Extraesophageal manifestations of gastroesophageal reflux disease: real or imagined?

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Purpose of review

Extraesophageal reflux disease is a common clinical presentation to gastroenterology as well as ear, nose and throat, allergy, and asthma clinics. The diagnosis and management of this condition is challenging. We review the current dilemma in this area and discuss the latest studies which help guide our therapies for patients with suspected extraesophageal reflux.

Recent findings

Diagnostic approach to patients with extraesophageal reflux disease involved the use of insensitive tools, which have hampered the ability to correctly identify patients at risk. Empiric trial using proton pump inhibitors is still the recommended initial approach to those suspected of having reflux as the cause for extraesophageal symptoms such as asthma, chronic cough, or laryngitis. Diagnostic testing should be reserved to those unresponsive to therapy. Most recent studies suggest that ambulatory impedance/pH monitoring performed on therapy may be most likely to help exclude reflux as the cause for persistent symptoms. Recent randomized placebo-controlled studies on chronic laryngitis, cough, and asthma have been disappointing in showing benefit of acid suppressive therapy.

Summary

Gastroduodenal reflux may cause symptoms such as chronic cough, asthma, or laryngitis. However, we are currently limited in our diagnostic ability to identify the subgroup of patients who might respond to acid suppressive therapy. Impedance/pH monitoring may be a step in the right direction; however, outcome studies are needed to better understand the role of acid or nonacid reflux in patients with extraesophageal symptoms.

Keywords

asthma, chronic cough, chronic laryngitis, extraesophageal reflux syndrome, reflux

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Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications [1]. The manifestations of GERD are classically described as heartburn and reflux, which are often referred to as 'typical GERD.' However, GERD may also present atypically and is referred to as extraesophageal syndrome by the Montreal definition [1]. Common extraesophageal manifestations include reflux cough syndrome, reflux asthma syndrome, and reflux laryngitis syndrome.

Potential ways that gastroesophageal reflux may contribute to these symptoms involve both direct (aspiration) and indirect (neurally mediated) mechanisms [2–5]. A disturbance of the normal protective mechanisms may allow direct contact of gastroduodenal contents with the larynx or airway. This reflux may cause symptoms by irritation directly, or reflux may stimulate a vagal reflex arc producing cough and/or bronchospasm. Animal studies have documented that substantial laryngeal injuries may be caused by both exposure to noxious agents present in gastric and duodenal juice [5–8]. Injury secondary to acid and pepsin is a known causative factor in reflux esophagitis. However, trypsin and conjugated and unconjugated bile acids can cause histologic change in the absence of acid as well [4]. The reflux of nonacidic material may produce symptoms and tissue injury that may not be effectively treated with proton pump inhibitors (PPIs).

In this monograph, we will discuss the relevant studies in the past year in the area of extraesophageal reflux syndrome with respect to diagnostic testing and therapeutics.

Diagnostics

The diagnosis of reflux and the establishment of a clear relationship between reflux and extraesophageal symptoms can be challenging. When extraesophageal symptoms due to reflux are suspected, most current guidelines suggest an empiric trial of PPI therapy (provided there are no red flag signs or symptoms such as dysphagia and weight loss) [9••,10]. However, the response to antireflux therapy has ranged from 60 to 98% in patients with suspected extraesophageal reflux-related symptoms, and studies often have shown mixed results, leading to confusion regarding the importance of the association between reflux and extraesophageal symptoms [8,11–16].

Patients with suspected extraesophageal GERD syndromes who fail acid suppressive therapy are often referred for further diagnostic testing to establish the presence of GERD. One of the most commonly employed testing modalities used by gastroenterologists is esophagogastroduodenoscopy (EGD). However, Baldi *et al.* [17] found a very low sensitivity for EGD in patients with reflux cough syndrome and suggested that EGD should not be included in the diagnostic workup of such patients. Esophageal and pharyngeal pH monitoring is another common diagnostic testing modality employed in patients with extraesophageal GERD syndromes. Vaezi *et al.* [18] found that pH monitoring using pH sensors located in the proximal esophagus provided excellent specificity (greater than 90%), but had poor sensitivity and reproducibility. Other studies have confirmed that pH testing using catheters and wireless pH monitors have poor sensitivity as well [19–21]. These trials show that although reflux may be implicated as a cause of extraesophageal GERD symptoms, normal asymptomatic volunteers may have abnormal reflux events as well. Most recently, Sun *et al.* [*22*•] tested the Restech pH catheter for the detection of oropharyngeal acid reflux. The Restech pH catheter uses a nasopharyngeal catheter to measure the pH in either liquid or aerosolized droplets. This catheter is thought to reduce patient discomfort, allowing better understanding of extraesophageal reflux pathophysiology. It also provides a hydration monitor that can exclude erroneous results caused by drying of the pH sensor. In this study, they established normal values for acid reflux in the oropharynx for asymptomatic, normal patients. They suggest that further data on patients with GERD and laryngitis are now needed.

An important clinical question that remains unresolved is whether esophageal pH and impedance monitoring should be conducted on or off acid suppressive therapy. Pritchett *et al.* [23••] tested patients with heartburn, cough, chest pain, shortness of breath, hoarseness, or regurgitation with impedance and pH monitoring on twice-daily PPI therapy and then repeated their evaluation in the same patient population off therapy using wireless pH monitoring. They found that most (64%) patients with refractory symptoms on therapy had normal impedance monitoring results, suggesting causes other than GERD. However, if testing with impedance monitoring was abnormal on therapy, a strong positive predictive value for baseline esophageal acid reflux could be established. Therefore, they recommended that impedance/pH monitoring be conducted on therapy initially to evaluate PPI-resistant reflux suspected symptoms, because it can exclude the greatest number of patients from further testing. Additional studies in this area are ongoing to determine the cost-effectiveness of such an approach.

Chronic cough

GERD is generally considered one of the three main causes of chronic cough, along with asthma and upper airway cough syndrome, formerly called postnasal drip (PND). Gastroduodenal refluxate is thought to trigger cough by irritation of the upper respiratory tract by macroaspiration or microaspiration, irritation without aspiration, and by simulation of an esophageal-bronchial cough reflex [19]. Also, an increase in intraabdominal pressure during coughing episodes may be sufficient to overcome the lower esophageal sphincter basal pressure to provoke reflux events as well [24,25]. However, many patients with reflux-induced cough do not have typical GERD symptoms. Everett and Morice [26] found that only 63% of patients with reflux-associated cough displayed classic reflux symptoms. These patients often had symptoms associated with eating and were more likely to exhibit cough in the upright position, during daytime hours, during phonation, and upon arising from a supine position.

The common tests used to diagnose typical GERD have only limited utility in the diagnosis of GER-associated cough. It is clear that reflux-induced cough does not correlate well with esophagitis. In one study of 45 patients suffering from cough thought secondary to chronic reflux, for example, only 15% had endoscopy-proven esophagitis [17]. The role of 24-h esophageal pH monitoring has also shown limitations. Although the sensitivity of pH monitoring has been reported as high as 90%, the specificity of this test has been quite low [27–32]. Patterson and Murat [33] found that only 1% of the total cough episodes in patients were associated with hypopharyngeal reflux events.

Nonacidic reflux triggering chronic cough is a concept that has also gained interest over the past decade. Irwin *et al.* [34] reported that patients who had initially failed PPI therapy had marked improvement after fundoplication. More recently, the role of impedance monitoring for

the detection of nonacidic reflux has been explored. Impedance monitoring has the ability to detect both acidic and nonacidic reflux. Most impedance monitoring studies have shown no increase in reflux events in patients with chronic cough compared to normal controls [35–38]. However, Patterson *et al.* [39] suggested that patients who have a positive symptom association probability (SAP, an index of the correlation between reflux episodes and symptoms) on impedance monitoring may have more reflux episodes that cross the upper esophageal sphincter than SAP-negative patients. Of note, there was no difference detected between these groups in the number of reflux episodes crossing the lower esophageal sphincter.

Recent studies have explored the temporal relationship between reflux events documented by pH or impedance monitoring and episodes of coughing. Sifrim *et al.* [40] used ambulatory pressure-pH-impedance monitoring and found that although the majority of cough events did not immediately follow reflux events, 31% of patients did have cough within 2 min of a reflux episode. In addition, Blondeau *et al.* [35] reported that of 100 patients with suspected reflux-associated cough, 23% had a significant temporal correlation between coughing spells and reflux during impedance/pH monitoring. More recently, Decalmer *et al.* [41] found that in a group of patients with chronic cough, impedance monitoring showed a significant temporal cough-reflux association in 56% of patients. However, given the lack of outcome studies with impedance monitoring, the clinical relevance of these findings remains suspect.

The treatment of patients with suspected reflux-associated cough has also been studied extensively. Vaezi and Richter [42] found that treatment with omeprazole resulted in complete resolution of symptoms within 2 months in 10 of 11 patients with GER-associated cough. Another study found that 56% of patients who had both cough and typical symptoms of GERD had resolution of their cough symptoms with omeprazole treatment [43]. Unfortunately, other studies have not found such a good response of chronic cough to antireflux therapy [44]. This suggests that other causes of cough should be investigated in patients who are unresponsive to aggressive acid suppression, and definition of the role of nonacid reflux in this group will require outcome-driven studies.

Asthma

Although asthma and GERD are both common conditions in the general population, it has been documented that patients with asthma have a much higher prevalence of GERD than would be expected by chance alone. A 24-h pH monitoring has shown that up to 80% of asthmatic patients have abnormal acid reflux [45]. Although most asthmatic patients with GERD have typical reflux symptoms, approximately 40% do not [46••]. Conversely, symptoms commonly associated with asthma, including cough and chest pain, are often found in patients with GERD, and this symptom overlap can make it difficult to determine the nature of the association between the disorders. There are two leading pathophysiologic theories to explain the association between GERD and asthma: aspiration of refluxed gastric contents causes bronchospasm and refluxed acid stimulates sensory afferent nerves in the distal esophagus that trigger a vagally mediated reflex of bronchospasm [47].

Controversy surrounds the benefit of how therapy targeted at GERD improves asthma control. In placebo-controlled study reported in 1999, Kiljander *et al.* [48] found that PPI therapy did not improve asthma in patients who had GER documented by 24-h pH monitoring. In 2003, Sontag *et al.* [49] evaluated the effects of fundoplication, ranitidine, and placebo on asthma symptoms in patients who had both asthma and GERD. In this patient population, 75% of patients treated with fundoplication had improvement in nocturnal symptoms, compared to only 9.2% of those treated with pharmacotherapy alone and to only 4.2% of control patients. In 2006, a controlled trial suggested therapeutic benefit for PPIs in the subgroup of asthmatic patients with both nocturnal respiratory and GERD symptoms, but no benefit for those without nocturnal symptoms [50]. Littner *et al.* [51] found that patients with asthma and symptomatic GERD who were treated with acid suppressive medications did have an improvement in asthma-related quality of life and a reduction in asthma exacerbations, but acid suppression did not affect daily symptoms. Most recently, the American Lung Association Asthma Clinical Research Centers published data showing that patients with poor asthma control who were already receiving inhaled corticosteroids and who lacked typical reflux-related symptoms did not have improvement in asthma control with the addition of twice-daily esomeprazole therapy for 6 months [52]. In this randomized, double-blinded, controlled study, patients underwent ambulatory 24-h pH monitoring at baseline. Approximately, 40% of patients had abnormal reflux; however, those patients were no more likely to respond to PPI therapy than those with normal pH monitoring results.

Current guidelines suggest that patients with both asthma and symptomatic GERD should be treated with acid suppressive medications [53]. Consideration of antireflux medication for patients who have poorly controlled asthma without GERD symptoms has also been proposed. However, given the findings noted above, such recommendations are not data-driven and we must await future trials to delineate the subgroup of patients with asthma who may benefit from aggressive acid suppression or surgical fundoplication.

Reflux laryngitis syndrome

Chronic laryngitis is defined as inflammation of the larynx that lasts more than a few weeks. The classical symptoms of chronic laryngitis include hoarseness, throat pain, sensation of a lump in the throat (globus), repetitive throat clearing, excessive phlegm, difficulty swallowing, heartburn, and voice fatigue. Most laryngitis is triggered by irritants like cigarette smoke. However, in patients not exposed to cigarette smoke or other irritants, reflux may play a role. This condition is often called reflux-induced laryngitis or laryngopharyngeal reflux (LPR).

Although reflux has been widely accepted as a common cause of chronic laryngitis, the results of diagnostic testing often challenge that concept. The two most commonly employed diagnostic modalities are laryngoscopy and 24-h pH monitoring. Laryngoscopy is the most common test used to diagnose reflux-related laryngitis. However, in 2002, Hicks *et al.* [54] evaluated pharyngeal changes in patients with suspected LPR and found that the hypopharyngeal lesions attributed to reflux were also found frequently in asymptomatic control patients. In addition, the hypothesis that patients with suspected LPR have increased reflux events that can be documented by 24-h pH monitoring appears to be false. In 2007, Joniau *et al.* [55] conducted a systematic review of reports on patients with suspected LPR who underwent 24-h pH monitoring and found no significant difference between patients and normal controls in the frequency of pharyngoesophageal reflux events. The role of nonacidic refluxate in LPR is unclear and needs further study by impedance monitoring. Most recently, Kotby *et al.* [56] performed a critical analysis of the literature on LPR. Their search analyzed publications between 1977 and 2008. They found that the majority of reports published were review articles. Furthermore, most of the published studies on LPR included fewer than 30 participants, which, the authors felt, was inadequate. The authors also concluded that the 'golden test' for the diagnosis of LPR was still not available.

The treatment of LPR with acid suppressive medication generally has been disappointing. Qadeer *et al.* [57] performed a meta-analysis of eight different trials in which PPI therapy was employed for LPR. In this meta-analysis, only one study showed a statistically significant benefit for PPI therapy. Overall, they found that PPIs did not lead to a significant improvement in chronic laryngitis symptoms. In addition, the largest multicenter trial of 145 patients conducted by Vaezi *et al.* [58] found no significant difference in the resolution of symptoms or laryngeal signs of LPR between patients treated with twice-daily esomeprazole and patients treated with placebo for 16 weeks. Thus, future trials are needed to better understand the role of acid and/or nonacid reflux in patients with chronic laryngitis.

Conclusion

Symptoms of extraesophageal reflux may include cough, asthma, chronic laryngitis, hoarseness, and sinusitis, and extraesophageal reflux is diagnosed commonly in clinical practice. Symptoms are attributed to direct irritation of the larynx and airway by refluxed material and to neurally mediated pathways as well. The most recent studies suggest that gastroesophageal reflux may play a role in chronic cough, but the role of reflux in chronic laryngitis and asthma is far less clear. An empiric trial of PPI therapy is reasonable when GERD is thought to be contributing to extraesophageal symptoms. More invasive diagnostic testing should be reserved for those unresponsive to PPI therapy, and the predominant role of such testing should be to exclude reflux as the cause of patients' persistent symptoms. Recent data suggest that esophageal impedance/pH monitoring conducted while the patient is taking antireflux medication may be the single most important test for determining the contribution of reflux to extraesophageal symptoms. However, further clinical data on the cost-effectiveness of this approach are needed. Additionally, future trials are needed to identify the subgroup of individuals with extraesophageal reflux symptoms who may benefit from PPI therapy or surgical antireflux therapy.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 415).

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