Respiratory and laryngeal symptoms secondary to gastro-oesophageal reflux

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Gastro-oesophageal reflux may cause a range of laryngeal and respiratory symptoms. Mechanisms responsible include the proximal migration of gastric refluxate beyond the upper oesophageal sphincter causing direct irritation of the larynx and lower airway. Alternatively, refluxate entering the distal oesophagus alone may stimulate oesophageal sensory nerves and indirectly activate airway reflexes such as cough and bronchospasm. Recognising reflux as a cause for these extraoesophageal symptoms can be difficult as many patients do not have typical oesophageal symptoms (eg, heartburn) and clinical findings on laryngoscopy are not very specific. Acid suppression remains an effective treatment in the majority of patients but there is growing appreciation of the need to consider and treat non-acid and volume reflux. New opinions about the role of existing medical and surgical (laparoscopic techniques) treatment are emerging and a number of novel anti-reflux treatments are under development.

Introduction

Gastro-oesophageal reflux disease (GORD) is defined as a condition which develops when the reflux of gastric contents causes troublesome symptoms and/or complications. Studies suggest that the prevalence of GORD may be as high as 20% in the general population and that this may be increasing worldwide.^{1,2}

The majority of reflux events are confined to the body of the oesophagus, but episodes traversing beyond the upper oesophageal sphincter (UOS) and reaching the laryngopharynx do occur.³ In the most recent consensus statement on GORD, the existence of a number of extraoesophageal reflux (EOR) syndromes was recognised.⁴ An established association with reflux was recognised for a number of these syndromes—namely, cough, asthma and laryngitis. For other conditions, including idiopathic

pulmonary fibrosis, otitis media and sinusitis, a clear association with reflux was considered less certain. In this article we focus on the common respiratory and laryngeal symptoms associated with EOR, the possible mechanisms responsible, investigations and current management options available.

Laryngeal symptoms associated with reflux

Laryngeal symptoms are described in up to 72% of patients with GORD (table 1). In a small 14-year follow-up study of healthy patients without symptoms with normal 24 h pH study at baseline, 39% developed laryngitis and almost half reported extraoesophageal symptoms—in particular, frequent throat clearing and cough.⁵ The number with pathological acid reflux on pH-metry increased over time (possibly owing to increasing body mass index), but there was no association between the presence of laryngitis or symptoms and acid exposure in the posterior pharynx. Although the study was small and prone to type II error, it does suggest that the relationship between GORD and extraoesophageal symptoms is complex and that factors other than acid (non-acid reflux, smoking, voice abuse) may be responsible.

Laryngitis

Supraoesophageal structures are less tolerant of acid than the oesophageal mucosa.⁶ A causal relationship between laryngitis and reflux may be difficult to establish. This is further confounded by an inconsistent response to acid suppression with proton pump inhibitors (PPIs).^{7,8}

Respiratory symptoms associated with reflux

Respiratory symptoms, in particular cough and wheeze, occur in between 15% and 18% of patients with GORD (table 1).⁹

Chronic cough

Chronic cough is defined as a cough persisting for more than 8 weeks and GORD is thought to account for approximately one-third of cases referred for specialist evaluation.¹⁰ Temporal associations between acid reflux and cough recorded on 24 h pH-metry suggest a causal link but weakly acidic or non-acidic reflux can also induce cough.¹¹ Therefore treatment directed solely at acid suppression may not be successful. This important point will be developed later in this review.

Wheeze and breathlessness

The prevalence of GORD in asthma ranges from 34% to 89%, depending on the population studied and the methods used.^{12,13}

Mechanism of GORD-associated respiratory and laryngeal symptoms

Reflux theory

The oesophagus is protected from refluxate by its mucosal properties and anti-reflux clearance mechanisms (figure 1). However, the larynx and respiratory system can be damaged by the direct toxic effect of gastric refluxate, which may arise if protective mechanisms in the upper oesophagus and/or laryngeal area are ineffective. Recent evidence suggests that patients with laryngitis have a lower

threshold for distension-induced triggering of UOS relaxation, providing a possible mechanism for this extraoesophageal manifestation.¹⁴ Patients with GORD may actually be at increased risk of aspiration owing to impaired mechanosensitivity in the upper airway.¹⁵ However, recent evidence suggests that there may be compensatory heightening of chemosensitivity which may offset this risk.¹⁶

Reflex theory

This theory proposes the direct or indirect activation of laryngeal and airway reflexes by gastric refluxate entering the distal oesophagus. In a blinded study comparing distal oesophageal acid perfusion with saline perfusion a significantly greater cough frequency was observed when acid was perfused into the distal oesophagus compared with saline.¹⁷ In the same study when lignocaine was instilled topically onto the oesophagus, cough was prevented. We have previously demonstrated that distal oesophageal acid exposure may be associated with increased airway neuropeptide levels, supporting the relationship between acid reflux and airway nerve activation.^{18,19} Lang *et al*²⁰ have shown that in anaesthetised cats, applying acid to the oesophagus was associated with a bronchoconstriction and increased mucus secretion in the airway.

Cough-reflux cycle

The act of coughing may elicit a reflux event and so induce a cough-reflux-cough cycle. A recent study of 24 h ambulatory acoustic cough recording with simultaneous impedance/pH monitoring concluded that cough may indeed be self-perpetuating.²¹ However, rather than the strain of coughing inducing a reflux event which immediately triggers another cough, the repeated cough induces reflux events which lead to sensitisation (possibly centrally) of the cough reflex.

Table 1 Laryngeal and respiratory symptoms associated with reflux⁵⁹

Laryngeal symptoms associated with reflux
Excessive throat clearing
Globus
Paroxysmal laryngospasm
Laryngitis
Respiratory symptoms associated with reflux
Chronic cough
Wheeze and breathlessness

Figure 1 Mechanism of gastro-oesophageal reflux disease-associated respiratory and laryngeal symptoms including (A and B) reflux and (C) reflex theory. Reproduced with permission from *J Clin Gastroenterol* 2009;43:414–9.

Investigations

Confirming that EOR symptoms are directly due to GORD can be difficult as patients typically do not have reflux symptoms such as regurgitation and heartburn. For example, only one-third of patients with GORD-associated cough report dyspepsia. To further complicate the issue, clinical features of laryngitis on direct laryngoscopy are non-specific.²² However, there is histological evidence of a link between reflux and laryngeal mucosal damage.²³

Bulmer *et al*²³ have shown that pepsin (contained in refluxate) can cause damage to laryngeal mucosa, and immunohistochemical studies of laryngeal biopsy specimens have demonstrated the presence of pepsin. Recent technological developments, such as multichannel intraluminal impedance (MII) monitoring, may help to identify EOR episodes above the UOS and currently offers most hope of a reliable diagnostic test.

Direct laryngoscopy

To overcome the limited specificity of direct laryngoscopy the Reflux Finding Score (RFS) has been developed. The RFS is an eight-item validated clinical severity score based on findings at laryngoscopy.²⁴ A score >11 is strongly suggestive of laryngopharyngeal reflux.

Oesophagogastroduodenoscopy

Upper endoscopy is typically normal macroscopically in patients with EOR.

Barium swallow

Barium swallow is neither sensitive nor specific. Barium swallow may, however, detect structural abnormalities (including hiatus hernia) or dysmotility disorders including achalasia.

Oesophageal pH monitoring

There is some controversy about whether parameters established for GORD are appropriate to diagnose laryngopharyngeal reflux and to define pathological reflux in the context of respiratory symptoms. Reichel and Issing²⁵ have suggested that laryngeal reflux should use the definition pH<5 and not pH<4. The decision to perform pH studies 'on or off' PPI depends on the clinical situation. Ambulatory oesophageal pH monitoring while not receiving treatment may be of value to exclude excess acid gastro-oesophageal reflux. With regards to laryngeal symptoms, pharyngeal pH recordings above the UOS have been shown to lack sensitivity and to be poorly reproducible.²⁶ Oesophageal pH studies also did not predict response to treatment.²⁷ Using ambulatory oesophageal pH monitoring with distal and proximal pH probes in patients with chronic cough reveals a better correlation between distal acid exposure and episodes of coughing, in keeping with the reflex theory.²⁸

Oesophageal manometry

In one study 43 subjects with chronic cough underwent 24 h oesophageal manometry and pH testing, of whom two-thirds had abnormal manometry.²⁹

Oesophageal MII

Multichannel impedance was recently discussed in detail in a *Frontline Gastroenterology* article.³⁰ Sifrim and colleagues showed that in patients with cough almost one-third of cough episodes were temporally associated with reflux. In over half of these cases cough preceded reflux while in the other half cough was preceded by acid or non-acid reflux.³¹ When similar patients receiving a PPI at least twice daily were studied 19% still had a temporal association with non-acid reflux.³² In another study, a positive symptom association probability (SAP) for cough was noted in over one-quarter of the patients.³³ Patients with a positive SAP had both a greater number and a higher proportion of proximal reflux episodes in the pharynx than those with a negative SAP.

Management

Conservative treatment

Patients are generally asked to consider dietary and lifestyle modifications (table 2). Fizzy drinks should be avoided as they induce belching, which can encourage liquid reflux. Wendl *et al* found that regular coffee caused a statistically significant increase in GOR compared with tap water or tea. Decaffeinated coffee caused a reduction in GOR episodes.³⁴ The recommendations for patients with GORD to avoid chocolate are supported by Murphy and Castell.³⁵ Comparing postprandial reflux, the authors found that there was a significant increase in reflux after ingesting chocolate in the first hour compared with dextrose solution. Studies have documented the effects of alcohol on GORD. Vitale *et al*³⁶ documented impaired nighttime oesophageal acid clearance in healthy adults after drinking alcohol. This was also studied by Pehl *et al*,³⁷ who demonstrated increased GOR and impaired peristalsis in 12 healthy volunteers. Smoking has been shown to decrease lower oesophageal sphincter and increase GORD, decreasing salivary production and diminishing oesophageal acid clearance.^{38–39} Kadakia *et al* compared 24 h ambulatory reflux profiles in a group of 14 smokers with GORD while smoking and

Table 2 Treatment options

Conservative
Avoid alcohol, cigarettes, fizzy drinks, chocolate and caffeine ^{34–40}
Pharmacological
Proton pump inhibitors
Acid suppression and laryngitis: mixed evidence ^{7 8 41–44}
Acid suppression and cough: mixed evidence ^{46 47 60}
Acid suppression and asthma control: no evidence if no reflux ^{48–50}
H2 Antagonists
Consider ranitidine 300 mg to maximise acid suppression
Novel treatments
Pepsin receptor antagonist. baclofen/arbaclofen placarbil ^{51–54}
Surgery
Anti-reflux surgery ^{32 55–58}

abstinence for 48 h during monitoring. They concluded that there was a statistically higher oesophageal acid exposure during the smoking day compared with the non-smoking time. There is evidence that weight loss can improve GORD.⁴⁰

Medications

Acid suppression and laryngitis

Two placebo-controlled trials of a high-dose PPI in patients with symptoms and signs suggestive of chronic laryngitis failed to show any advantage of active treatment over placebo, as both groups tended to slowly improve with time.^{8–41} A meta-analysis performed showed that PPIs offer a non-significant modest improvement compared with placebo in EOR laryngitis.⁷ Other studies, however, have suggested that PPI therapy is beneficial in treating EOR laryngeal symptoms. El-Serag *et al*⁴² showed the benefit of PPIs in a small study of patients with laryngitis. Similarly, double-dose PPIs were shown to produce good improvement in RFS in a group of patients with laryngeal reflux.⁴³ A double-blinded, randomised, placebo-controlled trial showed the benefit of rabeprazole 20 mg twice daily in treating EOR symptoms as diagnosed by a symptom scoring system.⁴⁴ Acid suppression and cough medical treatment trials for reflux-associated cough have largely focused on acid suppression. They have generally been of poor quality, often small, open-label studies of insufficient treatment dose or duration. Only two randomised, double-blind, placebo-controlled trials of acid suppression (PPI treatment) have been reported, both showing only modest cough responses in selected individuals.^{45–46} Two Cochrane reviews on the treatment of GORD in adults and children with asthma and cough concluded that there was insufficient evidence to recommend the routine use of acid suppression. Current guidelines, albeit based largely on expert opinion, recommend intensive acid suppression (eg, omeprazole 20–40 mg twice daily and nocturnal ranitidine) for 3 months with the addition of prokinetic agents to improve oesophageal motility.⁴⁷

Acid suppression and asthma control

A number of uncontrolled studies using acid suppression have reported improvement in asthma symptoms but, in general, controlled trials have been less convincing. Some meta-analyses have shown no benefit in acid suppression over placebo in either adults or children with asthma.⁴⁸ Kiljander⁴⁹ suggested that high-dose esomeprazole for extended periods of time (3 months) was beneficial in selected asthmatic patients (those with reflux symptoms and nocturnal waking secondary to asthma). However, acid suppression is often prescribed to patients with poorly controlled asthma without any reflux symptoms and in an attempt to test the validity of this practice a large double-blind, parallel-group study of high-dose acid suppression in patients with poorly controlled asthma without reflux symptoms was carried out. All 412 participants underwent 24 h

oesophageal pH manometry at baseline and were randomised to receive either 40 mg of esomeprazole twice daily or placebo for 6 months. Although 40% of subjects had abnormal reflux on pH monitoring, there was no evidence of improvement in asthma symptoms (asthma diaries) or lung function (peak flow, spirometry and airway reactivity) in the PPI group. These findings are now considered definitive and advocate strongly against the use of PPIs in asthmatics with minimal or no reflux symptoms.

Acid suppression summary

Other explanations include PPI resistance, rapid metabolism, reduced bioavailability, compliance or improper dosing time. For the treatment of EOR, PPI should be given twice daily on an empty stomach 30 min before meals in high dose for at least 8 weeks before reassessing symptoms. Patients whose symptoms improve should continue to receive PPI treatment for at least 6 months before reducing treatment. The dose can then be tapered slowly as there is a risk of acid hypersecretion rebound if the PPI stopped quickly. H2 receptor antagonists work best on a fasting stomach. They are usually prescribed nocturnally in addition to PPI therapy.⁵⁰

New medical treatments

Pepsin in non-acidic refluxate can damage hypopharyngeal cells.⁵¹ Therefore pepsin receptor antagonists or inhibitors of pepsin activity may be future possibilities for treatment of EOR. Baclofen, a γ -aminobutyric acid agonist which inhibits transient lower oesophageal relaxations, has been shown to reduce the number of reflux episodes and the number of associated symptoms.⁵² Baclofen was shown to increase the capsaicin-induced cough threshold in 70% of the patients with chronic reflux cough compared with placebo in a randomised, double-blind, controlled study.⁵³ More recently, Gerson *et al*⁵⁴ conducted a multicentre, randomised, double-blind, crossover study comparing arbaclofen placarbil (a prodrug of the active R-isomer of baclofen) with placebo in patients with GORD and showed that arbaclofen placarbil decreases reflux and associated symptoms in patients with GORD.

Antireflux surgery

Surgery can improve symptoms in patients with typical GORD symptoms but there are immediate surgical risks and long-term side effects, including dysphagia and bloating. A recent meta-analysis that included 1232 patients with laparoscopic fundoplication showed short-term benefit and there was significant improvement in health-related Quality-of-Life Scores up to 1 year after surgery.⁵⁵ This meta-analysis, however, did not include studies that specifically compared EOR with GORD. One group performed a meta-analysis of fundoplication surgical outcomes specifically for patients with EOR and demonstrated that a variable proportion (15–95%) of patients with various

symptoms of EOR improved after surgical fundoplication.⁵⁶ The Society of American Gastrointestinal and Endoscopic Surgeons guidelines suggest that in patients with GORD surgery can be considered for EOR symptoms.⁵⁷ MII-pH testing on treatment can be used to select patients most suitable for surgery.^{32 58}

Conclusion

EOR can cause respiratory and laryngeal symptoms. There are consequences of both underdiagnosis (incorrect treatment) and overdiagnosis (inappropriate use of PPIs) of EOR. In the future we need to be able to develop new methods to diagnose accurately which laryngeal and respiratory symptoms are secondary to EOR and identify those most likely to respond to treatment.

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