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Investigation of extraesophageal gastroesophageal reflux disease

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Abstract

The most common extraesophageal manifestations of gastroesophageal reflux disease (GERD) include chronic cough, asthma and laryngitis. There are two mechanisms proposed to explain extraesophageal syndromes caused by GERD. The first one is a direct way via irritation and/or microaspiration and the second one is an indirect, vagally mediated way. The investigation of extraesophageal manifestations of GERD is difficult and the empirical therapy with proton pump inhibitors usually double dose for at least three months is still the most common approach.

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

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Introduction

Gastroesophageal reflux disease (GERD) is a commonly diagnosed chronic disorder in the western countries [1]. According to the Montreal Classification, GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [2]. Despite the fact that GERD typically presents with esophageal symptoms such as heartburn and regurgitation [3], it may also present with extraesophageal symptoms. The most common extraesophageal manifestations of GERD include chronic cough, asthma and laryngitis (Table 1) [2].

There are two mechanisms proposed to explain extraesophageal syndromes caused by GERD. The first one is a direct way via irritation and/or microaspiration and the second one is an indirect, vagally mediated way [4-9]. Irritation occurs with the entrance of gastroduodenal contents into the pharynx and larynx with or without microaspiration in deeper airways due to the disturbance of the normal protective mechanisms. In the second mechanism, symptoms are caused by vagally mediated esophago-tracheal-bronchial reflex when reflux reaches the lower esophagus [10,11]. It is known by embryological studies that esophagus and bronchial tree share a common innervation via the vagus nerve.

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Conflict of Interest: None

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Table 1 Montreal definition of gastroesophageal reflux disease and its constituent syndromes [2]

Esophageal syndromes	Extraesophageal syndromes
Symptomatic syndromes	Established association
Typical reflux syndrome	Reflux cough
Reflux chest pain syndrome	Reflux asthma
	Reflux laryngitis
	Reflux dental erosions
Syndromes with esophageal injury	Proposed association
Reflux esophagitis	Sinusitis
Reflux stricture	Pulmonary fibrosis
Barrett's esophagus	Pharyngitis
Adenocarcinoma	Recurrent otitis media

Note: the listed manifestations may present alone or in combination

Nowadays, several tests have improved the diagnostic field of typical GERD. However, the investigation of extraesophageal manifestations of GERD is still difficult, and new methods and studies are needed to improve these diagnostic problems.

GERD-related cough

Beside asthma and postnasal drip, GERD has been confirmed to be one of the main three causes of chronic cough, accounting around 20% of cases [12-16]. Chronic cough is defined as cough that persists for longer than 8 weeks. GERD should be investigated in patients who are not taking any cough-inducing medications, who are non-smokers or exposed to other environmental irritants and who have normal x-ray and no evidence of asthma or postnasal drip

[12,13,17]. The American College of Chest Physicians suggest that GERD-related cough typically occurs during daytime, in the upright position and is non-productive [12].

Irritation of the upper respiratory tract with or without microaspiration is reported as a possible mechanism, but this hypothesis remains controversial [18]. Microaspiration may occur due to impairment of the protective reflexes or due to excessive challenges of pharyngeal reflexes [19]. Several studies have reported ineffective esophageal peristalsis in patients with chronic cough with or without acid reflux, suggesting that poor esophageal clearance might be related to cough episodes [20-22]. On the other hand, infusion of acid into the distal esophagus increases the frequency of coughing [5] and cough reflex sensitivity [23]. In a recent study, it was found that the proximal extent of reflux events is not important for provocation of cough [24]. Both central and local reflexes are considered to induce cough [17]. In addition, cough itself may promote reflux events. An increase in intra-abdominal pressure during cough episodes may provoke reflux events by overcoming lower esophageal sphincter basal pressure [5,25].

Unfortunately, the common tests used to diagnose typical GERD are less useful to diagnose GERD related cough. It has been proven that only a minority of patients with chronic cough and GERD have typical symptoms and/or evidence of esophagitis. Typical GERD symptoms such as heartburn and regurgitation are present in 25% approximately of patients with reflux cough [5,26]. In one study it is reported that 63% of patients with reflux-related cough, were experiencing also typical reflux symptoms [27]. In another study only 7 of 45 patients suffering from chronic cough related to GERD, had endoscopy-proven esophagitis [28]. Thus, endoscopy has limited utility in this group of patients. Besides that, it has been reported that 24-h esophageal pH monitoring has as low as 66% specificity in patients with reflux related cough [10,13,29-32]. Baldi *et al* found that only 53% of the patients with chronic cough had pathological reflux related to their symptom during 24-h pH monitoring [28]. In addition, Patterson and Murat found that only 1% of the total cough episodes in patients were associated with hypopharyngeal reflux events [33].

It is nowadays believed that non acid and weakly acid reflux can also be associated with symptoms such as cough and regurgitation in patients "off" and "on" proton pump inhibitor (PPI) therapy and therefore the threshold of pH 4 has been questioned [34-37]. Impedance monitoring can detect both acid and non acid reflux and is very useful especially in patients who are resistant to PPI therapy. Blondeau *et al* studied 100 patients with chronic cough (77 "off" and 23 "on" PPI therapy) using impedance-pH monitoring. It was reported that acid reflux could be a potential mechanism for cough in 45 patients and weakly acidic reflux in 24 patients [38]. In another study ambulatory pressure-pH-impedance monitoring was used and it was 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 [36]. Greater prevalence for both reflux-cough and cough-reflux associations than other techniques have been reported by studies using ambulatory acoustic systems to record cough sounds [39,40].

It is important to consider the differences between association reflux-cough and causality. This is particularly true in extra-esophageal GERD symptoms. Only in cough, is possible to try to analyze the one to one association using symptom associated probability (SAP) or symptom index (SI). It is much more complex to do so with symptoms such as globus or hoarseness.

Even if the SAP or SI are positive, the causality is not proven. Only outcome studies can prove causality, but unfortunately most placebo controlled clinical trials have failed to demonstrate a gain effect (vs placebo) of medical antireflux therapy and most published surgical trials are not controlled and potentially affected by high placebo effect.

The treatment of patients with suspected reflux related cough remains controversial. Vaezi and Richter found that in 10 of 11 patients with GERD-associated cough, treatment with omeprazole resulted in complete resolution of symptoms within 2 months [41]. In a first meta-analysis of placebo-controlled studies, most of which included only a few patients, a certain effect of PPI treatment on chronic cough in patients with GERD appeared probable [42]. However, a recent Cochrane review found that there was no significant difference between placebo and PPI treatment [43]. Similar results are reported from a large randomized controlled trial in patients with laryngeal reflux and ENT manifestations [44]. Esomeprazole 40 mg for 16 weeks failed to show any benefit compared to placebo. Interestingly, Reiche *et al* reported a case of cough induced by omeprazole, therefore physicians should be alert to the possible onset or exacerbation of cough during PPI therapy [45].

On the basis of current knowledge, other causes of cough should be investigated in patients who do not respond to PPI therapy and the role of non acid reflux should be defined. Recent studies suggest that impedance-pH monitoring with careful analysis of the symptom-reflux temporal relationship may help to select the right patients who can truly benefit from treatment of GERD [46,47]. In the case of negative results during the investigation "off" therapy, we should avoid PPIs and repeat pH-impedance monitoring after 6-12 months [18]. A recent follow-up study showed that most of patients with chronic cough had improved after 2 years [48]. The empirical therapy with PPI usually double dose for at least three months is the most common approach. Baldi *et al* have found that a four-week trial of double-dose PPI therapy appeared to be an effective criterion for selecting those patients who will respond well to standard PPI therapy. More than 80% of those patients who responded to PPI therapy had a positive response to the initial trial [28]. In patients who have documented reflux and do not respond to PPI therapy, it is proposed to perform a pH-impedance monitoring "on" therapy and define the role of non acid reflux. Antireflux surgery may be the solution for patients with refractory acid or non acid reflux and a good temporal correlation between reflux events and symptoms. Allen and Anvari studied surigical treatment of GERD in treating chronic

cough and reported that laparoscopic Nissen fundoplication is effective in the control of cough in patients with GERD, with or without primary respiratory disease. After surgery, half of the patients had complete resolution and one third had significant improvement of their cough. In addition, it has been shown that the response to surgical treatment may be dependent on the presence of typical GERD symptoms [50]. Further investigation should be conducted to determine the role of reflux inhibitors such as baclofen and lesogabaren in patients with chronic cough [51-55]. Additionally, some centrally acting agents such as morphine and gabapentin may have therapeutic benefit in these patients by inhibition of the esophago-bronchial reflex and central sensitization [56,57].

GERD-related asthma

Asthma and GERD are frequently associated, as it is concluded by a systematic review of studies [58]. It has been shown that asthma patients do indeed go on to develop GERD, but an increased incidence of asthma in patients with GERD should be considered controversial [58]. Asthmatic patients whose symptoms are getting worse after meals, and or patients who do not respond to anti-asthmatic therapy should be suspected of having GERD-related asthma. Similarly, patients who have GERD symptoms before the onset of asthma symptoms should be considered to have reflux induced asthma [59]. Kiljander *et al* found that slightly more than half of asthmatic patients had abnormal esophageal acid exposure by pH monitoring. However, one third of these patients had no typical reflux symptoms [60]. Additionally, Legett *et al* studied patients with difficult to control asthma by using 24-h pH monitoring with distal and proximal pH probe [61]. It has been shown that the prevalence of reflux at the distal probe was 55% and at the proximal probe 35%. A large population-based epidemiological investigation showed that subjects with the combination of asthma and GERD had a higher prevalence of asthma and respiratory symptoms as compared to patients without reflux symptoms [62]. Moreover, Sontag *et al* reported that compared to controls, asthmatics have significantly more frequent and more severe day and night reflux symptoms and significantly more of the pulmonary symptoms attributed to GERD [63].

There are two proposed mechanisms that can explain the correlation between GERD and asthma. Direct contact of gastric acid with the upper airway, in some cases due to microaspiration, and a vagovagal reflex triggered by acidification of the distal portion of the esophagus can cause bronchospasm [64]. The relationship between GERD and airway hyperactivity can be detected using provocation tests during lung function assessment. Airway hypersensitivity can occur in parallel with GERD. This can be demonstrated with capsaicin or citric acid tests. Whether increased GER can provoke such hypersensitivity is still controversial.

Moreover, it has been shown that night-time reflux has a major role in the pathogenesis of supra-esophageal complaints [64]. During nighttime there are changes that provoke this situation, such as slower gastric emptying, decreased saliva production, decreased swallowing frequency and reduction in voluntary clearance behavior [18]. Additionally, asthma itself can provoke GERD. During asthma exacerbation there is negative intra-thoracic pressure which can facilitate reflux events and medication used to treat asthma, such as theophylline, β-agonists, steroids, may promote gastroesophageal reflux as well.

There is great controversy regarding the role of antireflux therapy in asthma control. An older study by Kiljander *et al* found that in asthmatic patients with documented GERD by 24-h pH monitoring, there was a reduction in nocturnal asthma symptoms, whereas daytime asthma outcome did not improve after an 8-week omeprazole treatment [60]. A controlled trial suggested therapeutic benefit for PPIs in the subgroup of patients with both nocturnal respiratory and GERD symptoms. In subjects without both conditions, no improvement could be detected [65]. Moreover, Littner *et al* reported that in adult patients with moderate to severe persistent asthma and symptoms of GERD, PPI treatment for 24 weeks did not improve daily asthma symptoms or pulmonary function. However, patients had an improvement in asthma-related quality of life and a reduction in asthma exacerbations [66]. The American Lung Association Asthma Clinical Research Centers reported that treatment with proton-pump inhibitors does not improve asthma control, despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma [67]. Additionally, a Cochrane review for asthmatic patients found only minimal improvement of asthma symptoms with antireflux therapy [68]. On the other hand, there are limited high-quality data on the role of antireflux surgery in asthma control. Field *et al* reported that surgery may improve reflux and asthma symptoms and decrease medication requirements, but it has little effect on pulmonary function [69]. There are some controlled studies which have been reported comparing H2-receptor antagonists and fundoplication. In one study cimetidine and surgery were both associated with improvement in asthma symptoms and medication, but not with improved pulmonary function compared to placebo treatment [70]. Sontag *et al* studied patients who had both asthma and GERD it was reported that antireflux surgery has minimal effect on pulmonary function, pulmonary medication requirements, or survival, but significantly improves asthma symptoms and overall clinical status, compared to ranitidine and placebo [71]. Thus, it is not clear yet if surgery can improve quality of life of asthmatic patients.

Current data suggest that patients who suffer from both asthma and GERD should be treated with antireflux medications [72]. The initial empiric trial of twice daily PPIs for 2-3 months is recommended and then treatment should be adjusted to the minimal dose necessary to control symptoms. For those unresponsive to this initial approach, combined impedance-pH monitoring should be performed "on" therapy to detect patients with persistent acid reflux or non acid reflux. Patients with difficult to treat asthma and/or nocturnal symptoms without typical reflux symptoms should be investigated "off "therapy. This investigation may help detect patients with pathological

reflux and evaluate the temporal correlation between reflux events and respiratory symptoms. To conclude, one should be cautious to delineate the subgroup of asthmatic patients who may benefit from acid suppressive medication or surgical fundoplication and future trials are needed to identify better GERD and asthma association.

GERD-related laryngitis

Chronic laryngitis is defined as inflammation of the larynx that lasts several weeks and is frequently diagnosed in the ENT specialist's office [8]. Symptoms may include hoarseness, throat clearing, cough, globus sensation, throat pain, voice fatigue and heartburn. However, these symptoms are not specific and often occur due to postnasal drip, voice overuse, environmental irritants and smoking [73]. Chronic laryngitis and difficult-to-treat sore throat are associated with acid reflux in as many as 60% of patients [74]. It has been proposed but not proven that failure to diagnose laryngopharyngeal reflux may result to more severe complications, such as ulcers, granuloma, subglottic stenosis and lower airway disease [75].

Laryngoscopy is the first-line investigation that is usually performed to diagnose reflux related laryngitis. In the past, endoscopic lesions such as vocal cord ulcerations were associated with GERD [76,77]. More recently, laryngeal findings in reflux related laryngitis often include posterior cricoids erythema, vocal cord erythema/edema and arytenoid erythema/edema [78]. However, in an older study it was reported that the majority of asymptomatic control patients had hypopharyngeal lesions attributed to GERD [79]. Milstein *et al* also found that several signs of posterior laryngeal irritation, which are generally considered to be signs of laryngopharyngeal reflux, are present in a high percentage of non-symptomatic individuals and that these signs were more often detected with flexible than with rigid laryngoscopes [80]. More recently, Vavricka *et al* challenged the diagnostic specificity of laryngopharyngeal findings attributed to gastroesophageal reflux and found no difference in the prevalence of laryngeal lesions between patients with known GERD and normal subjects [81]. The only difference was noted in the posterior pharyngeal wall cobblestoning. 24-h pH monitoring is often used as a diagnostic tool, but again it has limitations. In a systematic review of reports, it was found there was no significant difference between the prevalence of pharyngoesophageal reflux events in patients with reflux laryngitis and healthy controls, when undergoing 24-h pH monitoring [82]. Most studies use dual pH sensors, usually placed 20 and 5 cm above LES, to correlate proximal esophageal and hypopharyngeal acid exposure with extraesophageal manifestations of GERD. Unfortunately the placement of the proximal pH sensor is inaccurate or the sensor does not work adequately due to dehydration when it is located above the UOS.

In addition, Kotby *et al* conducted a critical analysis of the literature between 1977 and 2008 and concluded that there is not a "gold standard" test for the diagnosis of laryngopharyngeal reflux [83]. Impedance monitoring should be further used to determine the role of non acid reflux, especially in patients who continue to have symptoms, despite PPI therapy. Additionally, the Restech catheter, which is a transnasal catheter with ion flow sensor able to measure the pH both of liquid and aerolized droplets in the posterior oropharynx, is under investigation and it has been proposed that it could increase the diagnostic yield in laryngopharyngeal reflux. However, recent studies showed very poor specificity of Restech measurements, making its use in clinical practice very controversial [84,85].

Treatment of reflux related laryngitis with acid suppressive therapy is generally disappointing. Qadeer *et al* conducted a meta-analysis of eight different trials and concluded that PPI therapy was not beneficial for patients with chronic laryngitis symptoms [86]. Furthermore, in a large multicenter trial there was no evidence provided of a therapeutic benefit of treatment with esomeprazole 40 mg b.i.d. for 16 weeks compared with placebo for signs and symptoms associated with chronic laryngitis [44]. Nevertheless, when reflux related laryngitis is suspected, PPI therapy is recommended for 3 months until further scientific data become available [87].

Concluding remarks

The management of patients with extraesophageal manifestations of GERD remains challenging. In the absence of specific diagnostic methods capable of identifying individuals who might respond to antireflux therapy, an empiric trial of PPI therapy is the common approach. More invasive diagnostic testing should be reserved for those with poor or partial response to the initial PPI therapy to exclude reflux as the cause of patients' persistent symptoms. Future trials are needed to improve these diagnostic problems and identify the subgroup of individuals with extraesophageal reflux manifestations who may benefit from PPI therapy or antireflux surgery.

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