Pediatric Otolaryngologic Manifestations of Gastroesophageal Reflux Disease

Mark A. Gilger, MD

Address
Baylor College of Medicine, Texas Children's Hospital, Room 1010, 6621 Fannin, Houston, TX 77030-2399, USA.
E-mail: mgilger@bcm.tmc.edu

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In adults, an estimated 4% to 10% of chronic, nonspecific laryngeal disease seen in otolaryngologic clinics is associated with gastroesophageal reflux disease (GERD). Although no such estimates exist in children, many investigators have reported extraesophageal manifestations of GERD, of which the most common is the association of GERD with asthma and chronic cough. A variety of signs and symptoms of otolaryngologic disease also have been attributed to GERD, including hoarseness, laryngitis, chronic rhinitis, sinusitis, globus pharyngeus, recurrent croup, laryngomalacia, stridor, subglottic stenosis, otalgia, vocal cord granulomas, and oropharyngeal dysphagia. However, proof of the association between these manifestations of otolaryngologic disease and GERD is sparse. Furthermore, the manifestations of otolaryngologic disease often occur in the absence of such classic systems of GERD as heartburn or chest pain. This review explores the role of GERD in otolaryngologic disease in children.

Introduction

Gastroesophageal reflux disease (GERD) is a common condition affecting up to 10% of the adult population in the United States [1,2]. It affects infants and older children in different forms, but accurate estimates of the incidence and prevalence of GERD in children are lacking. Up to 50% of normal infants may have regurgitation that spontaneously resolves by the age of 2 years [3,4]. As such, gastroesophageal reflux is a normal physiologic process in healthy infants, but it is considered pathologic in older children [5]. Gastroesophageal reflux is generally defined as the spontaneous passage of gastric contents into the esophagus. Reflux is believed to occur during episodes of transient relaxation of the lower esophageal sphincter (LES) or through inadequate adaptation of the sphincter tone to changes in abdominal pressure [6].

In 1968, Cherry and Margulies [7] suggested an association between GERD and otolaryngologic disorders in their report of adults with contact ulcer of the larynx. Since that time, an increasing number of clinical reports have been published. Therapeutic trials and pH monitoring studies have suggested an increase in association of GERD in extraesophageal disease. In adults, an estimated 4% to 10% of chronic, nonspecific laryngeal disease seen in otolaryngologic clinics is associated with GERD [8]. Although no such estimates exist for children, several investigators have reported extraesophageal manifestations of GERD [9•,10–15]. For example, an apparent life-threatening event in infants and a variety of chronic respiratory disorders in older children have been associated with GERD, including reactive airway disease, chronic cough, and recurrent pneumonia. The most common is the association of GERD with asthma and chronic cough [13–15].

Many signs and symptoms of otolaryngologic disease, such as hoarseness, laryngitis, chronic rhinitis, sinusitis, globus pharyngeus, recurrent croup, laryngomalacia, stridor, subglottic stenosis, otalgia, vocal cord granulomas, and oropharyngeal dysphagia have been attributed to GERD (Table 1) [9•,10–12]. The causative relationship between GERD and the majority of these disorders has not been established because most of the studies have been uncontrolled and consist of small samples of children from referral centers. Furthermore, the manifestations of otolaryngologic disease often occur in the absence of such classic GERD symptoms as heartburn or chest pain. However, a recent investigation by El-Serag *et al.* [9•] compared 1980 children with GERD to 7920 children without GERD. In this case–control study, the investigators found that GERD in children without neurologic disease was associated with a several-fold increase in the risk of sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis.

Anatomic Considerations

To understand the extent of supraesophageal complications of GERD, one must appreciate the nature of the human aerodigestive tract, which involves one of the most complex, integrated networks in the body. In comparison with the aerodigestive tract anatomy of other mammals, humans

Table 1. Otolaryngologic manifestations of GERD in children

Chronic rhinitis, sinusitis, cough, and sore throat
Laryngitis
Hoarseness
Globus pharyngeus
Oropharyngeal dysphagia
Otalgia
Vocal cord granuloma and ulcer
Recurrent croup
Laryngomalacia
Stridor
Subglottic stenosis

exhibit a lower, more caudal position of the larynx, which results in a permanent expansion of the oropharynx. This anatomic feature underlies the distinctive breathing and swallowing patterns of humans compared with other mammals. The enlarged oropharynx provides humans with the articular production of speech. Although this evolutionary development has shaped humankind, the unique aerodigestive tract morphology of humans may actually predispose to an array of supraesophageal complications of gastroesophageal reflux [16]. Unlike rumination, seen in many herbivores, chronic gastroesophageal reflux in humans is not a normal or productive activity. Indeed, the human aerodigestive tract has not been selected by evolution for the purpose of dealing with constant retrograde emissions into the supraesophagus. Two aspects of the human aerodigestive tract may be designed especially poorly to handle supraesophageal reflux: a low laryngeal position and a relatively unprotected posterior larynx. These features provide access to an increased surface area of the oropharynx and remove the larynx itself as a potential roadblock to the path of reflux materials [16]. From an evolutionary perspective, our highly derived aerodigestive tract morphology may actually predispose humans to supraesophageal complications arising from gastroesophageal reflux [16].

Pathogenesis and Pathophysiology

An estimated 7% to 10% of the adult population of the United States experiences daily heartburn [17]. Several studies have shown that healthy people without reflux symptoms have GERD. However, very few people experience supraesophageal complications of GERD. Although no epidemiologic studies have evaluated the prevalence of reflux-induced aerodigestive tract complications in the general public, clinical experience suggests that the prevalence is relatively low compared with that of esophageal complications in GERD. These observations suggest the existence of potent airway defense mechanisms against esophagopharyngeal and pharyngolaryngeal reflux of gastric contents [17].

Airway-protective mechanisms against gastroesophageal reflux can be divided into two categories: 1) "basal mechanisms"—those that are constantly maintained without stimulation, as in LES and upper esophageal sphincter (UES) pressure; and 2) "response mechanisms"—those that are not constantly active but that become active upon stimulation, such as distention of the esophagus and mechanical stimulation of the pharynx [17]. For gastric contents to cause damage to the upper airway, the basal mechanisms (functional barriers) must first be overcome. These barriers include LES pressure and secondary peristaltic activity of the esophageal body and the UES. GERD is generally thought to be caused by significantly decreased pressure of the LES and inappropriate or transient relaxation of the LES. Although it is commonly accepted that transient relaxation is the most important factor, even this is uncertain. For example, Fouad *et al.* [18] found that ineffective esophageal motility is the most common esophageal manometric abnormality in GERD, actually exceeding the prevalence of transient relaxation of LES pressure. The pressure of the UES has been studied less, but it is known that UES pressure may decrease significantly at night, and over half of adult patients with larynx-induced symptoms had such findings in one study [19]. After refluxate enters the esophagus, a variety of response mechanisms come into play, stimulated by esophageal distention and mechanical stimulation of the pharynx. These include secondary esophageal peristalsis, the esophago-UES contraction reflex, the esophagolaryngeal closure reflex, the cricopharyngeus contraction reflex, and secondary pharyngeal swallowing [17].

Several possible mechanisms underlie reflux-induced symptoms of the airway: 1) gastric acid stimulation of receptors within the esophageal body, causing symptoms in the pharynx via neural reflex arc; 2) a second neural reflex arc between the esophageal body receptors and cardiovascular and respiratory systems, in which acidic fluid may activate these receptors, causing bradycardia and apnea; 3) stimulation of laryngeal chemoreceptors, leading to reflex apnea; and 4) direct damage of the mucosa of the pharyngo-laryngologic tract (Table 2) [20,21]. Direct, acid-induced damage is generally believed to be the most common mechanism. These complex defense mechanisms have not evolved to accommodate repeated retrograde reflux of a highly acidic nature. Repeated reflux may compromise the reflux closure mechanisms of the larynx, further damaging their effectiveness [21].

Otolaryngologic Manifestations of Gastroesophageal Reflux Disease

The typical manifestations of GERD in children, listed in Table 3, include a variety of signs and symptoms associated with esophageal disease [22••]. Table 1 lists many otolaryngologic manifestations of GERD in children. It is important to appreciate the latter more unusual symptoms of GERD. Because these otolaryngologic symptoms of GERD often occur in the absence of classic GERD symp-

Table 2. Proposed causes of GERD-induced otolaryngologic disease

Direct damage of the otolaryngologic tract by the refluxate (acid-peptic damage)
Reflex stimulation after esophageal reflux
Laryngeal chemoreceptors
Sensory stimulation of esophageal body receptors
Pharyngeal reflex arc
Cardiovascular/respiratory reflex arc

Table 3. Symptoms of GERD in children

Recurrent vomiting
Weight loss/poor weight gain
Regurgitation
Irritability
Heartburn/chest pain
Dysphagia/feeding refusal
Apnea/apparent life-threatening event
Abnormal neck posturing

toms, this phenomenon is often referred to as "silent GERD." Although awareness of silent GERD is growing, documentation of acid reflux as its cause is sparse.

Anatomically, the larynx and associated structures would be the first extraesophageal organs exposed to acid reflux. It seems logical to assume that disorders of the larynx would be the most common problems caused by gastroesophageal reflux, whereas disorders involving structures that are more distal, such as pharyngeal and tubotympanal disorders, would be less common. Brouchard *et al.* [23•] performed a retrospective analysis of the indications for esophageal pH study and followed up on those patients with otolaryngologic symptoms. Of 3000 esophageal pH studies performed in children over a 16-year period, only 105 of the children were referred for otolaryngologic symptoms to rule out gastroesophageal reflux. This study illustrates several points. First, otolaryngologic manifestations of gastroesophageal reflux are rarely considered, accounting for only 3.5% of all pH studies performed. Second, abnormal 24-hour pH studies were more commonly found in children with stridor, laryngomalacia, and laryngitis (*ie*, laryngeal disorders). Finally, pH study was not beneficial in children with recurrent otitis, dysphonia, or laryngeal papillomatosis. Specific otolaryngologic manifestations of GERD are reviewed in the following sections.

Chronic rhinitis and sinusitis

Rhinitis and sinusitis are frequently reported to have an association with GERD. For example, Contencin and Narcy [24] performed nasopharyngeal pH monitoring in 14 children with rhinopharyngitis and GERD, comparing them to 18 children without these symptoms. They found a significantly higher incidence of nasopharyngeal pH of less than 6 in the rhinopharyngitis group. Brouchard *et al.* [23•] found sinusitis, stridor, laryngitis, and laryngomalacia to be the most common otolaryngologic manifestations of GERD and recommended pH studies in any child with these symptoms. Bothwell *et al.* [25] reported a dramatic reduction in the rate of sinus surgery after initiation of medical treatment for GERD. Although these studies certainly suggest an association with GERD, some of them are problematic. For example, Contencin and Narcy [24] note that their use of a pH of less than 6 is significant for gastroesophageal reflux. Unfortunately, there are no normative data to support this contention.

Laryngitis, hoarseness, laryngomalacia, and stridor

Putnam and Orenstein [12] reported a case of a child with hoarseness and gastroesophageal reflux documented by esophageal biopsy and pH probe studies. They noted that the hoarseness resolved with medical therapy for gastroesophageal reflux. Similarly, Hanson *et al.* [26] reported that, in their series of 182 adults with endoscopically documented chronic laryngitis, 96% responded to antireflux therapy. Waki *et al.* [27] reported a retrospective analysis of 66 children who required hospitalization for recurrent croup. They found that 47% had an additional diagnosis of gastroesophageal reflux and recommended that children who had two or more episodes of croup be evaluated for gastroesophageal reflux and other airway abnormalities. Ulualp *et al.* [28] reported that pharyngeal acid reflux was more prevalent in patients with posterior laryngitis than in healthy control subjects. In this study of 20 adult patients compared with 17 healthy control subjects, ambulatory pH monitoring revealed that 75% of those with laryngitis exhibited pharyngeal reflux, compared with only 11% of control subjects. These authors also noted that abnormal esophagoscopy correlated poorly with the existence of laryngitis. Matthews *et al.* [29] attempted to determine the incidence and frequency of reflux in children with laryngomalacia using 24-hour double-probe pH monitoring. They found that 100% of the children had pharyngeal acid exposure assessed by the proximal pH probe, but only 66% of these same children had abnormal acid exposure measured by the distal esophageal probe. They recognized that normal values for pharyngeal acid exposure have not been established. Nevertheless, these authors concluded that most if not all children with laryngomalacia have laryngopharyngeal reflux. These studies are provocative in their association of GERD with laryngeal disease, but they also point out the inconsistencies of pharyngeal pH and esophagoscopy in determining acid reflux as a causative agent of laryngotracheal disease.

Globus pharyngeus

Globus pharyngeus, or the sensation of having a "lump in the throat," has often been associated with gastroesophageal reflux. Unfortunately, data supporting this relationship do not exist. In addition, the differential diagnosis is broad and includes many disorders with no discernable association with GERD, such as osteophytes of the spine,

Table 4. Diagnostic studies for otolaryngologic causes of GERD in children

24-Hour pH study
Esophagoscopy with biopsy
Laryngoscopy
Barium swallow/upper gastrointestinal series
Nuclear scintigraphy ("milk scan")

tonsillar hypertrophy, goiter, lymph nodes, and pharyngeal or esophageal masses [30].

Subglottic stenosis

GERD is widely held to play a causative role in subglottic stenosis. For example, in the canine model, Little *et al.* [31] demonstrated that trauma to the subglottic perichondrium was more severe when gastric juice was applied. Yellon [30] found at least one positive test for gastroesophageal reflux in 80% of children with subglottic stenosis. However, Zalzal *et al.* [32] reported that, in patients undergoing laryngotracheal reconstruction for subglottic stenosis, testing or treatment for GERD showed no benefit. Here again, although elegant animal studies seem to confirm that gastric acid irritation worsens or potentially causes subglottic stenosis, the clinical data remain controversial.

Otalgia and chronic otitis

Gibson and Cochran [33] reported on six children referred to their practice for recurrent otitis media. Each child was found to have either esophagitis or an abnormal pH probe. After medical treatment for GERD, all of the children improved, and four had complete resolution of their symptoms. Rozmanic *et al.* [34•] reported that 15 of 27 patients referred to them for chronic tubotympanal disorders had evidence of pathologic gastroesophageal reflux. Interestingly, they noted that daytime pH monitoring yielded significantly more episodes of reflux than did nighttime. In addition, distal pH monitoring was pathologic in six of 11 patients, whereas proximal pH monitoring showed that only three of 11 had pathologic GERD. Paralier *et al.* [35] reported a high frequency of pathologic GERD in 66% of infants with subchronic otitis. Nineteen of 22 patients with reflux found by pH study were asymptomatic and thus were diagnosed as having silent GERD.

Diagnostic Approaches

A variety of medical tests can be used to evaluate the role of gastroesophageal reflux in otolaryngologic disease (Table 4). Unfortunately, none of them is diagnostic. Indeed, the diagnostic test of choice for confirmation of GERD as a causative factor in aerodigestive disease appears to be resolution of symptoms after antireflux treatment [36•].

pH Monitoring

The most common test for evaluation of gastroesophageal reflux in otolaryngologic disease is pH monitoring (pHmetry) [37,38]. Several variations are used, including single, double, triple, and even quadruple probes. Single-probe pH monitoring measures the frequency and duration of acid reflux in the distal esophagus [22••]. The record of a patient's symptoms during the pH study can be used to correlate abnormal acid reflux with specific clinical scenarios. Dual-probe pH monitoring generally places the proximal probe just below the larynx. Triple-probe pH monitoring is not as well defined, but it generally places probes in the distal and proximal esophagus and just above the larynx.

Whether pHmetry actually proves the role of GERD in ear, nose, and throat disease is controversial. For example, Blecker *et al.* [39], using single-probe pH monitoring, found that 63% of children with chronic pulmonary disease had abnormal pH studies. Using a double probe, Contencin and Narcy [40] concluded that pH drops to 6 were indicative of pharyngeal reflux. Unfortunately, there are no normal values for pharyngeal reflux in children for comparison. Vijayaratnam *et al.* [41] also used a dual-probe technique, but they did not demonstrate a higher incidence of proximal esophageal acid reflux in infants with respiratory symptoms. Some investigators have reported false-positive pharyngeal reflux studies with ingestion of acidic foods [42] and "pseudoreflux" caused by loss of mucosal contact with the pH probe [43]; others have noted that hypopharyngeal reflux can occur in healthy control subjects [44].

Barium contrast radiography

The upper gastrointestinal series is useful for diagnosis of anatomic abnormalities of the esophagus, stomach, and duodenum. Compared with pH monitoring, barium contrast radiography is neither sensitive nor specific for the diagnosis of GERD. Although a common and simple test, its brief duration causes false-negative results, whereas the frequent occurrence of nonpathologic reflux causes false-positive results [22••]. Thus, barium contrast radiography is not a reliable test for GERD, much less for otolaryngologic manifestations of acid reflux.

Scintigraphy

Nuclear scintigraphy involves ingestion of a technetium-labeled formula or food. It is useful for demonstration of reflux, both acidic and nonacidic, as well as for estimating gastric emptying. Unfortunately, the correlation of scintigraphy with pH monitoring is poor, and normative data are lacking. Except for those instances in which scintigraphy detects the presence of suspected aspiration, its use is limited for the assessment of otolaryngologic manifestations of GERD.

Esophagoscopy

Endoscopy of the esophagus and mucosal biopsy can accurately diagnose esophagitis, stricture, and Barrett's esophagus and exclude other problems such as infectious esophagitis, Crohn's disease, and other structural anomalies [22••]. Whether esophagoscopy is useful in diagnosis of otolaryngologic manifestations of GERD remains controversial. Some investigators have reported esophageal biopsy results that are consistent with GERD in children with ear, nose, and throat problems [45,46]. Others, however, have found that the appearance of the esophageal mucosa and biopsy does not accurately predict or correlate with otolaryngologic manifestations of GERD [28].

Laryngoscopy

Laryngoscopy is the most logical method to evaluate the structures of the oropharynx for evidence of mucosal injury by acid reflux. Kamic and Radzel [47] performed laryngeal biopsies on 44 patients with posterior laryngitis and found hyperplasia of the prickle cell layer. In those patients with laryngeal ulcers, they observed abundant lymphocytes and plasma cells. McMurray *et al.* [48] reported increased eosinophils in laryngeal biopsies of patients with suspected pharyngoesophageal reflux, somewhat similar to findings in esophageal biopsies with GERD. Although these findings suggest acid-related laryngeal mucosal injury, no biopsy data are available from normal healthy children to corroborate these results.

Conclusions

GERD is a common disorder with a wide spectrum of signs and symptoms (Table 3). The pathogenesis of GERD is multifactorial, and as a result, it can be remarkably difficult to diagnose. In some patients, if such classic symptoms as heartburn and chest pain are not present, they are said to have silent GERD. This appears to be the case for diseases of the ear, nose, and throat (Table 1), which are now frequently identified as more unusual manifestations of GERD. A variety of diagnostic tools are available to evaluate many of the complications of GERD with reasonable precision, but unfortunately this does not hold true for the otolaryngologic manifestations. Although the association of GERD with laryngitis, stridor, laryngomalacia, and subglottic stenosis is clear, proof of acid reflux as the cause remains elusive. The best diagnostic test is still resolution of symptoms after antireflux treatment. To answer the question of whether GERD causes ear, nose, and throat disease, randomized, prospective, controlled studies are needed to determine the value of multiple-probe pH testing and intraluminal impedance monitoring [49,50]. These trials should also determine whether pharyngeal pH is diagnostic of acid reflux and if laryngeal biopsy is diagnostic of GERD.

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