Extraesophageal GERD and Management

6

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6.1 Etiology

Extraesophageal reflux (EER) manifestation has become a major pathophysiological problem with increasing clinical importance. EER can be either primary cause or major contributing factor to a variety of commonly occurring extraesophageal problems, if the reflux of stomach content causes troublesome symptoms and/or complications.

Increased attention to GERD has shifted focus to how and under which circumstances reflux influences physiologic processes in the upper airway beyond the esophagus [1].

As demonstrated in Table 6.1, extraesophageal reflux results in either direct reflux-associated symptoms due to direct contact between stomach content and mucosal structures or indirect vagal reflex responses elicited from the esophagus [2].

The clinical experience shows that symptoms mediated by EER are often nonspecific and overlap with those of other medical conditions.

As long as patients report on classic GERD symptoms (i.e., heartburn, epigastric regurgitation), EER is assumed to cause existing upper airway symptoms. Nevertheless, even in the absence of classic GERD symptoms, EER has to be

Table 6.1 Pathomechanism of extraesophageal reflux manifestations

Direct reflux-associated pathomechanism	Indirect reflex-associated pathomechanism
Direct reflux induced injury of the extraesophageal tissue (caused by contact with gastric acid)	Reflex responses elicited from the esophagus by the vagus nerve–mediated esophagobronchial reflex

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considered and reviewed in all circumstances of any unspecific upper airways disorder. Patients with EER do not necessarily need to present classic GERD symptoms; rather, a large group of patients have "silent reflux" that can manifest in unspecific upper airway symptoms [3]. The percentage of patients with "silent" EER situation devoid of classic GERD symptoms is meanwhile estimated at about 20%.

However, the clinical situation is not clear in every patient, as organic lesions and reported symptoms do not always correlate. Thus, the exploration and diagnostics require a high degree of clinical experience and expertise.

On the one hand, patients with clinically "typical" reflux-associated organic lesions can be either symptomatic or asymptomatic concerning GERD. On the other hand, patients can report on severe EER symptoms without any detectable mucosal alteration in the extraesophageal region.

In patients with unspecific extraesophageal complaints, it is important to parse out the onset, duration, relieving factors, and exacerbating factors for the chief complaint in any patient even considering the gastroesophageal medical history [4]. Patients with extraesophageal GERD manifestations, when evaluated through upper digestive endoscopy, often present only a low prevalence of esophagitis [5].

The physiologic mechanism of extraesophageal/laryngopharyngeal reflux can be attributed to a breakdown of one or more of the four barriers to reflux:

1. Upper esophageal sphincter.
2. Lower esophageal sphincter.
3. Esophageal acid clearance.
4. Epithelial resistance.

If the barrier functions of lower and upper esophageal sphincters are not working properly, the direct mechanism of refluxate aspiration can trigger a tracheal or bronchial cough reflex. In case of a reflex-associated process, a vagally mediated bronchoconstriction can be found.

A further important risk factor for EER seems to be the excessive workload of the diaphragm in forced breathing task with special stress to the lower esophageal sphincter. Recent studies pointed out that GERD and EER have to be considered also as a work-related disease in selected professions. An increased intra-abdominal pressure seems to initiate GERD with extraesophageal manifestations more often, like in opera singers, wind players, and glassblowers [6–8].

The connection between GERD and certain diseases of the airway has been classified by the Montreal definition of GERD in 2006 [9, 10].

Considering this classification, there is agreement concerning both established and proposed associations with EER syndrome (see Table 6.2).

Usually general practitioners, pulmonologists, and ENT specialists are confronted with EER manifestations.

From the interdisciplinary point of view, extraesophageal symptoms can be divided into pulmonary and ENT symptoms (Table 6.3).

Table 6.2 Consensus on extraesophageal symptoms concerning the Montreal definition and classification (2006)

Established associations with EER	Proposed associations with EER
• Reflux cough syndrome • Reflux laryngitis syndrome • Reflux asthma syndrome • Reflux dental erosion syndrome	• Pharyngitis • Sinusitis • Idiopathic pulmonary fibrosis • Recurrent otitis media

Table 6.3 Extraesophageal symptoms associated with GERD classified regarding medical specialties modified after Richter [11]

Pulmonary manifestation	Manifestation in ENT
• Bronchial asthma • Chronic bronchitis • Chronic cough • Aspiration pneumonia • Apnea • Pulmonary fibrosis	• Chronic cough • Globus pharyngeus • Vocal cord granuloma • Reflux laryngitis • Loss of dental enamel and dental erosion • Chronic rhinosinusitis with/without polyposis nasi • Recurrent otitis media with effusion/chronic seromucotympanon

Given the increasing prevalence of GERD and its role in oropharyngeal, laryngeal, and pulmonary alterations, there is a growing need for better understanding of the underlying mechanism of pathophysiology.

It is important to diagnose and manage extraesophageal reflux symptoms appropriately. The interdisciplinary approach is not yet sufficiently established in daily practice and need to be intensified.

6.2 Pulmonary Extraesophageal Reflux Manifestation

Among pulmonary patients, special emphasis is given to the high percentage of GERD related cofactors to bronchial asthma, chronic bronchitis, and chronic cough [12, 13].

Asthma as an inflammatory lung disease with reversible airflow obstruction and bronchospasm causes episodes of wheezing, coughing, chest tightness, and shortness of breath. Etiologically, environmental factors like allergens or other aero irritants, genetic factors, side effects of medication, and viral/bacterial infection have to be taken into consideration as well as the direct or indirect impact by extraesophageal refluxate.

6.3 Chronic Cough

Chronic cough has a significant impact on the well-being of patients and stresses the healthcare services in many ways [14]. Cough is one of the most common conditions seen worldwide by primary care physicians and specialists.

Meanwhile, GERD has to be regarded as one the three most important etiologies of chronic cough. Afferent triggers are mediated by chemoreceptors and nociceptors within the respiratory system. They provide feedback to the cough center within the medulla, which, in turn, activates an efferent cascade and reflex that involves instantaneously the closure of the glottis. Tight laryngeal closure permits creation of an increasing subglottic pressure and a transglottic pressure gradient, which is the precondition for expectorating material from the respiratory tract when the subglottic pressure threshold is exceeded.

The traditional approach to chronic cough considers first of all smoking and regular medication with angiotensin-converting enzyme inhibitors. Meanwhile, the focus has extended to the diagnosis and management of other cough trigger components. Further classic triggers are aerogenic irritants/allergies, postnasal drip, respiratory infection, bronchial asthma, voice mis−/overuse, and other reactive airway diseases. These etiologies have to be excluded before suspecting that reflux may play a major role in developing chronic cough syndrome [14–16].

Chronic cough syndrome related to reflux is often considered a diagnosis of exclusion. In clinical practice, the evaluation of patients with chronic cough frequently involves trials of empiric therapy before initiating respective diagnostics. Patients are usually referred to further interdisciplinary examinations, if an empiric therapy trial could not solve the problem.

A common medical problem is the worsening of chronic cough symptoms by phonation in patients with underlying irritable larynx syndrome. The irritable larynx syndrome describes throat irritation that results from repeated vocal fold trauma by voice mis- and overuse. It can manifest as a sensory neuropathy during chronic cough [17, 18]. If the cough threshold is already decreased then voice use can lead easily to heavy coughing attacks.

Chronic cough can cause repeated trauma to the vocal fold tissue resulting in irritation and swelling of the vocal folds with a foreign body sensation in the larynx. This often requires a behavioral change of a person's reaction to this cough sensation and vocalization. A swallow of water might help to break the cycle and overcome the cough reflex.

6.4 Globus Pharyngeus

Globus pharyngeus (GP) is a symptom regularly reported by patients in ENT practice. It makes up to 4% of ear, nose, and throat (ENT) referrals and is reported to have been experienced by up to 45% of the population [19]. GP is usually multifactorial and cannot simply be reduced to a single hypothetical factor.

It describes the subjective feeling of a painless lump in the throat or an abnormal laryngopharyngeal sensation. Though there may not be an identifiable physical cause for the symptom [20], it is often associated with persistent clearing of the throat, chronic cough, hoarseness, and swallowing impairment.

It has been proposed that regurgitation of stomach acid and digestive enzymes in EER induces chronic inflammation of the laryngopharyngeal structures

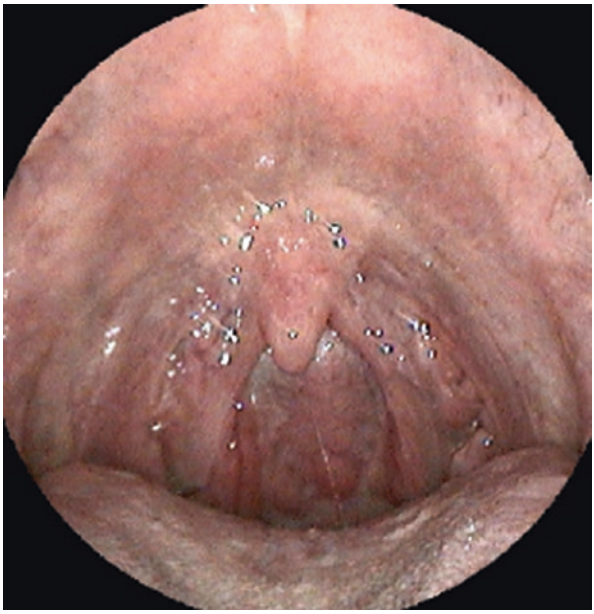

Fig. 6.1 Unspecific chronic lymphatic granulation of the pharyngeal mucosa in a GERD patient

resulting in unspecific inflammatory symptoms and GP symptoms [21]. Figure 6.1 shows a typical situation of unspecific chronic pharyngitis in a patient with suspected GP.

Anti-reflux treatment can often improve the clinical situation in GP, when EER plays a role on etiopathogenesis. EER is not the only reason for GP, but it can be contributing to the GP symptoms, as gastroesophageal reflux can be diagnosed in two-thirds of patients with GP [19]. However, the clinician should have in mind that EER can also be present in symptom-free controls without GP. Thus, GP is likely to be responsible for a subgroup of GP patients but cannot explain all GP cases [21].

6.5 Laryngopharyngeal Reflux Manifestation: Hoarseness, Vocal Fold Granuloma, and Benign Vocal Fold Alterations

Unspecific vocal and throat changes, which cannot be explained by other organic or functional voice disorders, indicate the possible influence of gastric or gastroduodenal reflux as a contributing or exacerbating factor, even in patients with no history of typical GERD. Laryngopharyngeal reflux manifestation is often associated with chronic cough syndrome and globus pharyngeus.

In 1991, Koufman operationalized laryngopharyngeal reflux [22]. A careful anamnesis and laryngostroboscopic examination can be enlightening. It can exclude laryngeal malignancy, benign vocal fold lesions, neurologic deficits, or phonation-associated vocal fold alterations.

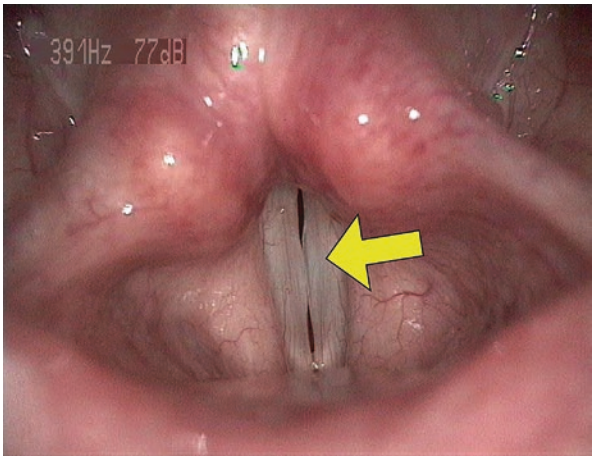

Fig. 6.2 Mild edema and swelling of the vocal fold edges in a female opera singer with GERD and phonation-associated vocal fold alterations

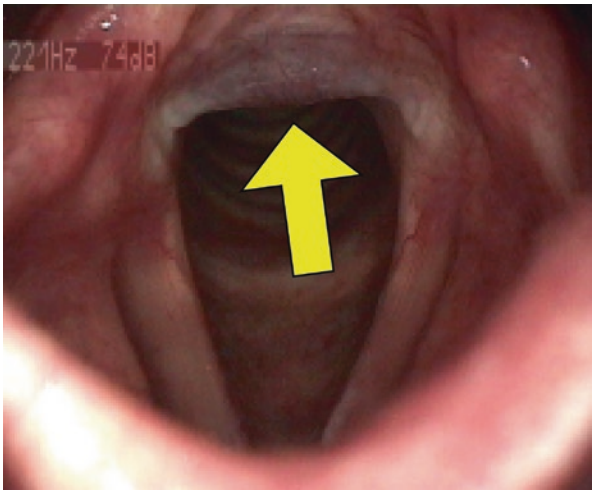

Fig. 6.3 Reflux laryngitis: posterior mucosal edema and thickening in the interarytenoid region

Typical laryngostroboscopic signs of reflux laryngitis are sulcus, pseudosulcus, thick secretions in the glottis, irregular free vocal fold edges (Fig. 6.2), erythema, interarytenoid mucosal edema (Fig. 6.3), posterior injuries such as ulcers and granuloma, and paradoxical movement of vocal.

Ulceration or granuloma in the cartilaginous part of the vocal fold has been strongly linked to reflux [23]. The mucosal damage by refluxate and the contact forces during phonation can cause either ulceration (contact ulceration) or granuloma (contact granuloma) as it is to be seen in Fig. 6.4. It is still difficult to determine the pathophysiologic relationship between reflux and granuloma [1].

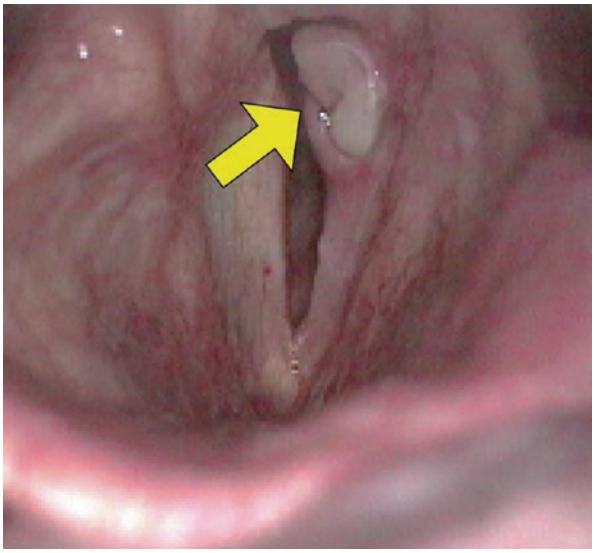

Fig. 6.4 Ulceration and granuloma in laryngopharyngeal reflux

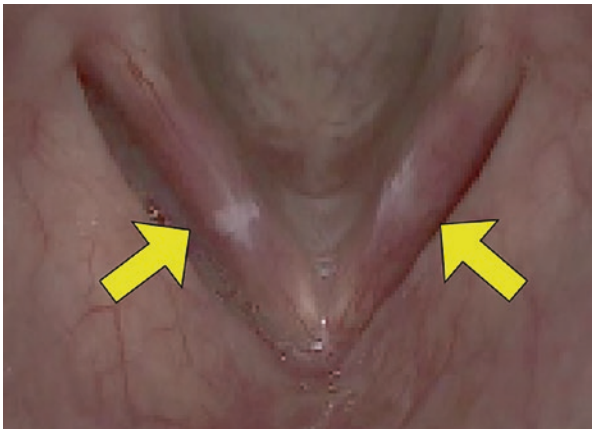

Fig. 6.5 Diffuse laryngitis with delayed wound healing

Meanwhile, laryngopharyngeal reflux has been associated with numerous other laryngeal alterations, including muscle tension dysphonia, Reinke's edema, laryngeal hyperirritability, laryngospasm, diffuse laryngitis, leukoplakia, glottic and subglottic stenosis, cricoarytenoid joint ankylosis, carcinoma, and other conditions [24, 25].

Many benign vocal fold lesions are of varying etiology and can be caused phonotraumatic secondary to voice overuse, misuse, or abuse. In situations without identifiable mass lesion or neurologic deficit, clinicians see a connection between vocal situation and reflux disease. EER is made responsible as a cofactor in many voice professionals and voice users, if the voice use alone cannot explain the development of the vocal situation. Reflux is believed to be a factor which negatively affects healing of vocal fold alterations after inflammation, phonotrauma, and also after laryngeal surgery (Fig. 6.5).

Table 6.4 Overview of patient-related outcome measures related to laryngopharyngeal reflux (modified after [1])

Study	Instrument	abbreviation
Wilson (1991)	Throat questionnaire	TQ
Deary (1995)	Glasgow-Edinburgh throat scale	GETS
Belafsky (2002)	Reflux symptom index	RSI
Carrau (2005)	Laryngopharyngeal reflux–health-related quality of life questionnaire	LPR-HRQL
Dauer (2006)	Supraesophageal reflux questionnaire	SERQ
Papakonstantinou (2009)	34-item Laryngopharyngeal reflux questionnaire	LPR-34
Andersson (2010)	Pharyngeal reflux symptom questionnaire	PRSQ

So far, patient symptoms have become a primary decision-driving method to identify those with LPR. Patient-reported outcome measures have become a principal diagnostic tool for LPR and monitoring the treatment outcomes [1, 4].

The most common patient-reported outcome measures related to laryngopharyngeal reflux have been summarized in Table 6.4.

The current controversies on LPR and GERD underline the problem of clinical interpretation of laryngostroboscopic findings as being reflux-related. Although clinical experience underlines the connection between LPR and EER, little success has been reached with correlation to investigations between specific laryngoscopic findings and the presence of reflux [26–28].

Regarding the need for further diagnostics, many colleagues argue that it is easier and more cost effective to treat laryngopharyngeal reflux empirically with a PPI than to spend additional time and effort investigating possible EER.

6.6 Vocal Cord Dysfunction

For the vocal cord dysfunction (VCD), several synonyms are in clinical use: paradoxical vocal fold movement (PVFM), paradoxical vocal fold movement disorder, and also induced laryngeal obstruction (ILO). VCD can be diagnosed already in children. Vocal cord dysfunction is a functional laryngeal dysfunction first described in the Nineteenth Century, as VCD causes paradoxical closing/adduction of vocal folds during inspiration, resulting in acute, episodic dyspnea. VCD is often mistaken for asthma, but is not responding to typical antiasthmatic treatment. Laryngoscopy during the acute respiratory event remains a gold standard for the diagnosis of vocal cord dysfunction. Exercise, psychological conditions, airborne irritants, rhinosinusitis, gastroesophageal reflux disease, or use of certain medications may trigger vocal cord dysfunction [29]. For many individuals, the role of postnasal drip and GERD in the pathogenesis of VCD is central, as they are often associated with VCD and likely lead to increased laryngopharyngeal sensitivity and hyperreactivity [30]. The patients need to be further examined in terms of the underlying pathogenesis of VCD. Management of VCD requires identification and treatment of underlying disorders. Treatment of acute episodes includes reassurance,

breathing instruction, and inhalation of a helium and oxygen mixture (heliox). Long-term management strategies include treatment for symptom triggers and speech therapy [29].

Usually, respiratory struggle during physical exertion (EILO = exercised induced laryngeal obstruction), asthma, and respiratory allergies have been suspected as underlying pathological factor. But refluxate of gastric contents can also induce laryngospasm and VCD. An interdisciplinary approach is needed to avoid unnecessary utilization of medical resources and potential delays of proper treatment [31]. In patients with suspected VCD, a gastroenterological examination including gastroscopy is strongly recommended.

6.7 Dental Erosions

Dental erosion can be considered as an extraesophageal manifestation of gastroesophageal reflux disease [9, 32, 33]. The association between acid reflux and dental erosion was first described by Howden in 1971 and was later confirmed in other studies. As dental erosion occur more often in patients with GERD, and subjects with unexplained dental erosions should be referred to gastroenterologists for further diagnostics.

Dental erosions are defined as a physical result of pathological, chronic, localized, painless loss of dental hard tissue, and the outer surface is chemically destroyed by acid or chelates [34]. Dental erosions are usually of multifactorial etiology. Even the interaction of all etiologic factors may cause a synergistic effect. According to the depth of the lesions, they might be divided into surface and deep ones, according to the localization into generalized and localized ones and according to pathogenic activities into manifesting and latent ones.

The connection between GERD and erosive changes on teeth is not absolute because not everyone with a diagnosed GERD presents also erosive teeth changes. GERD may be a risk factor for dental erosions only if it is in combination with refluxate regurgitation.

Further reasons for dental erosions might be attrition, abrasion, and abfraction [34]:

- *Attrition* is a defect of both dental tissue and restoration and is caused by tooth-to-tooth contact during mastication or para-functioning. Occlusal surfaces are smooth, shiny, evened, and hard and on amalgam fillings facets are observable. The bottom of the defect may be located both in enamel and in dentine [35].
- *Abrasions* occur with direct contact between the tooth and an external substance (tooth whitening paste, anti-nicotine, soda). Dental abrasion is most commonly seen at the cervical necks of teeth, but can occur in any area, even interdentally from vigorous and incorrect use of dental floss. Acid erosion has been implicated in the initiation and progress of the cervical lesion, while toothbrush abrasion has long been held as the prime cause of cervical abrasion [36].

- *Abfraction* is a defect which is characterized by loss of dental tissue in the cervical region. It is caused by compression and stretching forces which take place during dental flexure. At inadequate occlusal relation, the changes are localized mainly vestibular and they are of a wedged shape [37].

Dental erosion can result in tooth sensitivity, poor esthetic appearance, loss of occlusal vertical dimension, and functional problems. Clinicians must have thorough understanding of the causes of dental erosion as identification of the cause is the first step in its management. The inspection of the oral cavity in search for dental erosion should become a routine maneuver in patients with GERD [34].

6.8 Postnasal Drainage

Daily, the human body produces between 0.75 and 1.5 L of secretions from the upper airway, which has to be swallowed into the esophagus [38]. Thus, postnasal drainage is not a syndrome [39], but has to be considered as a rather normal physiologic process.

Clinical experience is that patients describing postnasal drip/drainage often complain on significantly thickened secretions, which the body recognizes as abnormal, thus manifesting in frequent throat clearing and cough.

Patients with globus sensation, postnasal drainage, or cough traditionally are first of all thought to be allergic. Thus, they are initially treated with antihistamines, decongestants, and cough protecting drops. All of these interventions usually increase the viscosity of the secretion and can exacerbate symptoms.

Therefore, hydration and avoidance of any drying medications can improve the symptoms.

Nevertheless, in patients with therapy resistant and persistent postnasal drainage symptoms, also extraesophageal symptom manifestation has to be considered.

6.9 Chronic Rhinosinusitis (CRS) With and Without Nasal Polyposis

The prevalence of chronic rhinitis is estimated to be high as 30% of the total population [40].

Chronic rhinosinusitis (CRS) is defined as an inflammatory disorder of the nose and the paranasal sinuses lasting for at least 12 weeks.

According to the EPOS 2012, it is characterized by the following clinical features [41]:

- nasal blockage/congestion/obstruction and/or,
- rhinorrhea: nasal discharge, anteriorly or posteriorly,
- ± facial pain/pressure
- ± reduction/loss of smell.

and either endoscopic signs of:

- polyps and/or,
- mucopurulent discharge and/or edema primarily in the middle meatus and/or,
- changes within the ostiomeatal complex and/or sinuses on computer tomography.

It affects approximately 15% of the adult population and may be divided into three clinical subtypes [42]:

- CRS without nasal polyps (CRSsNP) in Fig. 6.6,
- CRS with nasal polyps (CRScNP) in Fig. 6.7, and
- allergic fungal rhinosinusitis (AFRS).

Allergic rhinitis is considered as the most common etiology and is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose [43]. Over the past decade, extraesophageal reflux has been hypothesized to be one of the possible factors of the nonallergic rhinitis with nasal hyperreactivity that contributes to the development and worsening of chronic rhinosinusitis (CRS). GERD has to be excluded in any nonallergic, noninfectious chronic rhinitis. Otherwise, the treatment outcome might be poor.

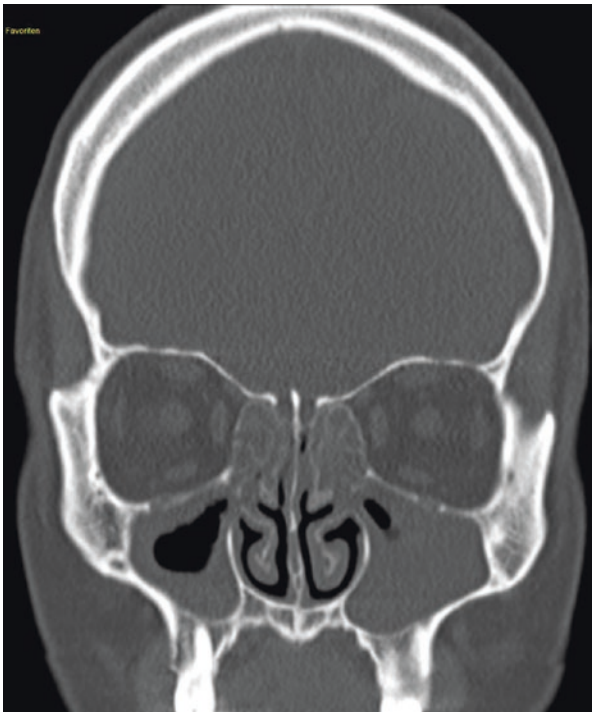

Fig. 6.6 Computer tomographic image of a patient with chronic rhinosinusitis due to GERD

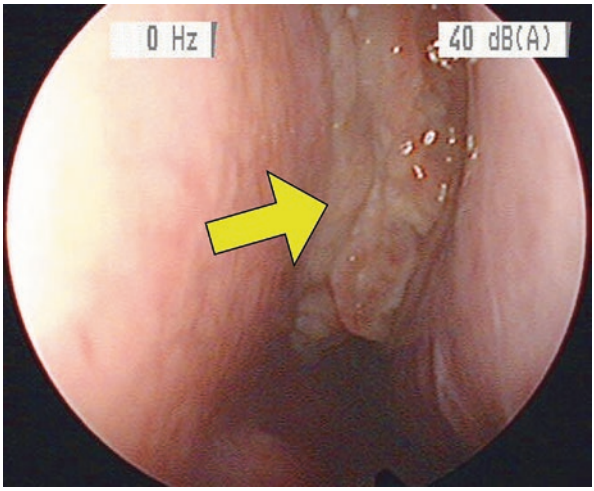

Fig. 6.7 Polyposis nasi during rigid anterior rhinoscopy

From the pathophysiologic point of view, two potential mechanisms are considered in order to explain how GERD and CRS may interact: direct cytotoxic effect of gastric refluxate displaced to the nasal cavity or an indirect mechanism due to a reflex from esophagus to the sinuses via the autonomic nervous system [44]. Several studies have tried to identify reflux or reflux components in the nasal cavity. As to acid, it has so far not been possible to document an increased incidence in patients with CRS compared to controls [44, 45], but in a small group of medically refractory CRS, most patients had a positive pharyngeal pH probe.

In other studies, patients with recurrent CRS had significantly more reflux events in the esophagus, but did not show more direct extraesophageal reflux signs [46].

However, pepsin could be found regularly in nasal lavage in patients with CRS [47]. Another ongoing discussion on direct reflux-associated association considers the evidence of *Helicobacter pylori* in the nasal and paranasal cavities. The bacterium was detected in the mucosa from ethmoid cells in many patients with CRS in comparison to controls [48]. But it seems to be present not only in patients with CRS but also in control subjects in the same percentage [49].

When it comes to an indirect GERD manifestation, as the underlying pathophysiological mechanism of CRS, it is believed that this can be an analogue of the reflex between gastroesophageal reflux and bronchial constriction [50]. Wong made an acid infusion test by installing saline and acid in the esophagus and measured an increased nasal mucus production. However, the number of participants in this study was low, and the result was not statistically significant.

6.10 Otitis Media

Acute otitis media (AOM) and chronic otitis media with effusion (OME) are among the most frequent causes for visits to the doctor especially in children in the age of 1 to 3 years [51]. There are several well-known conditions that cause or facilitate the

development of middle ear infections. The most important etiologic factors seem to be upper respiratory infections (including bacterial infections), anatomical characteristics, an immature immune system, allergies, and enlarged adenoids [52]. The acute otitis media with purulent effusion (AOM) is predominantly caused be single microorganism, most commonly *Haemophilus influenzae*, and also *Streptococcus pneumoniae*, *Alloiococcus otitidis*, or *Moraxella catarrhalis*, whereas otitis media with non-purulent effusions (chronic seromucotympanon) seems to be caused by predominantly polymicrobial entities and nonbacterial agents [53].

Enlarged adenoids are considered as the main reasons for chronic dysfunction of the Eustachian tube resulting in otitis media with effusion in younger children. Usually it can be treated successfully with adenoidectomy and paracentesis. In few children, the symptom of middle ear effusion reoccurs after adenoidectomy.

Here in consequence, it is necessary to identify other possible risk factors. Extraesophageal reflux is considered as one contributing risk factors of OME.

Extraesophageal reflux can cause inflammatory changes in the Eustachian tube and middle ear, with consequential development of middle ear inflammation [51]. Twenty-four–hour monitoring of oropharyngeal pH and detection of pepsin in the middle ear fluid are suitable methods for detecting EER in children with OME.

Otitis media with effusion occurs frequently in younger children with resulting conductive hearing loss. This is one of the important causes of hearing loss, which can lead to profound effects on language skills and cognitive development of children.

Pepsin and pepsinogen in otitis media with effusion are predominantly caused by LPR and should be considered as LPR predictors [54, 55].

6.11 Diagnostics and Management

Patients with extraesophageal reflux symptoms may require an individual antireflux treatment and/or referral to a gastroenterologist for further appropriate diagnostics.

Diagnosis of extraesophageal reflux manifestation has traditionally relied on symptomatology, questionnaires, laryngoscopy, stroboscopy, endoscopy, pH-monitoring, and radiologic examinations including barium swallow.

Combined multichannel intraluminal impedance and pH-monitoring provide an advance in EER/LPR diagnostics.

The Peptest, an immunoassay used to detect pepsin, can be used to diagnose extraesophageal reflux, especially in children with chronic otitis media with effusion [51].

First-line therapy for patients with extraesophageal reflux symptoms are lifestyle changes. Certain foods, body position, smoking, alcohol, and obesity should be considered in the GERD treatment.

Current guidelines for extraesophageal reflux manifestation suggest an initial empiric trial of proton pump inhibitors for at least 3 months in patients with suspected GERD symptoms. For those patients who improve with PPIs, GERD is

presumed to be the etiology. In patients with refractory reflux and failure to respond to a 3-month trail of behavioral changer and gastric suppression by adequate doses of PPI, combined multichannel impedance/pH monitoring might provide the single best strategy for evaluating reflux symptoms [56].

Nevertheless, the treatment of any extraesophageal manifestation has to consider not only the antacid medication (PPI) but also the surgical intervention, lifestyle changes/diet, voice therapy, antiallergic co-medication, and any other disorder-related treatment.

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