosocial sequelae as predominant. The chapter provides an overview of the psychological and social impact of dysphagia on patients and their caregivers. Embarrassment due to inability to eat and drink in a social acceptable way leads to social isolation. Diminished self-esteem, fear, anxiety, frustration, and depression may be experienced. Eating habits may be overturned, especially in case of more restricted diets and introduction of enteral feedings. Over time, patients find a range of coping strategies, which may be beneficial for some, while negative for others. Caregivers have to cope with changes of their role and responsibilities; in reaction to these, affective symptoms may arise. Implications for clinical practice are discussed, including a multidisciplinary and holistic assessment of the patient and the caregiver to be performed periodically, personalization of the counseling, skill-building programs, and interactions with other patients.

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1 Introduction

Eating and drinking are fundamental activities in our lives. Meals in part rule the organization of our days. Eating habits reflect a person's social, cultural, religious, geographical, and economic background. The taking of food and drink is a social event that symbolizes acceptance, friendship, and community. Hence, it is not surprising that the onset of a swallowing problem may lead to psychosocial sequelae.

Among dysphagia's complications, studies have mainly focused on physical consequences, i.e., aspiration pneumonia, malnutrition, and dehydration. Martino et al. (2009, 2010) have investigated the perceptions of patients, caregivers, and clinicians of the relevance and the interaction of dysphagia sequelae. All interviewed participants agreed on the fact that psychological, pulmonary, and nutritional status may be affected by swallowing impairment. However, when ranking the importance of these three complications patients considered the psychological consequences of greatest importance, whereas caregivers and clinicians placed greater value on biomedical consequences. Moreover, clinicians and caregivers recognized only few of the psychological consequences reported by patients. When analyzing dysphagia's complications from clinicians' point of view, pulmonary, nutritional, and psychological sequelae are considered separately (Fig. 1). Each one of the complications is believed to be related to the severity of dysphagia but no interaction with each other was identified. Caregivers described a causal feed-forward or feedback relationship between the three consequences (Fig. 2). For instance, choking (pulmonary) is perceived to be linked to the fear of it (psychology), leading the patient to avoid eating and drinking and therefore increasing the risk of malnutrition and/or dehydration (nutritional), which will ultimately expose the patient to a higher probability of developing lung infection (pulmonary). Patient's view depends on the duration of swallowing impairments. The connection between pulmonary (i.e., choking) and psychological (i.e., fear) was predominant for acute patients with the onset of dysphagia within the last 3 months, while little attention was given to nutritional status (Fig. 3). In chronic patients, psychological consequences of dysphagia were judged to be the most relevant complication of

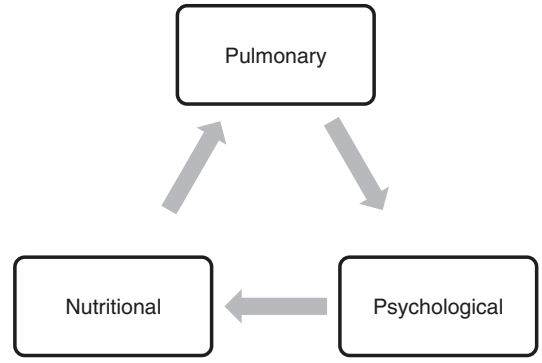

Fig. 2 Dysphagia complications from carers' perspective (adapted from Martino et al. 2010)

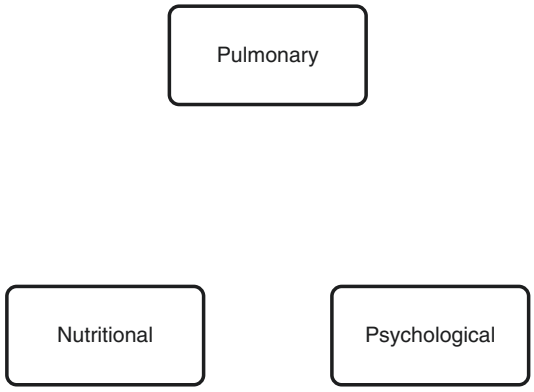

Fig. 1 Dysphagia complications from clinicians' perspective (adapted from Martino et al. 2010)

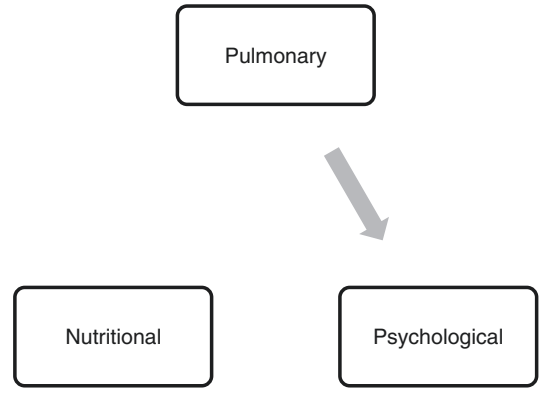

Fig. 3 Dysphagia complications from acute patients' perspective (adapted from Martino et al. 2010)

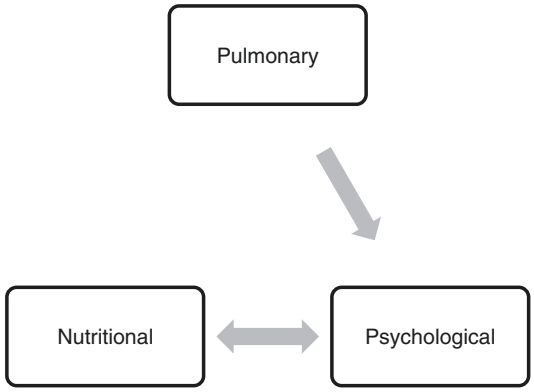

Fig. 4 Dysphagia complications from chronic patients' perspective (adapted from Martino et al. 2010)

dysphagia. Compared to acute patients, pulmonary complications were ranked as less important while nutritional status acquired importance and has a potential feed-forward and feedback interactions with the psychological dimension (Fig. 4).

Thus, stating the difference in the perspectives of clinicians, caregivers, and patients concerning dysphagia consequences, it stresses the need for clinicians to better understand and take into account the social and psychological burden experienced by individuals with dysphagia and their families.

2 Social Participation

Wedding reception, birthday party, family celebrations, religious ceremonies, working meeting, and dating are strongly associated with meals, banquets, aperitifs, and appetizers. Consequently, eating and drinking are not just nutrient supply, but form an important part of social interaction, being linked to many of the most enjoyable activities and having an impact on how individuals see themselves in relation to others.

Full social participation is suggested to be a key outcome indicator for rehabilitation (Heinemann 2005; Piškur et al. 2014). Individuals post-stroke, for instance, give more emphasis to engagement in social world over discrete physical function when appraising their recovery (Burton 2000). Therefore, examining the impact of dysphagia on social participation is of greatest importance. The International Classification of Functioning, Disability and Health (ICF) defines participation as "involvement in a life situation or as 'the lived experience' of people in the actual context in which they live" (WHO 2001). However, the ICF does not define social participation and a specific definition for this concept is still lacking (Piškur et al. 2014). For the purpose of this chapter we may accept Levasseur and colleagues' definition of social participation as "a person's involvement in activities that provide interaction with others in society or the community" (Levasseur et al. 2010).

An important issue for patients with dysphagia is eating and drinking in socially acceptable manner. Individuals with dysphagia experience feelings of uncertainty, particularly in the acute phase, regarding on how to behave in the company of others (Medin et al. 2010). Socially acceptable behaviors include staying clean during meals and adequately managing saliva. Having to continually wipe the mouth or to have a handkerchief available because of scialorrea or food dropping may be perceived as a stigma (Miller et al. 2006). The possibility to suddenly start coughing during mealtime in company of other people is source of anxiety and embarrassment. The comparison between their present way of eating with their own values regarding what is acceptable or not may lead to different behaviors (Medin et al. 2010). Studies focusing on the social burden of dysphagia report a high percentage of patients avoiding eating with others or outside their homes because of their swallowing problem (Ekberg et al. 2002; Farri et al. 2007; Medin et al. 2010; Patterson et al. 2015). Other people comprise formal caregivers, spouses, family members, friends, and unfamiliar people. Only few patients become withdrawn from close family mealtimes, feeling understood by familiar others and generally appreciating the help they gave. On the other hand, unfamiliar people make it more difficult for some individuals, feeling uncomfortable, embarrassing, and hard. Regardless of the familiarity, patient's slowness when consuming a meal results in remaining at the table long after others had finished and therefore contributing to the perceived burden of dysphagia and detriment of the personal

and social enjoyment of eating (Miller et al. 2006). Patients alter their social habits connected with eating, avoiding eating out at restaurants, clubs, and friend's homes, as well as stopping inviting friends for a meal. Changes are observed also with regard to religious rituals such as taking communion at the local church. Therefore, it derives an increased sense of isolation due to dysphagia (Ekberg et al. 2002).

However, dysphagia does not always result in the same restriction to social participation, being related to what was important to each person. Positive coping strategies may be found; however, what might be a solution for one family proved negative for another. Whereas some individuals struggle to "get back to normal" as things were before the onset of dysphagia, others simply try to get by somehow making some adjustments and adaptations. Development of coping strategies may be reached thanks to different mechanisms. First of all, by trial and error and testing what work and what do not work in eating situations the person discovers new ways of doing things. Moreover, getting advices from others may help finding ways of mastering eating in social contexts (Medin et al. 2010). Of particular importance for patients are adequate information by health-care providers and strategies and methods learned during the rehabilitation therapy (Farri et al. 2007). Positive coping strategies may include:

- Eating smaller portion and more often allowing patients to manage their portion in the time relatives and friends take for the whole meal
- Finding restaurants serving food they can manage (e.g., adding extra sauce)
- Retaining a role in group eating situations (e.g., entertaining children) (Patterson et al. 2015).

3 Affective Response to Swallowing Impairment

Several emotions are felt by persons with dysphagia. Fear of chocking is a prominent feature during mealtimes, especially in the first period after the onset of the swallowing disturbance. Feeling of guilt may be experienced as well, because of the disruption caused to the whole family in terms of extra time and energy to spend in meal planning and cooking. The sense of diversity compared to their peers may lead to loss of self-esteem.

Studies have reported the presence of affective complaints in almost half of the patients with dysphagia (Ekberg et al. 2002; Verdonschot et al. 2013, 2016). In particular, Verdonschot and colleagues conducted two studies aiming to detect symptoms of anxiety and/or depression and to investigate their relationship with signs of dysphagia in a sample of patients following head and neck oncological treatment (2013) and in a sample of individuals with oropharyngeal dysphagia of different etiology (2016). Although no causal relationship was demonstrated due to the cross-sectional design of the study, the authors identified some connections between affective complaints and dysphagia. The severity of diet restriction was not found to be a determinant of clinically relevant symptom of anxiety, while patients with a more restricted diet showed higher risk of having symptoms of depression. On the other hand, no significant association between clinically relevant depressive symptoms and the FEES outcome variables was found, while clinically relevant symptoms of anxiety were significantly associated with some FEES variables (piecemeal deglutition and post-swallow vallecular pooling). Apparently, a greater severity of oropharyngeal dysphagia did not increase the probability of having affective complaints. The authors suggested that patients experiencing more severe dysphagia often had a long history of disease and therefore may have already adapted to their physical limitations, unlike patients with mild dysphagia in the early stages or acute onset of disease.

Indeed, changes in affective response to swallowing impairment have been reported by other authors. Martino et al. (2010) analyzed patient's perception of psychological issues related to dysphagia in acute patients (with dysphagia onset of 3 months or less) and in chronic patients (with dysphagia onset greater than 3 months).

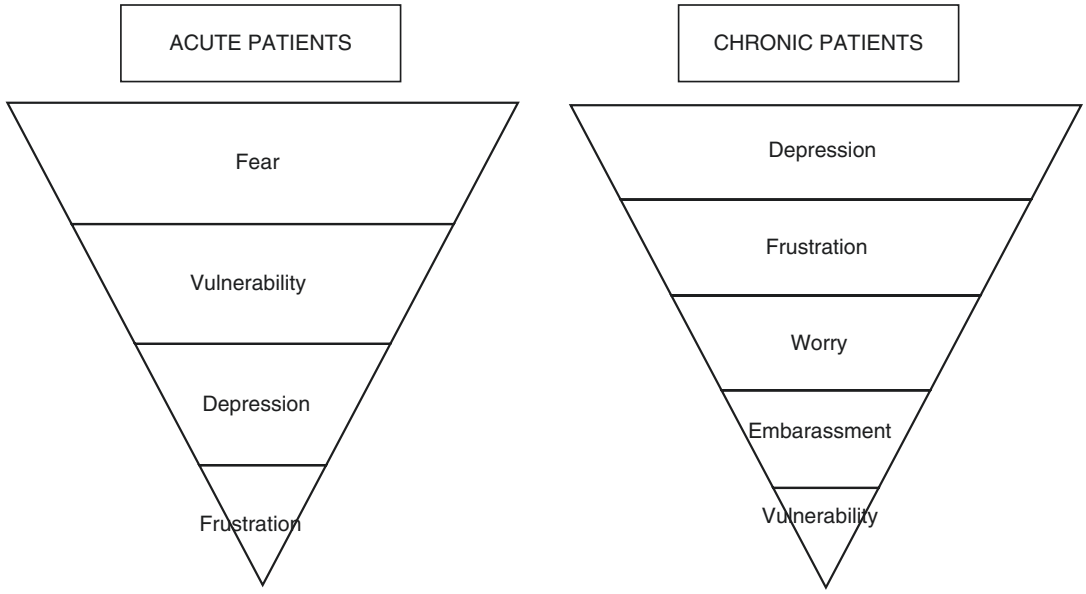

Fig. 5 Comparison of relevant psychological domains between patients with acute and chronic dysphagia, according to Martino et al. (2010)

Their results showed differences between acute and chronic patients on how they perceive and prioritize major psychological dimensions, as summarized in Fig. 5. Generally, acute patients experience increased anxiety, while chronic patients increased depression. The "fear of choking to death" is prevalent in individuals with acute onset of dysphagia. In this population the issue of fear is overwhelming, leading some patients to refuse drinking prescribed fluids even when they are thirsty to avoid the risk of choking. The sense of vulnerability related to the inability to predict or manage the symptoms of dysphagia intensifies the feeling of fear. On the other hand, chronic patients develop adaptive strategies that help them better manage their dysphagia symptoms, increasing the sense of control and decreasing the feeling of vulnerability. Together with it, the feeling of fear changes into a more measured "worry" of choking. The ability to consciously apply environmental supports as well as food selection criteria gives them self-confidence. However, over the course of the disease the possibility of chocking, especially in public venues, is not experienced as frightening anymore but as embarrassing. Moreover, the realization of the limitations because of their swallowing problems, the feelings of deprivation over not being able to eat the foods they liked, the loss of hope for swallowing recovery, and the need to continually manipulate social eating situations may make them either depressed or frustrated.

Nund et al. (2014c) investigated the mechanisms underlying the emotional adjustments in a sample of patients with dysphagia secondary to head and neck nonsurgical treatment. In particular, they identified three phases:

1. Entering the unknown
2. Making practical adjustments to live with dysphagia
3. Making emotional adjustments to live with dysphagia

Entering the unknown was a key theme especially because patients stated that they had not anticipated the severity and duration of swallowing impairment. This stresses the need for adequate education from health professionals regarding the potential side effects of dysphagia, including both the physical aspects and its

potential impact on other aspects of life. Emotional adjustments and changes in perceptions are required to live with dysphagia. Some patients addressed taking a positive attitude, while others spoke about not letting their difficulties with food become a barrier. Ultimately most of the patients reached a point in their recovery where they had accepted the changes to their swallowing ability. Other strategies to make emotional adjustments to live with dysphagia include remaining hopeful that their eating abilities would return to normal, enjoying food vicariously through other people and what they could eat, shifting their focus from food and meals, and believing that there was always someone who was worse off than they were. The support received from family, friends, and other patients is fundamental. Family members were identified as a significant source of support for people with dysphagia, particularly regarding meal preparation and encouragement to keep eating. Patients highlighted the importance for their family/friends to understand their eating difficulties, though it does not always occur.

4 Eating Habits

One of the first studies which specifically investigated the psychological and social burden of dysphagia showed that more than half of the 360 dysphagic patients from different European countries had to modify their eating habits because of their swallowing impairment (Ekberg et al. 2002). Food is selected for its nutritional content and on what people could "get down." The meaning of food may be reduced to its medicinal and nutritional qualities. Patients adapt their eating habits to alleviate the condition by eating and swallowing more slowly, taking sips of liquid in between bites of food, chewing food longer before swallowing, and changing the routine of mealtimes eating less but more often.

Texture modification is a common strategy for oropharyngeal dysphagia. However, patients' nonadherence with prescriptions for modified boluses is a recurring issue, with many patients expressing a strong dislike of the altered textures (Swan et al. 2015). When puree diet is recommended, people complain that their food is boring due to meal repetition (Patterson et al. 2015). Residents' transition from normal food to texture-modified food involved the experience of eating food out of necessity and hunger, rather than eating food for enjoyment and pleasure, involving a change to the meaning of eating (Ullrich and Crichton 2015). The degree of distress associated with the transition markedly depends on the comprehension of the rationale for the texture modification by the patients and their families (Ullrich and Crichton 2015). Swan et al. (2015) conducted a review of literature on the effect of bolus modification on health-related quality of life (HRQoL), defined as the way the disease or disorder affects the individual not only from a physical point of view, but also from psychological, social, and environmental views in combination with the individuals' underlying value system. The review showed that generally:

- Participants receiving less modified textures had better HRQoL than those receiving more modified textures.
- Modifications to food textures may have a more substantial impact to HRQoL than modifications to fluids.

Therefore, clinicians should be aware of the potential negative impact bolus modification may have on HRQoL and take this into consideration when choosing to prescribe bolus modification, especially in patients with chronic dysphagia. Moreover, strategies to assist the transition to a modified diet should be adopted by health professionals, providing appropriate information and opportunities for negotiation and familiarization with the texture-modified food as well as establishing periodical follow-up procedures.

5 Enteral Feeding

Eating habits are further overturned by the introduction of enteral feeding. The time schedules related to feeding tube require a reorganization of the daily routines of the patients and their families. Life has been described as "happening 'between feedings'" (Penner et al. 2012). When a

nighttime feeding is not scheduled, the time required for feeding during the day may leave only little time for other responsibilities or leisure activities, consequently affecting patients and caregivers' social lives.

On the other hand, enteral feeding meets the goal of ensuring an adequate nutrition to the patients. This was found to be a key theme for caregivers, who feel frustrated when they perceive that their nutritional intake was inadequate only relying on oral feeding (Penner et al. 2012). Moreover, shorter meals are experienced as more enjoyable for both patients and their caregivers when feeding is provided through a mixed oral and enteral nutrition (Sleigh 2005). Indeed, mothers of children with dysphagia who are fed orally report of prolonged mealtimes lasting between 5 and 8 h a day and meals are described as "a battle" or "a war" (Craig et al. 2003).

Despite these advantages, an initial opposition to the suggestion of gastrostomy is common, as well as the non-adherence with the nihil per os regimen once the gastrostomy-tube (G-tube) is inserted. Several studies have focused on the concerns and the reasons for non-adherence among parents of children with neurodevelopmental disorders and G-tube (Craig et al. 2003; Petersen et al. 2006). The following themes can be identified:

1. Seeing the G-tube as a confirmation of the permanence of the disability
2. Perceiving the G-tube as a "failure of the caregiver"
3. Viewing the loss of oral feeding as a denial of a basic or an essential human instinct and nature
4. Fearing increased discrimination from an added stigma
5. Negatively impacting mealtime associations and familial bonding
6. Preventing the child's pleasure in eating.

First of all, gastrostomy may be sometimes perceived as the last resort, the signal that the child will never go to feed properly. This sense of resignation is associated with a feeling of failure of their parental role to properly care for their children, being unable to manage mealtime problems. The loss of the maternal experience of feeding the child has deep significance for caregivers. Being eating the "natural" way to receive nutrition, parents are afraid that their child could be seen as somewhat "less human." Traditional forms of food, such as small amount of food by mouth or otherwise regular foods provided through the G-tube, are believed to have a higher value than enteral nutrition formulas from parents' perspective. The G-tube exhibits an advantage over the nasogastric tube in terms of visibility, partly reducing the stigmatizing effect connected with enteral nutrition. A concern that gastrostomy feeding might exclude the child from participating in school and family life was raised. Meals are recognized to be a "special time" for both familial bonding and closer contact with peers. However, some parents considered the gastrostomy a facilitator rather than a barrier to social interaction by allowing the child to "join in" with peers during school meals instead of concentrating solely on oral feeding. As the relationship with food is highly individual, parents highlighted the importance for the child to experience different tastes, textures, and enjoyment of food.

A complex process of negotiating a new normal starts after the introduction of enteral feeding. A main aspect of this process is negotiating changing roles (Penner et al. 2012). Indeed, caring for someone who is dependent on tube feeding means that caregivers need to acquire new skills and unique knowledge in relation to its use. Caregivers often feel little prepared and anxious about undertaking this responsibility. Information, communication, and support are important facilitators of the negotiation process (Mayre-Chilton et al. 2011; Penner et al. 2012).

6 Impact on Caregivers

Regardless of the introduction of enteral feelings, the onset of dysphagia has a social and psychologic impact not only on patients but also on their families. Caregivers are strictly involved in the management of dysphagia. Thus, considering affective symptoms and limitation in participation of caregivers because of their kins'

swallowing impairment is mandatory during the taking charge of patients with dysphagia.

Concerning affective symptoms, Serel Arslan et al. (2017) have recently explored anxiety level of caregiver of neurological patients with and without dysphagia. They found that caregivers of neurological patients with dysphagia had higher anxiety level than caregivers of neurological patients without dysphagia, concerning both momentary and long-lasting anxiety, independently of dysphagia severity, types of feeding, condition of dependency in eating and drinking, and dysphagia duration. It suggests that dysphagia causes additional burden for caregivers of neurological patients, increasing their anxiety level. To explain this finding, several aspects related to life with a person with dysphagia should be taken into account.

First of all, as already discussed in the previous paragraph, living with a person with dysphagia also mean changes to the carer's roles and responsibilities. Nund and colleagues stated "additional roles taken on by the carers included problem solver, household manager or 'parent', nutritionist, chef, and life coach" (2014a). Caregivers become the primary responsible for dysphagia care and management, having to control food consistency modifications and body positioning as well as to continuously observe the patient throughout the meal. Caregivers may have concerns about adequate nutritional and fluid intake in order to avoid medical complication. Along with these responsibilities, the fear of choking is an additional worry. Therefore, during food preparation caregivers should take into account both the quality of nourishment and the type of texture. This requires spending more time planning, shopping, and cooking for meals. Moreover, carers would often have to prepare two separate meals, leading to time restriction in daily life for other activities.

Conflicting emotions are associated with the increase of responsibility. Caregivers may feel incapable of providing sufficient care and problem solving during dealing with dysphagia. Moreover, at times the patients may request and be served their favorite dishes, although they may be unsuitable for swallowing safety, resulting in severe dysphagia symptoms that frighten the carers and made them feel uncomfortable (Johansson and Johansson 2009). Carers may experience feeling of guilt as they can eat whatever they wish, while their partners do not. Thus, they may either eat by themselves so as the partner does not see what they are eating or suppress their own choice of food (Penner et al. 2012).

Loss of affinity during meals has been reported (Johansson and Johansson 2009; Nund et al. 2014a, 2016). Mealtimes provide environment for family interactions. While eating people often express different taste sensations in words or gustatory expressions, tokens of pleasure are part of the conversation when socializing. Some routines, such as sharing the breakfast time or drinking a coffee together, may represent a well-established routine in some relationships. Sitting and talking in a relaxed manner while eating is no longer possible. Some spouses may eat in different moments due to the feeling of discomfort that arises when they sit at a dinner table together. Occasionally, family members report to leave the dinner table because they could not cope with their next of kin's eating behavior. All these aspects may enhance the feeling of separation within a couple.

Furthermore, neurological disorders leading to dysphagia are often chronic disabilities. Difficulties in swallowing may have long-lasting consequences including inadequate oral nutrition, pulmonary diseases, and mortality. Thus, cumulative years spent in caregiving without swallowing improvements or recovery may increase caregivers' anxiety. Indeed, in the study of Serel Arslan et al. (2017) caregivers whose patients had a history of previous dysphagia treatment had higher anxiety level. The authors explained it by their expectations from dysphagia treatment, which did not resolve the swallowing impairment though.

Distinct consideration should be made for mothers of children with swallowing disorders. In case the swallowing impairment occurs since birth, mothers have to relinquish the dream of breastfeeding (Sleigh 2005). A redefinition of mother identity must occur (Hewetson and Singh 2009). It implies making sense of societally, professionally, and personally held perceptions and beliefs about the link between the mothering role and the ability to feed a child. The role of mother

is integrated with that of nurse. Gathering of information and establishment of routines and schedules may assist them in gaining control over the challenges of caring for their children.

7 Assessment of Psychosocial Burden of Dysphagia

Initial and periodical assessment of the psychosocial impact of dysphagia on patients and caregivers is advisable. Besides dialogue with patients and their family, clinicians may rely on some shared tools, such as the SWAL-QOL or the ICF framework. In any event, the multidisciplinary of the team, including psychologists, may allow a better analysis of psychosocial consequences.

7.1 Swallowing Quality of Life (SWAL-QOL)

The SWAL-QOL is a self-administered questionnaire assessing dysphagia-related quality of life and examining real-life functioning of persons with dysphagia via the patients' perspective. The authors of the tool defined quality of life as "an overall state of well-being that is a composite of: (a) the ability to fulfill usual and desired physical, role, and social activities; (b) the psychological effectiveness with which one performs usual and desired activities; (c) satisfaction with health care services related to dysphagia treatment; and (d) dysphagia symptom status" (McHorney et al. 2000a). Firstly developed in 2000 the SWAL-QOL tool has been validated in several languages and shows adequate psychometric properties (McHorney et al. 2000b, 2002).

The 44 items of the questionnaire cover ten domains:

- Burden
- Eating duration
- Eating desire
- Food selection
- Communication
- Fear
- Mental health
- Social functioning
- Fatigue
- Sleep

7.2 International Classification of Functioning (ICF)

The World Health Organization International Classification of Functioning, Disability and Health (WHO-ICF) defines health functioning as "an umbrella term, encompassing all body functions, body structures, activities and social participation" (WHO 2001). If an individual is affected by a disease, then an impairment, an activity limitation, and/or a participation restriction may result. Functioning thus does not coincide with the concept of QoL; however, it may affect psychological well-being (Maclean et al. 2009).

The ICF analyzes functioning based on five major components: body structures, body functions, activities, participation, and environmental factors and personal factors. ICF codes are available for all the components except for personal factors. Environmental and personal factors can be evaluated as either facilitators or barriers. All ICF codes had qualifiers that indicate the severity of the limitation or restriction. These universal qualifiers attached to the ICF codes ranged from 0 (no problem or within normal limits) to 4 (complete or profound problem). In addition, a value of 8 indicates unspecific information, while 9 indicates that it was unavailable. The letter C indicates a complication related to health and function.

Threats in 2007 firstly identified 60 ICF codes for body structures, body functions, activities, participation, and environmental factors and personal factors related to dysphagia. Afterward, Nund and colleagues in 2014 identified 52 ICF codes for dysphagia based on interviews to individuals with dysphagia after nonsurgical head and neck treatment (2014b). The identified ICF codes are summarized in Table 1.

The application of the ICF to dysphagia assessment has been suggested by these authors

Table 1 ICF codes for dysphagia (Threats 2007; Nund et al. 2014b)

Body functions		Body structures		Activities and participation		Environmental factors	
ICF code	Name of code	ICF code	Name of code	ICF code	Name of code	ICF code	Name of code
b110	Consciousness function	s3200	Teeth	d230	Carrying out daily routine	e1100	Food
b117	Intellectual function	s3203	Tongue	d2301	Managing daily routine	e1101	Drugs
b1301	Motivation	s3204	Structure of lips	d2302	Completing daily routine	e1151	Assistive products and technology for personal use in daily life
b1302	Appetite	s330	Structure of pharynx	d550	Eating	e240	Light
b140	Attention functions	s340	Structure of larynx	d560	Drinking	e250	Sound
b144	Memory functions	s510	Structure of salivary glands	d630	Preparing meals	e310	Immediate family
b147	Psychomotor functions			d730	Relating with strangers	e315	Extended family
b152	Emotional functions			d760	Family relationships	e320	Friends
b1642	Time management			d7600	Parent–child relationships	e325	Acquaintances, peers, colleagues, neighbors, and community members
b1643	Cognitive flexibility			d770	Intimate relationships	e340	Personal care providers and personal assistants
b1644	Insight			d7701	Spousal relationships	e345	Strangers
b1646	Problem solving			d850	Remunerative employment	e355	Health professionals
b1801	Body image			d870	Economic self-sufficiency	e410	Individual attitudes of immediate family members
b2102	Quality of vision			d9100	Informal associations	e415	Individual attitudes of extended family members
b250	Taste function			d9191	Ceremonies	e420	Individual attitudes of friends
b255	Smell function			d9204	Hobbies	e5800	Health services
b2700	Sensitivity to temperature			d9205	Socializing		
b28010	Pain in head and neck			d9300	Organized religion		
b450	Additional respiratory functions						
b5102	Chewing						
b5103	Manipulation of food in the mouth						
b5104	Salivation						
b51050	Oral swallowing						
b51051	Pharyngeal swallowing						
b530	Weight maintenance functions						

in order to provide health professionals with a more holistic view of an individual's functioning and the real-life outcomes for people with dysphagia. Indeed, the behaviors represented by body functions codes that contribute to successful eating and drinking can be markedly different in the person's natural environments. For instance, as food is highly culturally characterized, two people with technically the same severity of dysphagia may function very differently because of their culture. Personal factors include demographic information, and personality traits, such as coping style and motivation. Eating and drinking are individual experiences. When persons have dysphagia, preferences and personality traits influence both their reaction to dysphagia and patients' compliance to clinicians' prescriptions. Moreover, the application of the ICF framework may help clinicians to identify most critical aspects for patient functioning and, consequently, focus dysphagia treatment on these (Sonies 2000).

As dysphagia has an impact not only on the patients, but also on their caregivers and families, the group of Nund suggested the application of the ICF to study third-part disability of caregivers of patients with dysphagia in order to provide a more holistic and family-centered approach in the management of dysphagia (2016). Third-party disability refers to the "disability and functioning of family members" due to health condition of significant others (WHO 2001). The ICF codes related to the third-party disability are reported in Table 2.

However, several limitations of the ICF in describing functioning and participation of people with dysphagia have been highlighted. Firstly, some of the ICF codes oversimplify the meaning of the activities related to eating and therefore underestimate the effects of dysphagia. For example, the

Table 2 ICF codes related to third-part disability of dysphagia (Nund et al. 2016)

Body functions		Activities and participation		Environmental factors	
ICF code	Name of code	ICF code	Name of code	ICF code	Name of code
b152	Emotional functions	d175	Solving problems	e1300	General products and technology for education
		d2301	Managing daily routine	e310	Immediate family
		d2302	Completing daily routine	e315	Extended family
		d2400	Handling responsibility	e320	Friends
		d2401	Handling stress	e325	Acquaintances, peers, colleagues, neighbours and community members
		d550	Eating	e345	Strangers
		d6200	Shopping	e355	Health professionals
		d630	Preparing meals	e420	Individual attitudes of friend
		d660	Assisting others	e425	Individual attitudes of acquaintances, peers, colleagues, neighbours and community members
		d6604	Assisting others in nutrition	e450	Individual attitudes of health professionals
		d760	Family relationships	e5800	Health services
		d7701	Spousal relationships		
		d7102	Tolerance in relationships		
		d730	Relating with strangers		
		d7500	Informal relationships with friends		
		d870	Economic self-sufficiency		
		d9205	Socializing		

ICF defines eating as "Carrying out the coordinated tasks and actions of eating food that has been served, bringing it to the mouth and eating it in culturally acceptable ways, cutting or breaking food into pieces, opening bottles and cans, using eating implements, having meals, feasting or dining" (WHO 2001) but this definition does not take into account patient's enjoyment in eating. Analogously, meal preparation is considered in the ICF as executing a task: "Planning, organizing, cooking and serving meals with a large number of ingredients that require complex methods of preparation and serving, such as planning a meal with several dishes, and transforming food ingredients by combined actions of peeling, slicing, mixing, kneading, stirring, presenting and serving food in a manner appropriate to the occasion and culture." However, it undervalues the significance of the emotional, psychological, and social aspects of food preparation and its role in caregiving. Secondly, though personal factors are not classified in the ICF, the ICF overlook important aspects such as the person's unique individual experience in the classification of participation. Moreover, concerns on the ability of the ICF in reflecting the continuous changing nature of participation have been raised (Woodman et al. 2014) as well as the actual applicability of the ICF framework in clinical practice being fairly time consuming (Dong et al. 2016).

Therefore, although the ICF is a valuable tool to provide a more holistic approach to the management of people with dysphagia, there is still a need for the development of this classification to include the above-mentioned aspects.

7.3 Psychological Assessment

A screening of affective response to dysphagia is recommended in patients with dysphagia and in their caregivers. A multidisciplinary team, including not only swallowing experts but also psychologists, is recommended. Several screening tools for symptoms of anxiety and depression are available. Among these, the Hospital Anxiety and Depression Scale (HADS), a validated 14-item questionnaire, is frequently used as a psychological measurement of affective symptoms in the hospital setting (Zigmond and Snaith 1983; Bjelland et al. 2002).

8 Implication for Clinical Practice

On the basis of this overview on social and psychological impact of dysphagia, the following strategies should be implemented in clinical practice:

- Providing a multidisciplinary approach to the management of patients with dysphagia and their caregivers
- Investigating patients' previous eating habits in order to understand the impact of potential prescriptions
- Opening a dialogue with patients and caregivers on their needs to better mastering eating and meal preparation allowing a personalization of the information
- Providing periodical evaluations also in the long term including assessment of HRQoL and screening of affective symptoms
- Providing skill-building programs that target activities such as meal preparation and food consumption
- Encouraging the contact with other patients and caregivers to promote the sharing of positively coping strategies

Conclusion

Dysphagia affects social lives and psychological well-being of both patients and caregivers. It is important for clinicians to be aware of the presence of psychosocial issues related to dysphagia, to address them according to the patients' clinical recovery, and to consider the interplay between psychological and biomedical consequences. By adequately informing and educating patients and their families, assessing them, and offering the appropriate treatments, health professionals can reduce the social and psychological burden of swallowing impairments.

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Ethical Issues and Dysphagia

David G. Smithard

Contents

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Abstract

People with many different medical problems will develop swallowing problems or dysphagia. The management of dysphagia cannot be done in isolation, particularly as the end of life approaches. Interventions to assist in the provision of nutrition are in most countries a medical treatment. Decisions will need to be made that will be influenced as much by social, cultural and religious expectations and norms as by clinical status and medical information. The best interests of the patient will always be the overriding aim, but negotiation between the patient, family and medical team may be required.

Human life is sacred (including the ability to eat and drink socially) but only to the extent that it contributes to the joy and happiness of the one possessing it, and to those about him, and it ought to be the privilege of every human being to cross the river Styx in the boat of his own choosing, when further human agony cannot be justified by the hope of future health and happiness (Emanuel, Death and Dying, Rowan and Littlefield, 2004; Sánchez García et al. Nestle Nutr Inst Workshop Ser 72:101–108, 2012).

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1 Introduction

To survive man requires calories and water, in other words, to be able to eat and drink. Maslow described food as one of man's basic needs (Maslow 1943). However, to survive independently, the ability to swallow must be intact and one be able to feed one's self. Difficulty with swallowing is termed dysphagia. The term of dysphagia is derived from the Greek *dys* meaning bad or disordered, and the root *phag* meaning "eat". It refers to any sensation that the patient may complain of which makes swallowing and hence eating difficult.

Dysphagia is a symptom/syndrome with many different aetiologies having different frequencies and progression (Smithard 2016). Dysphagia may occur with, or as a consequence of, many medical conditions, ranging from cardiorespiratory through to reduced conscious level and terminal care. Some simple problems which may occur as a result of medical treatment (oral thrush secondary to antibiotics or immunosuppressants) or neglect/poor care (dry mouth, infected mouth) are remediable whereas others such as that associated with terminal phase of disease and management/care are more supportive than curative.

Dysphagia cannot be managed in isolation and holistic management of the person is important; there are many consequences of dysphagia including pain, malnutrition, choking, infection, breathlessness and distress (Table 1).

Table 1 Aetiology of dysphagia

Aetiology of dysphagia	Examples of effects resulting in dysphagia
Stroke/Traumatic brain Injury	Multiple. Lack of/no neurological control of the muscles related to swallowing
Dementia	Different factors at different times Lack of judgement Poor neurological control Food refusal
Parkinson's disease	Bradykinesia resulting in slow laryngeal movement
Motor neuron disease	Failure of airway protection and bolus control.
Cardiac failure	Difficulty breathing. Unable to stop breathing to swallow
COPD/Lung fibrosis	Unable to stop breathing to permit swallowing
Rheumatoid arthritis	Arthritis of the arytenoid cartilages , therefore difficulty closing the airway
Osteoarthritis	Pressure on the pharynx from behind, causing obstruction
Malignancy (Tongue, pharynx, larynx)	Difficulty manipulating bolus. Mechanical Obstruction
Ankylosing spondylitis	Head position, spinal deformity resulting in an unsafe airway
Myasthenia gravis	Fatigue and inability to protect the airway
Post extubation	Multiple factors secondary to the underlying pathological process, laryngeal paralysis and deconditioning
Frailty/Old age	Safe swallow but may precipitate into dysphagia if unwell or medication change (delirium)

2 Ethical Issues

Medical care is fraught with ethical and moral issues. As the population ages there will be a consequent increase in the ethical dilemmas around nutritional support of those refusing to eat whether dysphagia is present or not (Shintani 2013; Reynard et al. 2010).

During the process of care and compassion for any one person different ethical and philosophical approaches (Table 2) can be applied as the clinical situation changes; this movement may be more of an oscillation rather than a continuum. As a consequence of medical ethics, or care ethics, decision-making is never an off-the-shelf answer. Each decision needs to be bespoke and frequently requires much thought and discussion. The application of these principles is termed applied ethics as opposed to philosophical ethics, and makes allowance for the evidence from research, clinical situation, financial, morality, religious beliefs, and social and cultural attitudes.

These discussions are difficult and resultant decisions regarding dysphagia and general care will have a profound effect not only on the person but also on those caring for them. Consequently conflicts and divergent opinions, of personal moral and ethical values, will be displayed and expressed, which have the potential for harm, particularly if they are in conflict with those of the patient (Reynard et al. 2010; Nathaniel 2004) let alone the wider medical team.

As a consequence of the complexities affecting the ethical issues surrounding the management of dysphagia, general principles are discussed in the first part of this chapter followed by more disease-specific issues.

Table 2 Ethical theories employed in making clinical decisions

Utilitarianism	Utilitarianism is a normative ethical theory that places the locus of right and wrong solely on the outcomes (consequences) of choosing one action/policy over other actions/policies. As such, it moves beyond the scope of one's own interests and takes into account the interests of others
Deontological normative Monistic (Kant) Pleuralistic (Ross)	Its first formulation states "Act as if the maxim of your action were to secure through your will a universal law of nature;" its second formulation states "Always act so as to treat humanity, whether in your own person or that of another, as an end in itself, never as a means only." The phrase "prima facie" ('all things being equal') refers to the fact that these duties do not bind us absolutely, but rather that they generally hold—absent any further considerations. Two key duties are **nonmaleficence** (don't harm others) and **beneficence** (help others)
Relativism	What is right for a society at that time is right. What is right in on society may be wrong in another
Ethical egoism	Whenever people do something, it is only because they think something desirable for themselves will result from it
Virtue ethics	Desires and intentions to undertake a task
Ethics of care	Responses to care are contextual, driven by clues/evidence presented by the patient. There are times when the ethics of care must confront situations in which bona fide requirements of impartiality conflict with acting partially from care
Case based theory	Reactions and behaviour are influenced by previous experience as each case is reflected upon

3 General Principles

The management of dysphagia in any particular medical condition will need to be approached with an open mind, to ensure that simple remedial complications are not complicating the larger picture. It is very easy to focus on small problems and miss the whole picture.

Subsequent clinical approaches will be influenced on the phase/stage of the underlying disease process: i.e. early vs. late and the perceived benefit of any intervention. The bottom line is "Will life be continued or death postponed for a short period?" How will you know if the correct ethical decision-making has been sound? What will be the "care" measure used, and how will change/improvement be defined empirically (Fine 2006)? From the Hippocratic tradition it is acknowledged that to do no harm is on same side as to do good, and hence to realign treatment from curative to supportive where death is inevitable is entirely appropriate (Fine 2006). Any intervention must be for the benefit of the patient and not just the comfort of the carer.

4 Decision-Making

Effective decision-making has two facets: a consideration of all relevant facts (discussion) and clear communication of the outcome. There are many different discussions to be had in the management of a person with dysphagia and decisions to be reached on issues such as the provision of nutrition, symptom relief, right to life and right to die that are common to all yet at the same time different.

Discussion regarding the management of dysphagia is often complex, frequently emotive particularly where the provision of nutrition is concerned, needing to make provisions for many factors including social, moral, ethical, spiritual, religious, political/legal, family and healthcare professionals as well as any expressed wishes of the patient (Fig. 1) (Krishna 2011; Serradura-Russel 1992). Filial piety expressed as the desire and expectation to do all that is possible may drive some requests for interventions that do not provide any meaningful benefit. These factors often play out when professional staff and patient (and extended circle) may not share the same cultural or belief systems (Dikeman and Riquelme 2002; Riquelme 2007). Difficulties may potentially occur when there is no one definitive answer, and conflicts often exist, particularly when the choice is to continue with a normal diet despite advice to the contrary. Despite any or all difficulties, consensus needs to be arrived at (Ely et al. 1992) to enable the individualised and compassionate care to the patient to be delivered. Those patients that express a religious view tend to have a better self-esteem and are less likely to seek an early assisted death (Daalman and VandeCreek 2000).

Decisions are frequently a shade of grey rather than black or white. There needs to be an accepted balance of risk vs. safety. A balance between legality and morality; do what is right within the spirit of the law and what is best for this patient. In the presence of dysphagia, non-oral feeding nutritional support via the enteral or parenteral route carries risks. None eliminate the risk of aspiration and possible pneumonia. The greatest complication following the decision to non-oral feed is the danger that mouth care will be neglected or undertaken in an ineffective way, and the current managements are being challenged.

The ability to understand and manage risk is crucial in making decisions regarding feeding (Kaizer et al. 2012). Decisions taken by patients need to be understood in the realms of culture and belief systems. Support needs to be provided to assist them and the families to come to a

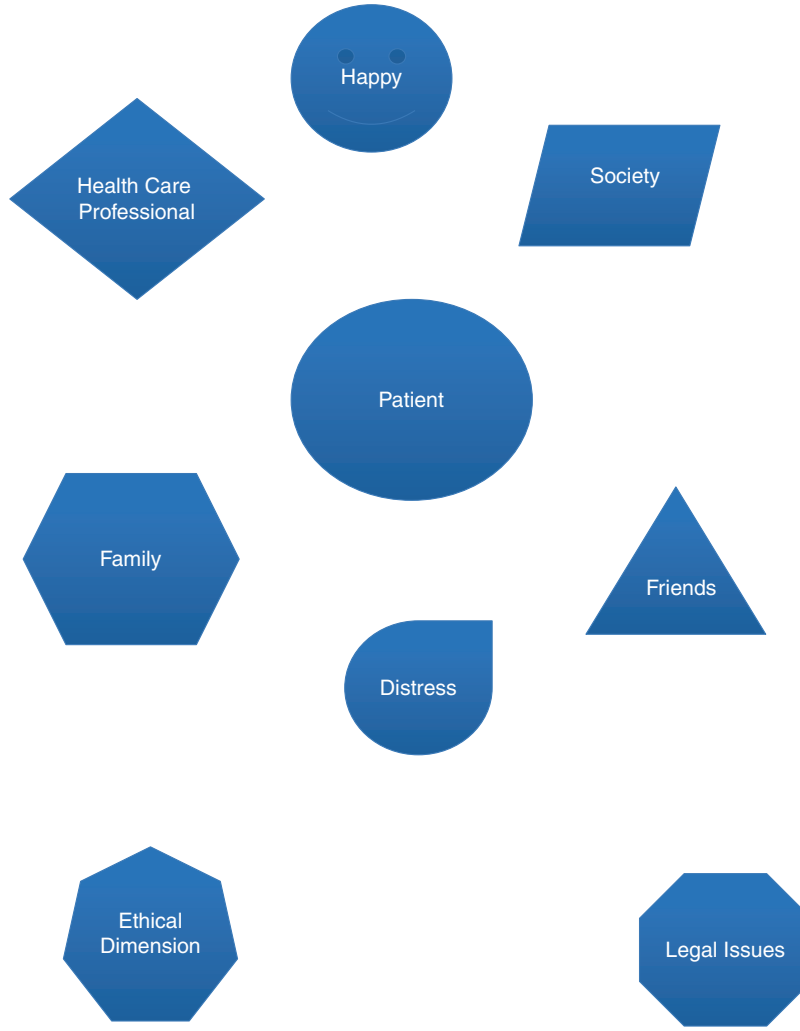

Fig. 1 The relationship between the patients, family, health care professionals and emotion mingle as if at a party, interacting with each other in a seemingly random manner, watched at a distance by ethics and legal

decision in conjunction with care staff (Kaizer et al. 2012). At the same time care staff need to be cognoscente of the risks of coming to a decision for their benefit rather than that of a patient, i.e. a treatment plan that they are comfortable with rather than one that is appropriate. Similarly the patient will need to be comfortable with the decision and their choice may depend on the value they place on their life (Fleming 2003; Sandman et al. 2008). Healthcare staff will need to understand that not agreeing or wanting to follow a particular treatment plan is not non-compliance but may be a reasoned choice (Sharp 2005).

Decision-making with respect to the withdrawal or non-commencement of treatment is a consensus decision that requires, ideally, the involvement of the patient (Krishna 2011). Where possible these discussions and decisions should be made in advance of a clinical situation or the need to consider withdrawing care.

The result of any discussion regarding the planning and delivery of any or no intervention needs to be documented and communicated to the wider team to ensure consistency of treatment and care, relieving pressure on individuals when the time arrives, and to avoid scapegoating of colleagues either overtly or inadvertently (Norberg et al. 1980).

5 Autonomy and Capacity

People are individual autonomous beings, who have the legal right to determine their course of treatment. We can characterise a person as autonomous if "… they do what they choose to do (because the choose to) and they choose to do what they do because they wants to" (Sandman (trans) et al. 2008, p 115). Freewill or autonomy suggests the ability to make choices and be responsible for the outcome (Haggard 2011). The role of patient autonomy (Hull 1992) is often taken as paramount, and the fear of going against this can sometimes paralyse healthcare delivery at the time of need. This freewill or autonomy, in general, can only be exercised in the right to refuse treatment which may result in conflict and angst with those delivering care (Strand 1995) particularly if the resulting decision appears to be harmful to the person making the decision.

To be able to exercise autonomy a person needs to demonstrate the mental capacity to make such a decision and understand the consequence of that decision (Mental Capacity Act 2005). Where the patient is adjudged to have capacity then no matter how ludicrous a decision may appear to be in the refusal of treatment this has to be accepted (Hotopf 2005; Kutner et al. 2017; Wanzer et al. 1984; Mental Health Act 1983).

Grisso and applebaum and stating Mental Capacity can be competent decision-making according to the appreciation standard requires recognition that one is suffering from a disorder and that the generally accepted risks and benefits of treatment apply to one's own situation … failures in appreciation often are considered to be core components of major psychiatric disorder (Grisso and Appelbaum 1995).

Competency or mental capacity is contextual and decision dependent, and is not immediately lost after a diagnosis of dementia is made. If someone is deemed not to have capacity, an advocate will need to be appointed (Wanzer et al. 1984; Mental Health Act 1983). Different legal systems/independent states will have different legal processes for this to be undertaken. As such a blanket decision regarding a person's ability to make decisions is not appropriate and as such an assessment needs to be made, at or before a major treatment choice is made (percutaneous endoscopic gastrostomy (PEG) insertion, laryngectomy), affording the patient the information in an understandable format (pictures, own language) and the time to make the decision. Where the medical condition has resulted in the inability to convey wishes, and yet there is no documentary proof of pre-existing desires, it may be difficult to interpret the difference between refusal and misunderstanding/fear (Watts and Cassel 1984). Care needs to be taken to ensure that the decision-making process is not clouded by delirium or depression. Any decision needs to respect dignity (Watts and Cassel 1984). To be certain that any capacity assessment has been undertaken fairly, then time must be allowed to make the decision and all mechanisms have been explored to ensure that information has been provided in an appropriate and understandable format. At times this will require translators to join the multidisciplinary team.

To be able to make a decision regarding the appropriateness of treatment a person required the mental capacity. The first principle is to assume that the person has capacity. Capacity may be affected by emotion, depression, infection, cognition, learning disability, communication and mental illness. Capacity depends on the ability to

1. Understand information provided relevant to the decision
2. Retain the information
3. Use or weigh the information
4. Communicate a decision

For this to occur, information needs to be provided in an appropriate format.

6 Consent and the Right to Refuse

The notion of obtaining informed consent from patients is based on the ethical and legal value for an individual's right to make decisions that affect his or her body (Bernat 2001).

Before any medical treatment/intervention can be undertaken, healthcare workers have an ethical and legal responsibility to obtain a patient's informed consent having determined whether they have the capacity to consent. However, legislation governing the conditions under which this is required and the format it is obtained vary from country to country (Nys et al. 2007). In the majority of instances consent is assumed or implied (blood tests, diet recommendations) and is of an oral nature and should be documented in the medical record. Formal consent needs to be obtained in writing with the patient or an advocate/proxy signing a legal document/consent form (Souza et al. 2013) and should be sought before any invasive (surgery, enteral feeding tube placement) procedure is undertaken (Souza et al. 2013). Consent must be willingly given and without coercion, as determined in Article 6 of the Universal Declaration of Bioethics and Human Rights. Under common law, patients have the right to give or withhold consent before examinations or treatments, irrespective of the medical practitioner's view of that decision.

7 Right to Life

As with many things the "right to life" is blurred and may depend on personal or societal norms; the over-riding situation and the competing interests of other rights (Feinberg 1997). To have a right to life, there needs to be a determination as to what life is and what the current and clinical terminology and context mean. Does life mean existence or is it more complex, in that to have life, there must be an ability to interact with your environment? Does having the right to life also infer or confer that there is a right to refuse or take one's life?

Unfortunately emotion appears to play an indispensable role in moral judgement (Suhler and Churchland 2011) and many judgements appear to be due to subconscious automatic cognitive processes. In recent years the debate has focussed on the right to end one's life or to involve a third party (usually medical) (Ganzini 2006; House of Lords Judgement 2001; Goldin 2016; Laurance 2007) and by definition contravening the right to life and the right to a family as determined in the European Convention and Human Rights Act (Chevalier-Watts 2010; European Convention on Human Rights 2015). The right to life is essentially the right not to be killed, i.e. the right not to have one's life taken away in a proactive manner. At the same time failure to intervene when indicated is just as legally problematical (this has often been the preferred choice of the physician). Article 2 of the European Convention on Human Right states that "Everyone's right to life shall be protected by law"; this covers the protection of life as well as the prevention of the removal of life (Chevalier-Watts 2010; European Convention on Human Rights 2015). Article 5 relates to the right to a family life and is also frequently used to argue for treatments to commence or be continued.

Despite this, some nations' or parts of countries' (Kenwright 2017; Chambaere 2010; Steinbrook 2008) medical staff can assist people in the request or the family request to prematurely end life and its inclusion criteria appear to be widening. This approach has been rejected in other countries (e.g. UK).

Leadership from Christian religious leaders has been confusing at times; for instance the Catholic Church has changed its opinion with the more recent papal declaration (Hamel 2015) supporting the sanctity of life over and above what is reasonable. There is a consensus from the Abrahamic faiths that life is sacred but not at all costs (Sachedina 2005; Dorff 2005; Engelhardt and Iltis 2005).

There has not been any overt debate about the potential pressure put onto a physician who has a point of view that is not concordant with that of the patient or family.

8 Nutrition

Feeding difficulties can arise in persons with physical or cognitive impairments at any stage of life including end of life. Patients with oral feeding difficulties often present healthcare workers with the legal, moral and ethical challenges discussed above. Some patients will be confronted with swallowing disorders and will need assessment and treatment, either by modification of nutrient selection or texture. Where a management programme has been devised, only 40% may follow the guidance given (Kaizer et al. 2012). Where feeding has become a chore or takes so much time and/or energy the use of enteral feeding can provide the calories and free time and improve quality of life.

There are several questions that need to be asked regarding the provision of artificial nutrition (e.g. whether, when, who, how), and the relevance will depend on the individual and the underlying medical condition.

The clinical conundrum is determining if a terminal phase has been reached or is intervention with parenteral/enteral nutrition and fluids appropriate. It is accepted that food and water are a basic human right so long as it can be taken orally, either alone or with help. Treatment for dysphagia by artificial hydration and nutrition is accepted as a medical intervention and an ethical issue in the majority of countries, as such some ethicists suggest that artificial nutrition and hydration are medical treatments that can legitimately be withheld if their risks, judged according to the patient's values, outweigh their benefits (Hyde and Rufo 2000; Cochrane 2014); others will argue that this is not the case (Kitwood 1997; Craig 1994); however, this implies that values are known or documented and this is frequently not the case.

Whether withholding nutrition can be considered an infraction on human dignity is the subject of continuous debate. The Roman Catholic Church has considered tube feeding a medical intervention that can be withheld under particular circumstances (Sachedina 2005). However, in 2004, at a 4-day conference by the Pontifical Academy for Life, Pope John Paul II addressed participants and stated that "artificial nutrition and hydration, was 'normal care' and 'a natural means of preserving life, not a medical act,' and, therefore, morally obligatory, independent of an assessment of benefits and burdens to the patient, the patient's family and the community" (Sachedina 2005).

The decision process will vary as to whether the ultimate underlying cause of dysphagia (e.g. stroke/brain injury) is potentially reversible or progressive (multiple sclerosis, malignance) and whether the purpose is to support recovery/prevent deterioration or primarily comfort. As the failure to provide a treatment (feeding) is legally and morally the same (Mental Capacity Act 2005; Clarke et al. 1994) though subconsciously the former is easier to live with, and where there is a reasonable doubt as to the potential benefit of enteral feeding, and if this decision is that of the provision of a medical intervention (cf antibiotics), then it would appear reasonable to undertake a therapeutic trial of nutritional support (Klocke 1992; Watts and Cassel 1984). If this is the plan then the length of time that feeding will continue and the outcome/improvement to be looked for need to be determined from the outset.

Article 3 of the European Convention refers to prohibition of torture and states that "No one shall be subjected to torture or to inhuman or degrading treatment or punishment" (Chevalier-Watts 2010; European Convention on Human Rights 2015). Passing feeding tubes and inserting intravenous lines are not without discomfort and risk. The use of artificial nutrition where there is no possible benefit to accrue, such as at the end of life, or where there is an expressed refusal by the patient, may be considered physical assault and torture.

There are many difficult and contentious issues around the provision of nutrition. The main question is *"whether to provide nutrition is appropriate or not"*. Generally enteral nutrition (particularly in the UK) is seen as a medical treatment. Consequently it can be stopped and started along the lines of any medical treatment; if there is doubt, a 2-week trial of enteral feeding should be attempted with outcomes monitored. The question that needs to be asked is this: Is this long enough and what improvements are expected in this time? What is clear is that no food equates,

eventually, to no life. The decision to provide nutrition or not must not be taken lightly, and must be done on individual case-by-case basis after full discussion with all parties involved including the patient if they are competent.

There are two further issues that frequently tax clinicians, firstly that of the person who wants to eat and drink, but whose swallow is unsafe and who are at high risk of aspiration. Providing the patient is cognitively intact and is deemed to have mental capacity, and after explaining all the risks that eating and drinking entail, they should be allowed to eat and drink. If capacity is an issue, a similar discussion should be done with their representative/advocate.

The second scenario is of someone who is capable of swallowing and is able to meet their own needs but refuses to swallow. This case scenario is difficult and very burdensome on all formal and informal carers. Restraint and forced provision of nutrition will only work whilst it is being administered, with the original position rapidly returning. In a patient with mental capacity this is not an option in some countries (Mental Capacity Act 2005).

Where restraint is being used, it should be used for the minimum period of time after seeking legal advice (Mental Capacity Act 2005; Gastmas and Milisen 2006). If restraint (physical/chemical) is required to keep a feeding tube in then its benefit needs to be questioned (Lo and Dornbrand 1992). If the goal is patient comfort there needs to be a predefined definition as to what is to be assessed and how quality of life is improved. Should extraordinary be a term to be used or rather should we look at appropriateness (Lo and Dornbrand 1992)?

Any decisions reached need to be communicated with the wider clinical team to ensure the delivery of a consistent approach to treatment and care.

9 End of Life

At the end of life, many patients will refrain from eating and drinking and will eventually die due to dehydration among other causes. When life is coming to a close and the terminal phase has begun, it is not an unusual scenario that some people make the decision to stop eating and drinking. They may see that ongoing life has no value (and their life is drawing to a close). If they have capacity this needs to be honoured. The right to refuse to eat and drink is, in some respect, no different to the right to refuse other forms of treatment/intervention (Quill et al. 1992). Is this an option we should make people aware of?

In a review of factors related to elderly person's not eating for one or more days, Frongillo, Rauschenbach and Williamson (Frongillo et al. 1992) determined that ethnicity, geographical area, living alone, health problems, mobility, age, difficulty swallowing and loss of appetite were factors which, among others, influenced food intake.

In all medical health systems, there is limited availability of resources, or the financial envelope is not great enough, and decisions regarding the management of any one person are coloured by the consequent effect that decision has on the healthcare provision to others.

Physical life is finite and as such healthcare staff and general population need to have an understanding of the finality of life (Cole 1992) and as a consequence ensure that the patient does not come to harm despite well-intentioned management decisions. Furthermore, there are instances where nutrition becomes an intervention that is no longer defendable and is not adding to the comfort of the patient. Beauchamp and Childress (1994) state, "The principle of non-maleficence does not imply the maintenance of biological life, nor does it require the initiation or continuation of treatment without regard to the patient's pain, suffering, and discomfort".

Physical death comes to all; often the only question is when, how and where. The timing and nature of a natural death cannot be predicted, but there comes a time when further medical care has been exhausted and benefit from more intervention is meaningless or futile. Bernat (2001) comments on medical futility as follows:

"The essence of futility is overwhelming improbability in the face of possibility. An act

is futile if the desired outcome, while empirically possible, is so unlikely that its exact probability may be incalculable".

Medical futility exists when a treatment or hoped-for benefit may, on the best evidence available, be predicted not to help a patient's medical condition. The therapy may not be able to provide benefit to the patient either because it is highly unlikely to produce the desired physiologic effect or because it produces the physiologic effect that does not confer benefit to the patient. Therefore the insistence on persevering with artificial nutrition may (as alluded to earlier) constitute torture and be ethically unsound (undertaking an intervention that has no benefit). Pope John Paul II refused hospitalisation and tube feeding when confronted with end of life. The provision of a treatment (in this case nutrition) that is not beneficial to a patient is morally and ethically wrong and may result in more harm than good.

When quality of life is sufficiently low and an intervention is futile, caregivers may justifiably withhold or withdraw treatment (Beauchamp and Childress 1994; Kasman 2004) and a palliative approach should be taken. Palliative care is defined by the World Health Organization (1995) as:

"The active, total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount". The goal of palliative care is achievement of the best quality of life for patients and their families.

In all conditions where there are end-of-life issues and competing demands and insights, there comes a time when certain interventions become unethical and as such may cause distress not only to the patient but also to care givers. Nathaniel has defined moral distress as [quoted by Austin and colleagues (2000)] follows:

> Moral distress is the pain or anguish affecting the mind, body or relationships in response to a situation in which the person is aware of a moral problem, acknowledges moral responsibility, and makes a moral judgment about the correct action; yet, as a result of real or perceived constraints, participates in perceived moral wrongdoing.

10 Social and Financial Burden

Social burden needs to be considered in the wider context of not only the immediate family but also society as a whole. This involves decision-making for the benefit of the greatest good, not just the person concerned (utilitarianism). Utilitarianism is a normative ethical theory that places the locus of right and wrong solely on the outcomes (consequences) of choosing one action/policy over other actions/policies. As such, it moves beyond the scope of one's own interests and takes into account the interests of others.

Medical decision-making impacts on society as a whole, decisions made to continue treatment, or in the context of dysphagia feeding (and enteral feeding) places a financial and social burden on individuals and society as a whole. Eating practices and mealtime regimes become disrupted; fear of choking, altered diets, slow eating and drinking, fatigue and embarrassment of eating in public all affect participation in social events (Ekberg et al. 2002; Saunders et al. 2011). Preparation of special diets and lack of compliance with the special diet can add to financial burden as well as stress and tension on older carers and families (Davis 2007).

The financial burden to society is not just that of the initial causative problem. It is also affected by the long-term burden of maintaining nutrition and hydration in some one severely disabled. The associated costs may be diverted from other clinical/social areas. Frequently decisions need to be made where the financial effect on society needs to be accounted for. Where there is a finite financial resource, and particularly where healthcare is not free at the point of delivery, the simple decision will come down to the fact that the family are unable to afford to fund the treatment. In other situations it is a matter of what is the best way to spend the limited budget for the benefit of the greater good in society. These financial costs, or the economics of health, "are concerned with the optimum use of scarce economic resources for the care of the sick and the promotion of health, taking into account competing uses of these resources" (Mushkin 1958). In England the National Institute for Health and

Clinical Excellence (NIHCE) provides guidance to the clinical effectiveness of any medical intervention (2006).

In the case of dysphagia, the costs can be considered direct and indirect. Direct costs are those related to the provision of nutrition, enteral tubes, etc. Indirect costs are those care costs incurred and the management of complications associated with enteral feeding (Shintani 2013; Elia 2006).

Other indirect costs are those associated the loss of productivity and formal and informal care. One possible reason for this lack of knowledge on the economic impact is that it is difficult to place a monetary value on its physical, psychological and social consequences, particularly as they coexist with underlying medical conditions and comorbidities. A further challenge is that healthcare systems vary from country to country (Saunders et al. 2011).

11 Common Medical Problems Associated with Dysphagia

Dysphagia accompanies many medical conditions. In the following paragraphs a few are discussed in more specific detail than the general issues discussed earlier.

11.1 Stroke

Swallowing problems following stroke are common (Smithard 2014) and may be a direct result of the stroke or secondary to or exacerbated by medication or comorbid disease. Recovery is good in many but is persistent in a few. Rehabilitation techniques are changing and the future looks exciting. Complications are frequent but the most common are related to nutrition. More work is required here.

Broadly speaking, within the first few days after a stroke, people fall into one of few categories. They may be getting better without dysphagia, and hence no intervention is needed; they may be dying, in which case supportive care and feeding are required. They may be getting better, clinically, but their swallow is slow; these people need nutritional support. Then there is the small group of people, often with a severe stroke, who appear to begin to start recovering but then plateau. Death is usually within a few weeks, should artificial nutrition be provided.

Over the years there has been much debate as to the best approach. There is no clear research evidence as to what should be done. In many institutions enteral feeding is commenced early (National Clinical Guidelines for Stroke 2016; Jauch et al. 2013), usually for the administration of medication. There is no clear research evidence for the timing of feed, nor the type of feed. It appears self-evident that where people are recovering nutrition is important. But what to do in the small group who are not improving or do not appear to be deteriorating, and what is there to do? Providing enteral nutrition may just postpone death with no perceptible clinical benefit; not feeding will ultimately lead to death. Many physicians will encourage the use of a nasogastric tube by day 2 to ensure the provision of medication.

The presence of dysphagia following stroke is known to impact the length of hospital stay (Altman et al. 2010; Bonita et al. 2014). A study examined the cost of post-stroke dysphagia in the USA and found that the cost for patients with dysphagia was US$4510 more per patient than for those without dysphagia (Bonita et al. 2014). People with dysphagia were more likely to be discharged to nursing homes than to their own home and had longer hospital stays than patients without dysphagia when age, comorbidities, ethnicity and proportion of time alive were controlled in the analysis (Bonita et al. 2014).

Non-compliance or refusal of acceptance of advice is not uncommon. The use of thickening agents does not have universal approval of stroke patients. The insistence on some to continue with thin fluids frequently causes distress to nursing staff. The decision to prescribe thickened fluids should be a last resort. Thickened fluids have been found to reduce fluid intake and increase the risk of dehydration (Whelan 2001; Cichero 2013), and ruin a decent Scotch.

There are, on occasions, those who can swallow, or can upgrade their swallow; those who

refuse to do so, phagophobia, require a multidisciplinary approach which is outside the discussion here. Failure to upgrade is not a problem so long as adequate calories, vitamins and trace elements are provided.

11.2 Neurodegenerative Diseases

Neurodegenerative disease includes multiple sclerosis, motor neuron disease, Huntingdon's disease, Parkinson's disease and dementia. These are many and varied medical conditions, but all have dementia associated either as part of the primary disease or as coexisting Alzheimer's disease or vascular dementia.

The role of enteral nutrition in people with neurodegenerative diseases needs to be understood in the overall social, moral and physical contexts. What is the purpose of the provision, what is the expected outcome and is there any evidence (Palecek et al. 2010; Robinson et al. 2005)? The act of feeding needs to be seen in the wider context of caring (Gillick 2000). No matter what the underlying pathology is, the person with dysphagia is still human and should be treated as such and afforded the dignity that comes with being a human being. Gillick argues that there needs to be a consensus pathway to manage dysphagia at the end of life (Gillick 2000). There needs to be an early discussion as to when life is at its end and what relationship this has to dying (Low and Ho 2017). Does the former mark the beginning of the latter? Approaches to ensuring nutrition provision in neurodegenerative disease may vary from coercion, restraint or undermining or ignoring of patients' views. Decisions may be made where staff consider their actions to be legal and ethical (Lejman et al. 2013) with the purpose of keeping the staff legally safe.

11.2.1 Motor Neuron Disease/ Amyotrophic Lateral Sclerosis (MND/ALS)

MND/ALS is progressive and fatal, with most being dead within 5 years (Pols). Dysphagia will affect in excess of 60% of people with MND/ALS. Spinal ALS will develop dysphagia; Franceschini and Maurao found that >70% had dysphagia and dysarthria may be the initial presentation in 30% (da Franceschini and Maurão 2015). Respiratory muscle dysfunction and progression are predictors of outcome (Polkey et al. 1999; Forbes et al. 2004; Veldink et al. 2002). The management of dysphagia depends on whether the aetiology is within the swallowing musculature or the ventilatory muscle/expiratory muscle (Polkey et al. 1999). Progression of dysphagia in those with limb as apposed to bulbar ALS may be more rapid; in part this may be due to changes in respiratory reserve (Shoji et al. 2015). Choking is not associated with food, but is presumably related to saliva entering the airway due to abnormal vocal cord movement (Polkey et al. 1999). However fear of swallowing increased as dysphagia worsened (correlation -0.806; $p < 0.001$).

In the case of MND or other conditions where there is respiratory failure, the management of the respiratory issues is as important as the management of dysphagia. The use of ventilation (via tracheostomy or NIPPV) may assist in increasing longevity and reduce the symptoms of dysphagia and is therefore needed to be factored into treatment. The use of surgery to manage dysphagia (laryngectomy, epiglottopexy) (Brooks and McKelvie 1983; Garvey et al. 2099) may all be offered to manage dysphagia and if beneficial from a symptom control perspective may also be considered. However as with all surgical procedures there needs to be a careful benefit vs. risk approach.

Advance planning needs to occur before communication degenerates or is lost (McClusky 2007). MND/ALS may develop frontal lobe problems. The discussions will revolve around the wish to determine when to die, whether to accept cardiopulmonary resuscitation should the need arise, ventilator support and the provision of nutrition. Other discussions will consider dignity in life and dignity in death (Pols and Limburg 2016). Surgery, ventilation and enteral feeding will not prevent death in the majority of people and therefore their role in symptom relief may be the prime objective, which brings the contrast between risk and benefit into strong relief.

11.2.2 Parkinson's Disease

Swallowing in Parkinson's disease is secondary to the degenerative process within the striatonigral pathway. As dopamine depletes, the risk/prevalence of dysphagia increases. Early changes in the swallow are subclinical, but as the swallow will slow down secondary to bradykinesia, oral incontinence occurs and malnutrition and dehydration due to the inability to meet nutritional needs may occur. A major problem with PD occurs when people become unwell, due to frailty, and as the PD dysphagia worsens or occurs, medication is missed and dysphagia and general Parkinsonian features are exacerbate (Carneiro et al. 2013).

In the presence of an intercurrent illness, there may be an acute exacerbation of any swallowing problems and should be managed as such; a nasogastric tube may be required for nutrition and possibly medication. If this is not possible then oral medication should be substituted for transdermal or subcutaneous medications (Baijens and Speyer 2009). The only ethical issues that arise will be around end-of-life decision-making (severity of illness, stage of Parkinson's disease) and then the general principals outlined above will apply (Fall et al. 2003).

11.2.3 Dementia

Dementia is an umbrella term. There are many different types of dementia which will present differently and have different pathway and prognosis. Eating is modulated by food preferences, environment, fear of eating, forgetting to eat, availability of food as well as ability to swallow.

In a prospective, longitudinal uncontrolled study of patients with severe dementia in the Netherlands, researchers found that the level of discomfort (dyspnoea, restlessness and observed pain and dehydration) was highest at the time of the decision not to start enteral tube feeding, and decreased in the days thereafter (Pasman et al. 2005).

Nutritional intake and associated weight loss may be associated with the brain lesions and hunger drive. However weight loss may be associated with recurrent admission to hospital and increased mortality (Pivi et al. 2012; Watson and Green 2006). Many studies of ANH in people with dementia are poorly designed or influenced by external factors such as carer preference, culture and religious faith, as to be unable to provide any meaningful direction.

In dementia, the use of tube feeding should be led by the clinical need. Acute medical problems may justify feeding especially as infection or acute delirium may precipitate/exacerbate dysphagia.

11.3 Frailty

Many older people have sarcopenia (Sagawa et al. 2016) and multiple comorbidities and as such multiple reasons as to why there may be dysphagia present. Presbyphagia is a frequent occurrence without aspiration as people have adapted their diet over time (Morley 2001). Voice quality may have changed and FEES may have identified that there is laxity and bowing of the vocal cords. Generally there is not much that can be done, but should injection of the vocal cords to "plump" them up be undertaken (Filho et al. 2006), with the purpose of improving voice quality and reducing aspiration risk? Is there enough evidence to recommend routine FEEs and vocal cord injection?

Many frail older people are admitted to hospital with an acute illness, which results in their homeostasis failing and frank dysphagia presenting. Extremely frail [Clinical Frailty Score 7–9 (Perna et al. 2017)] have a poor prognosis. These frail people will often reside in care homes where the prevalence of dysphagia is common (Leibovitz 2011). Management including interventional treatment (including enteral feeding) needs to be aware of the whole picture with respect to longevity as well as quality of life, before potentially wrong and catastrophic decisions are made. Age should not be the sole determining factor in determining the approach to nutritional provision (Malgram et al. 2011).

11.4 Quality of Life

Quality of life (QoL) is often difficult to assess, particularly as the patient, healthcare provider and carer may have different viewpoints. Several

studies have suggested that there is significant psychological and social impact associated with dysphagia with negative consequences for individuals' psychological well-being (Ekberg et al. 2002; Tibbling 1991). One study, which analysed QoL while eating in older nursing home residents (and could be extrapolated dysphagia in general), found that 84% said that eating should be enjoyable, but only 45% expressed that it was. An important 41% experienced anxiety and panic during eating, while 36% avoided eating with other people (Ekberg et al. 2002).

Functional changes in eating have a negative impact on QoL (Hickson and Frost 2004). Research on dysphagia associated with oropharyngeal and laryngeal cancer (Nguyen et al. 2005) and progressive neurological disease (Leow et al. 2010) suggests that negative change in QoL is strongly associated with both oropharyngeal and oesophageal dysphagia. Complications of dysphagia have a great impact on QoL of patients and national health budgets because they induce frailty, institutionalisation, comorbidities, decreased functionality, readmissions, higher drug intake and increased length of hospitalisation.

HRQOL (Health-Related QoL) is a key component to the management of any one with dysphagia. There will be changes as any comorbidity waxes and wanes (Amarantos et al. 2001). Eating brings positive social and psychological components to the quality of life (Amarantos et al. 2001) which can have positive effects on HRQOL.

What is measured when quality of life is measured? The WHOQOL Group (1995) describes it as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". This leads on to suggest that QOL will change as the situation changes, and as such anyone looking on will perceive QOL differently; this by its nature will lead on to conflict between family members, care givers/health professionals and the patient/person with the condition.

QOL measures used in research and to make health/social care delivery decisions often use functional assessment or disease burden. Is QOL a measure to judge normativity? This then presupposes that there is a universal agreement on what is normal. In the case of dysphagia, being able to swallow independently is the "normal", not how the swallow functions physiologically.

Conclusion

The management of swallowing difficulties is complex and fraught with difficulties. Decision-making needs to be bespoke and not formulaic. Decisions do not need to be taken with haste and there is often a time for a period of reflection and procrastination. Care and compassion of the patient are the clinician's first duty, which may result in a clash with family and carers. It is unethical to provide a treatment/intervention that is futile, with the sole aim of keeping the clinician and the family at ease with themselves.

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