Neurology of Swallowing and Dysphagia

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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).

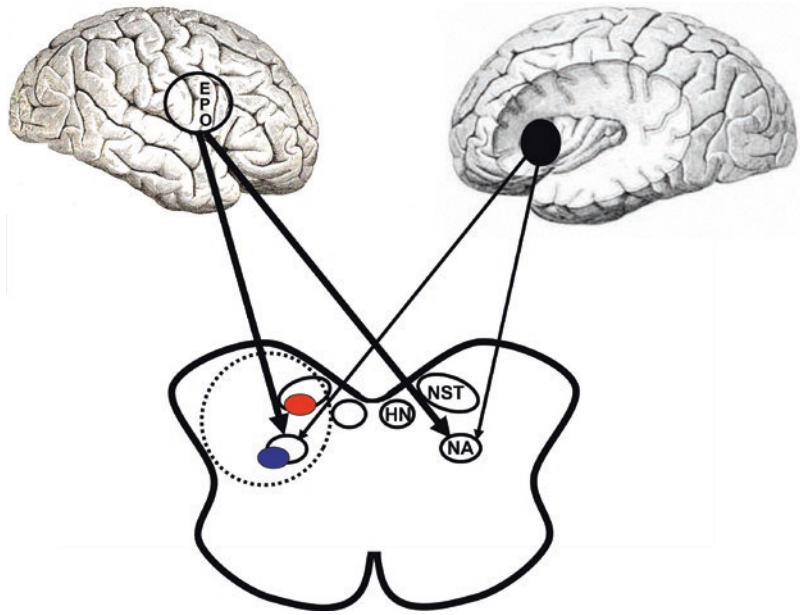

Fig. 1 Swallowing cortex, corticobulbar fibers, and lower brainstem. *Top left*: Right cerebral hemisphere with the frontoparietal operculum (*closed circle*) and the representational areas of the esophagus (*E*), pharynx (*P*), and oral region (*O*). In this example, the right hemisphere is swallowing-dominant, 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,

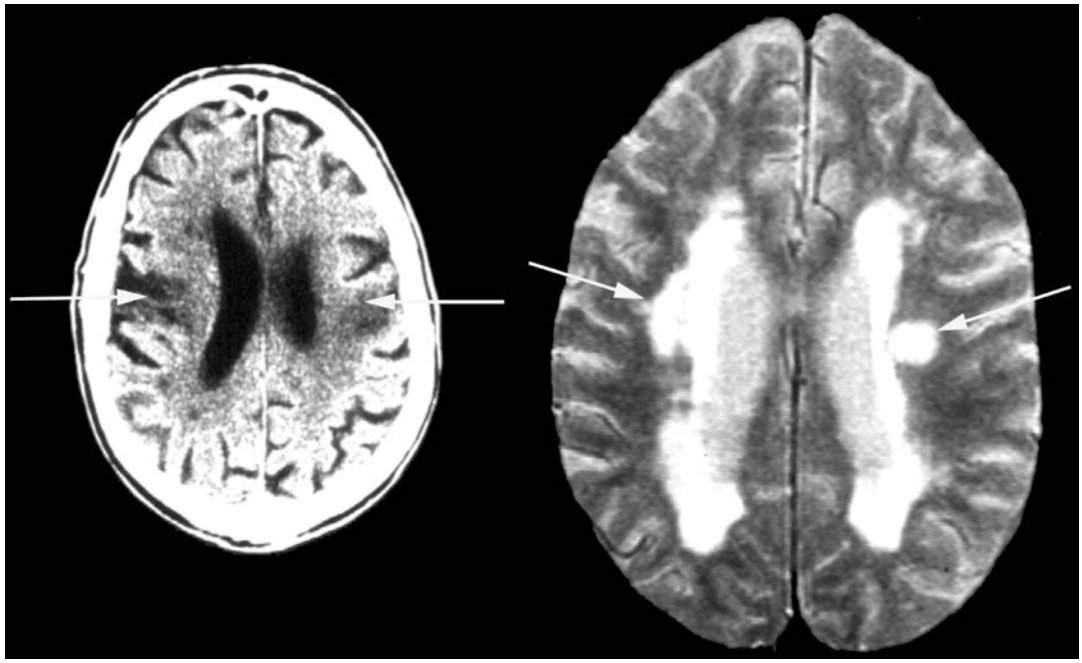

Fig. 2 *Left*: Cranial computed tomography showing bilateral infarctions (*arrows*) in the supply area of the middle cerebral artery affecting the frontoparietal operculum bilaterally causing the so-called bilateral anterior frontoparietal opercular syndrome (Foix-Chavany-Marie syndrome). *Right*: T2-weighted 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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