Extralaryngeal Manifestations of Laryngopharyngeal Reflux Disease

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KEYWORDS

• Laryngopharyngeal reflux • Extralaryngeal manifestations • Otitis media
• Obstructive sleep apnea • Vagal nerve • Subglottis stenosis

KEY POINTS

- Extralaryngeal manifestations of laryngopharyngeal reflux (LPR) likely include otitis media, obstructive sleep apnea, subglottic and tracheal stenosis, inflammatory lung disease, sinusitis, and dental erosive disease; however correlations are hampered by the lack of diagnostic clarity about LPR itself.
- LPR symptomatology may arise from either direct soiling mechanisms or through vagal irritative pathways and neurogenic alterations.
- Extralaryngeal manifestations of LPR are usually not relate to acid, and are more likely related to inflammatory responses potentially from other components of refluxate such as pepsin and bile acids.
- Management of extralaryngeal manifestations of LPR rarely includes proton pump inhibitor therapy, and instead should be directed to the symptom site, using a combination of lifestyle behaviors, barrier protection, and antiinflammatory approaches, with surgery utilized on a case-by-case basis for specific elements.
- Further research is required to clarify pathways contributing to symptom generation and therefore provide additional therapeutic options.

INTRODUCTION

The throat is a cross-road where the airway and the gut intersect. Both are derived from the same embryologic anlage, the foregut, where the respiratory primordium expands and the mesoderm and endoderm of the fourth, fifh, and sixth branchial arches develop a solid tubular ventral outgrowth that descends and branches, eventually canalizing, to give rise to the tracheobronchial tree and lungs. It takes with it the neurovascular structures of the arches—vagal innervation looking after both afferent signaling and efferent motor output. The vagus nerve travels extensively, descending

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Otolaryngol Clin N Am 58 (2025) 497–506
https://doi.org/10.1016/j.otc.2025.01.002 **oto.theclinics.com**

Abbreviations	
AR	allergic rhinitis
CPAP	continuous positive airway pressure
DE	dental erosions
ETDQ	Eustachian Tube Dysfunction Questionnaire
GERD	gastroesophageal reflux disease
IHC	immunohistochemistry
LPR	laryngopharyngeal reflux
ME	middle ear
OME	otitis media with effusion
OR	odds ratio
ORL	otorhinolaryngology gology
OSA	obstructive sleep apnea
PPI	proton pump inhibitor
RFS	Reflux Findings Score
RSI	Reflux Symptom Index
SGS	subglottis stenosis
SNOT	sino-nasal outcome test
UADT	upper aerodigestive tract

from the skull base through the neck, chest (and via the diaphragmatic hiatus), into the abdominal cavity to disperse its terminal branches. Because of this broad distribution, vagal innervation is responsible for widely divergent activities from cough, to swallowing, to regulating cardiac rate, through to sweating and digestive functions. It is largely sensory (80%–85%) and largely parasympathetic, decreasing heart rate and promoting digestion. These connected pathways, of many smaller peripheral nerves working back to the main vagal trunks contribute to *convergence*—or amplification of response. Because of these shared origins, referred sensations also produce confusing manifestations such as epiglottic contact triggering bradycardia, and contact with skin in the external auditory canal engendering a cough response. This vagal connectivity is also a driver in understanding commonly presenting symptoms in the otorhinolaryngology gology (ORL) clinic. Food bolus lodged at the lower esophageal sphincter (LES) is typically localized by a patient to the sternal notch, and slow motility in the esophageal body can trigger vocal fold adduction, cough, and even laryngospasm. In these cases, the vagal responses are protective, acting to maintain airway patency, but at other times, these responses can be intrusive and worrying to patients and bystanders alike. When we seek to understand what efflux of gastric content into the esophagus or beyond, might really do, we need to consider the role that these neural networks play in signaling and triggering responses.

It is now commonly accepted that extraesophageal expressions of retrograde transit of material from the gut occur and differ from the classic gastroesophageal reflux disease (GERD) symptoms of heartburn and regurgitation. The term laryngopharyngeal reflux (LPR) was coined to imply material enters the pharynx, however, mechanistically there does not need to be direct contact of gastric fluid to the laryngopharyngeal mucosa to manifest symptoms. Nor is there a need for acid to be present to cause a response, as other gastric enzymes such as pepsin or bile acids play a role in symptom generation due to their injurious effect on mucosal epithelial cells and ability to trigger nociceptive protective responses in the same way as acidified refluxate.[1–4] Nonacidic elements in reflux are also being used as biomarkers of disease, with the most common being pepsin, treated as a surrogate for LPR diagnosis when found outside the esophagus.[5] In actuality, even neutral pH material that flows retrograde through the LES into the distal esophagus can trigger vagally mediated esophago-upper esophageal

sphincter, esophago-bronchial, and esophago-pharyngeal reflexes.[6,7] So, escape of anything from the gastric body into the esophagus may produce a pharyngeal response. To extend this further, other tissues outside the larynx may also respond to refluxate soiling or neurogenic stimuli. However, these extraesophageal and extralaryngeal symptoms may also be produced by other disorders and this overlap can confuse diagnostic strategies, particularly given the lack of a definitive diagnostic test for LPR. Children may also demonstrate a different phenotypic presentation with more vague symptoms such as poor feeding, irritability, arching postures, poor weight gain, wheeze, apneic events, sleeping difficulties, and recurrent respiratory problems along with the more commonly attributed symptoms in older children such as sore throat, throat clearing, cough, halitosis, drooling, postnasal drip, globus sensation, dysphonia, laryngeal spasm and paradoxic vocal fold movement, and dysphagia.[8] Most symptoms are indicative of benign disease; however there are indications that reflux-spectrum disease may also play a role in development of malignancy in the upper aerodigestive tract (UADT), in the same way as it does in the esophagus.[9] Riley and colleagues performed an surveillance, epidemiology and end result programme (SEER) database age-matched and sex-matched review in 27,600 adults >66 years, identifying rates of malignancy in 6 UADT subsites and how the rate was altered if a concomitant reflux diagnosis was assigned.[9] The odds ratio at the larynx was 2.86, hypopharynx 2.54, oropharynx 2.45, tonsil 2.14, nasopharynx 2.04, and sinus 1.40 compared to those lacking a reflux diagnosis.[9]

In this context, we need to consider the symptoms we ascribe to LPR. Globus (foreign body) sensation, cough, throat mucus, hoarse voice, and sore throat are now widely accepted as being related to reflux events. However, other symptoms now suggested to have reflux-based origins include eustachian tube dysfunction, rhinosinusitis, dysfunctional breathing, obstructive sleep apnea, postnasal drip, noncardiac chest pain, tonsillitis, dental erosions, gingivitis, and asthma.[5,6,8] More than one-third of patients demonstrate atypical GERD symptoms, with noncardiac chest pain the most prevalent (23%), and pulmonary manifestations for example, asthma and bronchitis next most common (10%–14%).[6] Head and neck symptoms are reported to affect 10% to 15% of those with GERD, with hoarseness (14.8%) most common, closely followed by cough (13%) and globus sensation (7%).[6] In the ORL clinic, rates of these symptoms are greater and usually not accompanied by typical GERD symptoms, leading to a clinical diagnosis of LPR.

EXTRALARYNGEAL MANIFESTATIONS OF LARYNGOPHARYNGEAL REFLUX

A diverse range of extralaryngeal manifestations of LPR should be considered.

Otological and Nasopharyngeal Symptoms

Sinus disorders and dysfunction of the eustachian tube, middle ear infections, or chronic ear infection, particularly in children, have been linked to extralaryngeal reflux.

Allergic rhinitis and rhinosinusitis

A correlative cross-sectional study performed in Syria examined overlap of allergic rhinitis (AR) (as diagnosed by the Score for Allergy Rhinitis) and LPR (as diagnosed by the Reflux Symptom Index, RSI).[10] Diagnosis of asthma was also elicited. The authors report significant overlap of disorders with odds ratio (OR) of 2.59 for having AR with LPR. Asthma was associated with LPR symptoms (OR-3) and with AR (OR-6.7)[10]! Hamdan and colleagues identified 57 patients with positive allergen tests and administered them self-reported reflux scoring tools (RSI and Reflux Symptom Score; Reflux Findings Score [RFS]).[11] They found significant correlation between elevated scores

and presence of allergy response (OR: 5.6).[11] Yeo and colleagues performed a retrospective analysis of LPR symptoms and signs using the RSI and RFS and compared this to chronic rhinosinusitis symptoms on the sino-nasal outcome test (SNOT-22) and endoscopic scoring, and whether these changed with sinus surgical treatment. SNOT-22 ratings correlated with both preoperative and postoperative RSI scores and RSI and RFS scores significantly decreased after endoscopic sinus surgery.[12]

Otitis media

A systematic review examined 29 articles regarding both adults and children with chronic or recurrent otitis media with effusion (OME) and reported the majority of studies identifying pepsin or pepsinogen in middle ear (ME) fluid and a 28.7% rate of LPR and 41% rate of gastroesophageal reflux (GER) according to different parameters.[13] There was inconsistency in methodology prompting the authors to recommend future studies collect impedance-pH data in association with examining ME aspirations.[13] Yin and colleagues evaluated 60 adults with secretory otitis media using the RSI and RFS, the Eustachian Tube Dysfunction Questionnaire (ETDQ)-7, and oropharyngeal pH-meter.[14] The RSI and RFS were elevated in 73% of subjects, the ETDQ positive in all subjects, and the Ryan index (derived from oropharyngeal pH monitoring) was positive in more than 3-quarters of subjects.[14] Crapko and colleagues measured pepsin concentration in ME fluid from 20 patients.[15] They found 60% of patients and 56% of samples positive for pepsin with a wide concentration range (80–1000 ng/mL).[15] Typical normal concentration of pepsin in salivary samples is below 16 ng/mL.[16] Samuels and colleagues analyzed middle ear fluid from 30 children (<12 year old) undergoing tympanostomy tube placement identifying pepsin in 77% of patients.[17] A study in Indonesia compared 46 children with OME (type B tympanogram) to 46 children without OME.[18] Those positive for OME demonstrated higher RFS (78% abnormal in OME and 52% abnormal in non-OME groups). Children with raised RFS were more than 3 times as likely to have OME than children without reflux findings, but OME did not correlate with adenoid size or allergic rhinitis presence (as defined by nasendoscopy and questionnaire enquiry).[18]

Yüksel and colleagues reported 71 children presenting to the ear, nose, and throat Clinic with hearing loss and fullness, diagnosed as otitis media with effusion by otoscopy and tympanometry.[19] Children also underwent gastroesophageal scintigraphy or a 24-hour pH probe to examine for reflux. A total of 55% of children were positive on one test for gastroesophageal reflux. In the GERD-positive group, there was a higher rate of tonsillitis/pharyngitis, rhinitis, and adenoid hypertrophy but other airway symptoms (stridor, cough, throat clearing) did not differ between reflux positive and negative groups.[19]

Oral Symptoms

Saliva is a valuable multifunctional product of the salivary glands in the upper digestive tract, with 6 major salivary glands supported by a multitude of minor salivary glands. The usual rate of saliva production in the oral cavity is around 0.5 to 1 mL/min depending on the level of stimulation, and the constituents of the saliva include lysozyme, immunoglobulins, mucins, lactoferrin, amylase, and dissolved ions including calcium and bicarbonate. Functions include a neutralizing effect on acids, initial digestion of foodstuffs, mechanical flushing of particles, mineralization of teeth, antibacterial activity, acting as a solvent for tastants, and moisturizing mucosal surfaces and food boli. Without saliva, dentition is poorly protected and food manipulation very difficult, resulting in oropharyngeal dysphagia complaints. Inflammation of the gingiva can occur, with development of caries and periodontal disease. Discomfort can occur with food manipulation, and certain food types may be unpleasant to taste or feel.

Gingival and dental damage

Reflux disease may impact salivary flow.[20] Salivary flow volume and swallowing function (as defined by the repetitive saliva swallowing test) was significantly worse in patients identified by Watanabe and colleagues as having GERD, compared to older and younger adults without GERD.[21] Gingival and oral mucosal inflammatory changes were also more prevalent in GERD patients compared to non-GERD.[21] A large recent metanalysis reported prevalence of dental erosions (DE) in GERD assigned subjects at 51% and in GERD-free controls at just 21%, with an odds ratio[22] of >5. In a study of 80 patients with DE identified on the Basic Erosive Wear Examination, 27 (33%) were positive for GERD on instrumental evaluation with 5 patients demonstrating erosive disease and 1 Barrett's metaplasia.[23] The authors recommended assessing for reflux disease in those identified with DE.[23] The same associations have been identified in the pediatric literature where another recent metanalysis of more than 4500 patients, concluded that enamel erosion and dentine erosion was more prevalent in GERD cohorts compared to normal children.[24] Although GERD is not equivalent to LPR, it represents part of the spectrum of potential reflux injury, and to cause direct surface damage, refluxate must have traveled to the oral cavity. Therefore, associations described in these studies are likely to be a good surrogate for LPR effect and represent an extralaryngeal manifestation.

Rajab and Zaidan examined DE in adults with endoscopy-identified GERD and took *salivary* samples to test pepsin concentrations.[25] They reported increased risk of DE (80% vs 31%) and significantly greater pepsin concentration (43 ng/mL vs 20 ng/mL) in GERD patients (n = 40) compared with controls (n = 35).[25] Office-based testing of salivary pepsin is available and combined with dental examinations that observe DE, may be a prompt to dental carers to refer patients for evaluation of possible reflux disease.

Reflux may affect multiple tissues in the oral cavity. Adachi and colleagues compared erosive esophagitis findings with markers of periodontal disease (level of lactate dehydrogenase and hemoglobin in saliva) in 280 individuals.[26] They could not find a difference between those with erosive esophageal disease or those without erosions, in relation to periodontal blood markers.[26] However, in a follow-on study, the same group did identify significantly elevated markers of periodontitis in patients with *Helicobacter pylorii* positivity, and when treated for *Helicobacter*, periodontal disease blood markers reduced.[27] Milani and colleagues examined bile acids in saliva of 26 patients identified with GERD (suggesting extraesophageal exposure) and 40 asymptomatic adults.[28] They found a higher rate of DE in GERD patients compared to controls (27% vs 7%). Two primary bile acids were quantified, with the level of taurocholic acid about 10 times that of glycocholic acid.[28]

Tonsillitis

In 2008, a single case was reported of a 3-year-old scheduled for adenotonsillectomy, only to have surgery canceled due to finding subglottis stenosis (SGS) at attempted intubation.[29] The SGS was thought to be reflux-mediated and therapy was instituted for reflux to support the airway. In follow-up, a subsequent reduction in adenotonsillar hypertrophy by 3 weeks was also seen, obviating the need for any pharyngeal surgery.[29] Kim and colleagues reported pepsin in tonsil tissue samples in 84 children and adults with tonsil hypertrophy and tonsillitis, associated with transforming growth factor beta-1 expression.[30] They proposed reflux-mediated tonsil inflammation and hypertrophy, due to exposure to pepsin.[30] A recent study from Abičić and colleagues, found pepsin in saliva and tonsillar tissue of 76 children presenting for tonsillectomy (41/76 positive, 54%).[31] Children showing immunohistochemistry (IHC)-positive tonsil biopsies also presented significantly elevated RSI scores, but the IHC results did not

correlate with salivary pepsin level (as measured by Western-blot analysis).[31] In a cohort comparison study, Tumgor and colleagues compared 44 children listed for adenotonsillectomy to 20 children with normal pharynges and without reflux symptoms, finding 73% (n = 32) of those with adenotonsillar hypertrophy were positive for GERD by esophagitis or pH testing.[32] pH monitoring did not predict erosive disease, but LPR score was associated with pH study results.[32]

Examining a group of 150 adult patients undergoing tonsillectomy due to recurrent tonsillitis, Tan and colleagues divided them into those with LPR (by use of the RSI and RFS) and those without LPR, then compared postoperative complication rate.[33] There was a higher rate of bleeding in those with LPR (9 vs 1 patient) and high ratings of pain at day 7 and 14 postoperatively in the LPR group.[33]

Pharyngeal Symptoms

Obstructive sleep apnea

A large cross-sectional study of the National Ambulatory Medical Care Survey investigated the association of obstructive sleep apnea (OSA) with GER.[34] This reported an odds ratio of 2, for co-occurrence of GERD with OSA even when controlling for confounders such as age, sex, race, sinonasal disorders, laryngeal disorders, obesity, asthma, and lung disease.[34] This study investigated GERD but may indicate a propensity for LPR to also be found in association with OSA. Caland Noronha and colleagues evaluated 18 children with OSA and adenotonsillar hypertrophy through nasopharyngoscopy, symptom questionnaire, polysomnography, and simultaneous esophageal pH monitoring.[35] They could not identify a temporal relationship between apnea events and reflux, but did find abnormal sleep behaviors, elevated apnea-index and elevated emotional distress, and daytime problems as reported by the questionnaire.[35]

Treatment of sleep disordered breathing using a continuous positive airway pressure (CPAP) machine therapy, in 46 patients with coincident OSA, chronic cough, and GERD (diagnosed by polysomnography [PSG], symptom score, hypopharyngeal-esophageal multichannel intraluminal impedence pH [HEMI-pH] monitoring protocol), resulted in a significant improvement in cough symptoms.[36] The effortful breathing pattern associated with OSA may draw gastric content into the low-pressure thoracic cavity and turbulent airflow in the pharynx irritates the superior laryngeal nerve making this more prone to respond to inhaled or ingested irritants.[36] After expiration, there is very little pressure differential between the distal esophagus and gastric cardia, roughly 4 to 5 mm Hg, which a normal resting LES pressure (10–35 mm Hg) can overcome.[37] However, a strong inspiratory effort may abolish the gradient and force gastric content to move in a retrograde fashion.[37] Nearly half of patients with OSA have GERD signs (42%) and likely each condition exacerbates the other.[37] Interestingly, when lifestyle modifications and antacids were used alone, without CPAP, there was a partial reduction in cough symptoms, suggesting that the disordered breathing pattern may trigger the reflux-related cough, rather than cough triggering reflux.[36] Furthermore, evidence suggests that when patients undergo surgery for OSA, there is also a notable decrease in GERD symptoms (as measured by the Gastroesophageal Reflux Disease-Health Related Quality of Life Questionnaire, GERD-HRQ) pre-surgery and 6-monts post-surgery.[38]

Diagnosis

This still represents the primary difficulty in understanding extraesophageal manifestations of reflux disorders. A recent literature review exploring diagnostic tools used to “identify” LPR found 23 studies using a variety of methods—triple or single pH sensor, oropharyngeal pH, hypopharyngeal esophageal manometry with impedance

(HEMII-pH), salivary or laryngeal pepsin concentration, laryngoscopy and esophagogastroduodenoscopy.[39] In order to identify reflux contribution to the disorders discussed earlier, proposed investigations include pH with impedance studies which can detect liquid, gaseous, and solid reflux at both acidic and nonacidic pHs. Nonacid reflux is more closely correlated with extraesophageal symptoms and reflects the poor treatment efficacy of acid-inhibition-only treatment approaches to these disorders given the prevalence of nonacid and caustic substances felt to contribute to symptom generation. Scintigraphy with Tc-99m has also been proposed as a way to detect subtle lung aspiration of refluxate and evaluate esophageal motility, but is not widely available or readily performed.[6] We await a true diagnostic tool to measure and confirm extraesophageal reflux and until then a test-battery approach (combination of history, endoscopic examination, patient-reported symptom score, pH with impedance study, and possible pepsin estimations) likely offers the best current approach.

Management

Management options usually follow a step-wise progression from lifestyle and dietary strategies, to medication reconciliation and use, through to surgical options.

For children, altering feed consistency and volumes, avoiding acidic foods (both mother and child), treating constipation, avoiding second-hand smoke, and sleep positioning (supine) have also been advocated to manage reflux.[8] Multiple pharmacotherapeutic options are available and are discussed elsewhere; however, none are specific for managing extraesophageal reflux manifestations. Novel approaches are under investigation such as use of pepsin inhibitors. Early work repurposing antivirals previously utilized for human immunodeficiency virus therapy, such as fosamprenavir, in isolation or combined with alginate, to antagonize pepsin effects has been suggested for extraesophageal reflux.[3] Investigation of both an oral formulation and an aerosolized preparation that may allow for a more favorable side effect profile is being undertaken.[40,41] These antivirals appear to reduce inflammatory cascades and mucosal damage in animal models.[3,42–44]

Surgical interventions, in particular therapy directed at the LES such as fundoplication or novel pressure-enhancing LES procedures, are considered in patients failing medical therapies, when there is an absence of major esophageal motility disorder. Success rates though, are modest, often no better than 75% even in highly selected patients[45]

SUMMARY

Extralaryngeal manifestation of reflux disease is common and insidious but may be difficult to fully ascribe to reflux directly due to overlap with other common conditions. A high index of suspicion (through understanding physiologic pathways) can help to tease out symptom expression and thus guide management discussions with patients. Whilst diagnosis is still controversial, we are moving toward better options, and have finally acknowledged that proton pump inhibitor (PPI) therapy is neither a diagnostic tool nor primary treatment option for laryngopharyngeal symptoms given that acid is rarely the driving factor in symptom production. Promising new therapies will address nonacid components of refluxate and disrupted neurologic and inflammatory pathways.

CLINICS CARE POINTS

- In suspected cases of laryngopharyngeal reflux disease causing laryngeal or extralaryngeal symptoms, clinicians should employ a test-battery approach to support the diagnosis. This should include patient-reported tools, endoscopic assessments, pH and impedance studies, and evaluation of pepsin in saliva or tissue samples.

- A therapeutic trial of PPI does not confirm or refute the diagnosis of LPR and should not be used as a diagnostic tool.
- Combined therapeutic strategies are more likely to be successful in managing symptoms, including behavioral therapy, dietary management, and mucosal barrier medications for example, alginates, sequestering medication, antipepsin medication, prokinetic therapies, and rarely targeted surgical interventions. A multidisciplinary approach can assist with diagnosis, identification of complications, and therapy management.

DISCLOSURE

The authors have nothing to disclose.

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