Extraesophageal Reflux and Upper Aerodigestive Tract Diseases

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Key Words

Extraesophageal reflux · Head and neck diseases · Gastroesophageal reflux · pH monitoring · Reflux therapy

Abstract

Reflux disease can cause multiple disorders not only of the esophagus but also of the upper aerodigestive tract. In the last decade, an association between reflux disease and multiple head and neck diseases was described, including those of the larynx and pharynx as well as those of the nose, the sinuses and the middle ear. The present article summarizes these different diseases and possible pathomechanisms are explained. In particular, there is a need to differentiate between the classical gastroesophageal reflux disease (GERD) and the extraesophageal manifestation of the reflux disease, called extraesophageal reflux (EER). Both diseases are characterized by different symptoms and can cause different disorders. To differentiate between GERD and EER, double-probe pH monitoring is mandatory. At last, some aspects of reflux therapy are explained.

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Gastroesophageal vs. Extraesophageal Reflux Disease

During the last decade, there has been increasing interest in and awareness of diseases caused by retrograde reflux of acidic fluid from the stomach into the esophagus and even into the laryngopharynx. Reflux of gastric contents such as acid and pepsin can cause disorders of sub-sites in the upper aerodigestive tract including the larynx, the pharynx, the trachea, the lung, the paranasal sinuses and the middle ear (table 1). The public health impact of these diseases is reflected in earlier studies, where the number of people suffering from gastroesophageal reflux disease (GERD) in the United States has been estimated to be 75 million. Within this population, 50% of individuals also show signs of extraesophageal reflux (EER) [1].

EER is distinguishable from GERD in several ways. Whereas classic symptoms of GERD include heartburn, regurgitation and dyspepsia, symptoms of EER tend to be less specific and include frequent throat clearing, globus or foreign body sensation, cough or hoarseness [2–4]. Patients suffering from GERD are known to have an increased risk of developing esophageal cancer, while EER is associated with diseases and possibly with cancers of the larynx and the lungs as well as disorders of the paranasal sinuses and the middle ears. Finally, GERD and EER can have different diurnal patterns and relationships to upright versus supine positioning.

Table 1. Diseases and unspecific symptoms which are suspected to be associated with EER

Location	Disease/symptom
Larynx, trachea and lung	Laryngitis posterior Laryngospasm Subglottic and tracheal stenosis Leukoplakia Laryngeal cancer Functional dysphonia/hoarseness Vocal cord nodules Larynx granuloma Tracheal stenosis Asthma Chronic cough Chronic bronchitis Lung fibrosis
Pharynx	Globus sensation Chronic pharyngitis Dysphagia Burning tongue Zenker diverticulum OSAS Frequent throat clearing (throat irritation)
Nose	Vasomotoric rhinitis Chronic sinusitis
Ear	Chronic otitis media Glue ear

Clinical findings in GERD differ from those in EER. In patients with GERD, esophagitis can typically be detected by endoscopy. Patients with EER, on the other hand, often have edema and erythema of the arytenoid and interarytenoid mucosa, or laryngitis. The most objective means by which EER can currently be documented is pH monitoring in the hypopharynx, proximal to the upper esophageal sphincter (UES). Selective pH monitoring in the distal esophagus does not produce reliable results concerning EER, so monitoring is ideally performed over 24 h using two probes, one proximal to the UES and the other proximal to the lower esophageal sphincter (LES). Histologic differences between the esophageal mucosa and the mucosa of the larynx and pharynx confer different intrinsic resistance to peptic injuries. Even when the laryngeal mucosa shows signs of EER, the esophageal mucosa may be uninjured [4]. Postma [5] has described how a majority of patients with voice disorders who suffered from EER did not have GERD. Similarly, Little [6] has found that about half of the children with document-

ed EER have normal acid exposure times in the esophagus. Koufman et al. [2] noted that fewer than 20% of patients with EER (n = 59) suffered from esophagitis, diagnosed by esophagoscopy and histology. In contrast, Yelon and Goldberg [7] found esophageal abnormalities in 80% of patients with posterior laryngitis. By using a double-probe pH monitoring system, we found in our own patients that 1/3 of those with normal esophageal acid exposure times, i.e. having a DeMeester score ≤ 14.72 , suffered from EER. Regardless of the differences in these studies, the common conclusion is that pH monitoring in the hypopharynx is essential to detect EER. Double-probe measurement of the pH enables accurate interpretation of hypopharyngeal data (fig. 1). Even though the proximal probe is inserted under visual control, there is a risk of its displacement which is followed by recording artifacts and drops in pH. In order to assure the validity of the proximal measurements, every decrease in pH in the hypopharynx must be preceded by a pH decrease at the distal probe in the esophagus.

Normal pH Values of Gastroesophageal and Extraesophageal Reflux Events

Normal values for GERD have been well defined, but those for EER have been less well studied or agreed upon. The most widely used classification system for GERD is the DeMeester Index. This scoring system uses a pH of 4 as the threshold based on the observations of Tuttle, who in 1961 described pyrosis when acid (pH = 4) is perfused in the distal esophagus [8]. In the hypopharynx, the threshold for a reflux event is also commonly defined as a pH ≤ 4 . However, pepsin is active and thus injurious to the mucosa of the upper aerodigestive tract at a pH of up to 5. Thus, the use of the DeMeester Index may mistakenly exclude EER events that can cause mucosal injury. We are currently conducting a study to determine normal values for EER by collecting data on the number of reflux events at pH ≤ 4 , as well as the number at pH ≤ 5 .

Another controversial normative value concerns the number of EER events in healthy individuals. A scoring system comparable to that of GERD (DeMeester score) does not exist for EER. According to Koufman, asymptomatic healthy persons have no EER events, whereas Toohill et al. showed that 20% of investigated healthy volunteers had EER events (summarized in Postma [5]). Smit [9] detected up to three reflux episodes in healthy persons (n = 20) at the level of the UES and de-

Fig. 1. An extract from the 24-hour double-probe pH monitoring: to avoid false-positive results, it is necessary to compare the hypopharyngeal pH with the esophageal pH. An EER event must be preceded by a pH decrease at the distal probe in the esophagus.

scribed a mean reflux frequency of 1.8 in 24 h. He further found a total time with a $\text{pH} \leq 4$ of 0.01% (0.02% in upright position) in healthy subjects. Vincent et al. [10] also described physiological reflux at the level of the hypopharynx (median = 1 reflux/24 h, 95th percentile = 6.9 events). Further complicating the definition of physiological reflux is the fact that there is variability in the positioning of the proximal probe, with some studies using a position proximal to the UES and others using a position just distal to the UES. Our own data support a normal range of 2–6 physiological hypopharyngeal reflux ($\text{pH} \leq 4$) events in 24 h with the proximal probe positioned proximal to the UES.

For consistency, a hypopharyngeal reflux episode should occur directly after a reflux event is measured in the esophagus (distal probe). pH decline must not be a consequence of intake of food or beverage. Exclusion of postprandial events requires that the patients keep a dietary intake log that can subsequently be correlated with the 24-hour pH data.

EER and Laryngeal Diseases

The most studied target of EER has been the larynx. This may be attributed to the fact that the larynx is directly next to the esophagus and thus represents the first organ to be injured when gastric fluid refluxes beyond the esophagus. Laryngeal manifestations include inflammatory diseases, neoplasms and disorders of laryngeal function (table 1) in both adults and children.

Posterior laryngitis is the best-known manifestation of EER [11, 12]. Many clinicians diagnose EER based on laryngoscopy alone, whereby thickening of interarytenoid mucosa and erythema and/or edema of the arytenoid mucosa can be seen. The addition of double-probe pH monitoring to the subjective laryngoscopic diagnosis of EER suggests that 70% of patients with posterior laryngitis have more objective pH evidence of EER [3]. Furthermore, the absence of posterior laryngitis by laryngoscopy does not exclude EER. Ylitalo et al. [13] have described normal laryngeal mucosal findings in patients with up to 15 pH-confirmed EER episodes. This group also attributed various benign lesions of the larynx, such as granu-

lomata, ulcers and nodules to acid exposure and injury of the laryngeal mucosa. An association between EER and subglottic laryngotracheitis has also been observed [14]. Several studies have suggested that more than 50% of patients with such benign lesions suffer from EER [14–16].

It is well established that GERD increases the risk of esophageal adenocarcinoma and squamous cell carcinoma. Similarly, data support a higher incidence of laryngeal cancer in patients suffering from EER, apparently due to chronic inflammation. Glanz and Kleinsasser [17] suggested in 1976 that chronic inflammation can give rise to laryngeal cancer. Separate studies by Galli et al. [18] (esophageal 24-hour pH monitoring) and El-Serag et al. [19] (case control study) found an 80% incidence of GERD in patients with squamous cell carcinoma of the larynx and hypopharynx. Koufman and Burke [20] detected EER in 66% of patients (33/50) with early glottic cancer by 24-hour double-probe pH monitoring. These studies did not consider other lifestyle factors that can contribute both to reflux and to cancer development. A study using double-probe pH testing in patients with premalignant and malignant lesions of the hypopharynx and larynx who do not smoke or drink alcohol is warranted.

Finally, EER can also cause disorders of laryngeal function. Most patients with EER suffer from voice alterations. EER is also highly associated with paroxysmal laryngospasm [21]. Many patients with laryngospasm respond to antireflux therapy [22].

EER, Chronic Cough, Asthma and Obstructive Sleep Apnea Syndrome

EER may lead to mucosal injuries in the trachea, the bronchi and the lungs. Chronic cough and bronchitis are documented symptoms in 30–50% of patients suffering from GERD [23]. Harding et al. [24] noted improvement in asthma symptoms and/or peak expiratory flow rate by more than 20% in patients treated with a proton pump inhibitor (PPI), and pulmonary function improved in 75% of such patients overall. The pathophysiology of reflux-induced pulmonary diseases is poorly understood. Whether the refluxate actually enters the trachea, the bronchi and the lungs with the result of direct acid and pepsin mucosal contact is not clear. These pulmonary symptoms may be induced via a neural mechanism, mediated by a vagal reflex which is triggered by contact of the esophageal mucosa with the refluxate. Such a neural

pathway might explain why patients whose laryngoscopy is inconspicuous still respond to antireflux treatment. Double-probe pH monitoring would help to differentiate between GERD and EER in these patients and would lead to a better understanding of the mechanisms.

A similar correlation exists between reflux disease and obstructive sleep apnea syndrome (OSAS). Both EER and OSAS are being increasingly diagnosed. Valipour et al. [25] observed that symptomatic GERD is common in patients with sleep-disordered breathing, but noted no difference between patients with OSAS and those with snoring alone. Ing et al. [26] performed simultaneous polysomnography and single-probe pH monitoring (esophagus only) and were able to show that patients with OSAS had 5 times more reflux events than controls. Senior et al. [27] showed a decrease in the respiratory disturbance index from 62 to 46 in OSAS patients with GERD who were given antireflux therapy. A cause-effect relationship between GERD and OSAS remains unproven. Whether EER occurs and actually causes irritation of the laryngeal and pharyngeal mucosa, leading to airway obstruction or not, is unknown. It is recognized that apnea episodes are accompanied by negative intrathoracic pressure, which might cause gastric fluid to be sucked into the esophagus and be detected as GERD. Thus, GERD in OSAS patients could be either the cause or the result of apnea events.

EER, Globus Sensation and Dysphagia

Globus pharyngeus is a common symptom in otolaryngological patients in whom a morphological correlate cannot be seen. As a result, this condition was even formerly labeled as globus hystericus. Nowadays, it is widely believed that GERD and EER are able to induce globus pharyngeus (summarized in Koufman [28]). Woo et al. [29] reported that two thirds of patients with globus had GERD (detected by esophageal pH monitoring), and other authors describe an incidence between 10 and 90%. We have recorded EER among 75% of patients with globus, detected by double-probe 24-hour pH testing. However, it remains unclear whether globus symptoms result from esophagitis, esophageal dysmotility or from irritation of the pharyngeal mucosa after peptic injury. Reflux disease should be considered in the differential diagnosis of every patient with globus sensation.

The same mechanisms that might be responsible for globus may cause dysphagia, namely chronic irritation of the pharyngeal mucosa, esophagitis or dysmotility of the

esophagus. The percentage of patients with GERD suffering from dysphagia is estimated to be between 25 and 50% [28]. Unfortunately, studies using double-probe pH monitoring are lacking.

Additional Head and Neck Manifestations of EER

Recent studies have considered a possible association between EER and chronic sinusitis as well as chronic recurrent otitis media. Poelmans et al. [30] described the course of 21 adult patients with middle ear complaints (chronic serous otitis media and feeling of pressure in the ear). Of these, 17 (80%) showed evidence of GERD (esophageal 24-hour pH monitoring), and all patients responded very well to PPI therapy. It is difficult to imagine that there is direct contact of refluxate with the middle ear mucosa. Fluid would have to pass from the stomach through the esophagus, pharynx, nasopharynx, and eustachian tube to enter the middle ear. Surprisingly, Tasker et al. [31] identified pepsin and pepsinogen in 84% of middle ear effusions (n = 54), suggesting that this pathway actually exists. Regardless, the eustachian tube itself is very sensitive to peptic injury. Animal studies have shown that the exposure of both the nasopharyngeal and the middle ear mucosa results in eustachian tube dysfunction which predisposes to middle ear complaints [32]. Alternatively, a neurogenic influence mediated through vagal stimulation in the esophagus must be considered. These same theories may also apply to chronic sinusitis. Bothwell et al. [33] showed that 75% of children with chronic sinusitis had abnormal pH testing, and in 25/28 children sinus symptoms improved with medical antireflux treatment. Similar results have been found in adults [34–36].

Host Barriers to Reflux and Treatment

The two most significant barriers against reflux are the LES and UES. Hiatal herniation allows the barrier of the LES to be easily overcome, increasing susceptibility to GERD. During coughing, the tone of the LES can be overcome by increased intra-abdominal pressure. Furthermore, normal esophageal function, namely coordinated motility, is necessary to ensure esophageal clearance, which in case of a reflux event means immediate clearance from the esophagus towards the stomach. Esophageal clearance time is increased in patients with GERD [4].

Saliva performs a buffering function and acts as a neutralizing agent against gastric acid. Vagally mediated protective reflexes also play an important role. One of these reflexes is the so-called pharyngo-UES contractile reflex. This reflex is stimulated by acid entering the pharynx; the reflex is less sensitive in patients suffering from EER [4]. The epithelium itself is also an effective barrier against gastric contents. The intrinsic mucosal resistance differs between different levels of the upper aerodigestive tract. Thus, the susceptibility to peptic injury differs between the esophagus and other organs, including the larynx. Furthermore, the ability of different mucosal sites to recover from peptic injury may differ [28]. Because of this difference, reflux might be harmless to the esophageal mucosa while causing pathology in mucosa at other levels.

Treatment options for reflux disease include lifestyle changes, pharmacological therapy and surgery. Patients should avoid fatty foods, chocolate, mints as well as caffeine, nicotine, alcohol and carbonated drinks, since these substances tend to increase acid production and can reduce LES tone. Furthermore, patients should avoid any food intake 3 h prior to bedtime. In obese patients, weight reduction is useful to reduce intra-abdominal pressure. Several drugs are known to have the potential to decrease LES tone, including theophylline, nitrates, diazepam and dopamine. Elevation of the head of the bed is a useful maneuver to decrease intra-abdominal pressure.

Optimal pharmacological therapy includes the use of PPIs. PPIs are able to alter the pH in the stomach to levels above pH 5 where even pepsin is inactive [4]. In contrast to other antireflux drugs, such as histamine receptor (H_2) blocking agents or liquid antacids, PPIs must be taken 30–60 min before meals. In an empiric study, it was shown that 67% of patients with EER improved on an 8-week treatment program with the PPI omeprazole (2 × 20 mg) [4]. A dose of 20 mg omeprazole daily for 2 weeks, the so-called PPI test used in patients with GERD, seems to be inadequate for the treatment of EER symptoms. The need for more aggressive PPI therapy in EER was reported in a consensus conference report on laryngopharyngeal reflux in 1996 [37]. In addition to PPIs, it is sometimes necessary to supplement with histamine receptor (H_2) blocking agents (e.g. ranitidine) to overcome the so-called nocturnal acid breakthrough [4]. This phenomenon is well known in GERD patients and pertains to a decrease in the gastric pH to levels <4 at night despite therapy with a PPI. Nocturnal acid breakthrough can be seen in up to 75% of patients [38]. An alternative to the long-term use of drugs is surgical fundoplication and semifundoplication, with reconstruction of the LES.

Conclusion

EER and GERD correlate with numerous diseases and symptoms of the upper aerodigestive tract that are diagnosed and treated frequently by otorhinolaryngologists. Therefore, EER and GERD should be part of the otorhinolaryngologist's diagnostic spectrum. However, a differentiation between EER and GERD is necessary since there are major differences in the clinical presentation of each. Twenty-four-hour double-probe pH monitoring is the gold standard for diagnosing EER and GERD. Just

as the clinical symptoms of GERD and EER differ from one another, optimal treatment differs. Compared to GERD, EER must be treated longer and with higher doses of PPIs to be adequately controlled. Many questions concerning the pathologic mechanisms of diseases due to GERD and EER remain unanswered, but the high incidence of these complaints and the recognition of the negative impact of gastric contents far beyond the stomach has stimulated intense research in this important field, whose improved understanding is sure to be forthcoming.

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