REVIEW SERIES

Cough · 3: Chronic cough and gastro-oesophageal reflux

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The pathogenesis and clinical features of gastro-oesophageal reflux related cough are complex and the diagnostic tests available are of limited reliability. Treatment needs to be tailored to the specific needs of individual patients and other possible causes of chronic cough should be investigated. Treatment should only be considered to have failed when cough persists after administration of proton pump inhibitors at an adequate dosage for a sufficient length of time.

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Chronic cough, conventionally defined as a cough persisting for more than 8 weeks,[1] represents both a disabling symptom for the patient and a difficult management problem. In most instances, however, clearly defined causes are recognised,[1] of which gastro-oesophageal reflux (GOR) is one of the most common.[1–5] It has been proposed[6] that patients with GOR related cough meet a specific clinical profile: non-smoking patients with a normal chest radiograph and not receiving angiotensin converting enzyme inhibitors. GOR alone or in combination with other factors such as postnasal drip syndrome and/or asthma is the cause of chronic cough in 10–40% of adult patients.[2 5 7 8]

PRESENTATION

GOR related cough has two main but not mutually exclusive pathogenetic mechanisms—microaspiration of gastric contents and a vagally mediated oesophageal-tracheobronchial reflex.[9] When aspiration predominates, gastrointestinal symptoms are generally prominent and include heartburn, regurgitation, waterbrash, and sour taste; odynophagia, dyspepsia, night sweats, chest pain, and globus sensation may also be present.[10] At the level of the extrathoracic airway, recurrent aspiration phenomena may lead to pharyngolaryngeal symptoms such as dysphonia, hoarseness, sore throat, as well as gum inflammation and dental erosion.[11] Patients with pulmonary aspiration may report a variety of symptoms including chest pain, dyspnoea, sputum production, and wheeze.[12] When GOR related cough is reflex in origin, the gastrointestinal manifestations may be less evident or even absent in up to 75% of cases[13 14]; cough as the sole presenting symptom of GOR has also been reported.[7] A negative clinical history does not rule out GOR as the cause of chronic cough[6] since, in some instances, GOR related cough may have no distinctive clinical features.[8] However, an association between cough and GOR can be suspected on clinical grounds, most typically when cough is exacerbated by postural changes (especially stooping) or food intake.

Cough duration and descriptors

Symptom duration can be quite variable, ranging from several weeks to years,[8] and not significantly different from that observed when cough is due to other causes such as asthma and postnasal drip.[4] A study of patients with chronic cough showed that none of the cough descriptors such as paroxysmal, honking, propagating, brassy, and barking was consistently associated with GOR related cough.[8]

Timing and posture

It is commonly believed that nocturnal cough is typical of GOR, but the consistency of this relation was not confirmed by studies which specifically addressed this possibility: nocturnal episodes of coughing have been found to occur in patients with GOR disease as frequently as in those with other common causes of chronic cough.[8] This finding is in keeping with the notion that GOR events, as detected by prolonged oesophageal pH monitoring, are more frequent when patients are awake and upright.[7] Furthermore, transient lower oesophageal relaxation is suppressed during stable sleep,[15] and cough of any cause is less likely to occur during sleep since this reflex is inhibited.[16] In our experience, however, some patients with GOR related respiratory symptoms do report an increased occurrence of gastrointestinal symptoms of GOR with or without cough when supine. In such cases, a hypotonic or incompetent lower oesophageal sphincter (LOS) may be suspected.[17] Nocturnal cough has recently been shown to be predictive of proximal GOR in patients with a manometrically incompetent LOS.[18]

Association with food intake, drug consumption, and smoking

Foods can aggravate reflux symptoms by a number of mechanisms including gastric distension causing transient lower oesophageal relaxation, food contents directly lowering LOS pressure, and irritant effects on the inflamed oesophageal mucosa.[19] Significant exposure of the distal oesophagus to acid and impaired acid clearance can occur after consumption of moderate amounts of alcohol.[20] A number of medications, both prescribed and over the counter, can lower LOS pressure and cause oesophageal mucosal damage. The former group includes theophylline[21] and oral (but not inhaled) β adrenergic agonists,[22] while the latter group includes non-steroidal anti-inflammatory drugs and ascorbic acid. Xanthine-containing food may contribute to increase GOR episodes by the same

mechanism as that of theophylline. Cigarette smoking contributes to GOR via the pharmacological effect of nicotine which lowers LOS pressure and decreases acid clearance.[23] Patients often report that meals, especially when high in fat content, worsen the gastrointestinal symptoms of GOR.[24] Although an increase in the fat content of meals does not appear to affect oesophageal motility and the number of reflux events in patients with GOR,[25] fatty acids in the intestinal lumen may stimulate afferent nerves implicated in the facilitation of pain pathways.[26]

Sputum production
Reflux induced cough is more frequently dry, but sputum production of varying degrees may also be present.[8] Sputum production may be reflex mediated[27] and does not necessarily imply aspiration of gastric contents with subsequent airway infection.

Complications of cough
Cough is well known to cause several complications involving virtually all body systems,[28] but their prevalence in chronic cough due to GOR remains to be established. However, since such complications are a consequence of the large swings in intrathoracic and abdominal pressure produced by the intense repetitive muscle efforts of coughing, they are unlikely to be related to any specific underlying cause. It has been proposed that the mechanical events of coughing initiate a self-perpetuating positive feedback cycle whereby coughing from any cause may precipitate further reflux.[29] Recent lines of evidence suggest that reflux episodes lead to cough in the majority of cases.[30]

DIAGNOSTIC PROCEDURES
Manometry
Oesophageal manometry may be used to assess the physiological attributes of the oesophageal body and of the upper and lower oesophageal sphincters. Previous uncontrolled studies in patients with motility disorders have suggested an association between abnormal motility profiles and chronic cough.[31–33] More recently, impaired motility of the oesophageal body has been shown to be important in the development of GOR associated respiratory symptoms. Transient LOS relaxation is the major event leading to reflux,[34] although an important minority of reflux episodes (about 4%) occur because of defective basal LOS pressure.[35]

Barium radiography
The barium swallow has been used widely in the diagnosis of GOR, and movement of barium from the stomach into the oesophagus is considered diagnostic for GOR.[36] However, free reflux after the barium swallow has been detected in 30% of normal subjects and is absent in up to 60% of patients with GOR,[36] making it a rather insensitive and non-specific method for diagnosing GOR disease with a positive predictive value as low as 30%.[28] It is generally agreed that the major clinical usefulness of barium is for the study of local anatomical complications of GOR disease such as hiatal hernias or strictures.[37] However, in a few patients with chronic cough due to GOR but with a negative oesophageal pH study (see below), the barium swallow may be the only method to suggest GOR as a likely cause of cough.[2]

Bernstein test
This test aims to evaluate objectively the relationship between acid exposure and symptoms. It is performed by instilling either saline or an acid (0.1 N HCl) solution into the oesophagus, and is considered positive when symptoms are reproduced by acid but not saline instillation. The sensitivity of the test is approximately 80% for GOR,[38] but it is much lower (<30%) when used to reproduce cough in patients with proven GOR related cough.[2] The method may provide evidence of GOR but does not allow a relationship to be established between GOR events and symptom appearance.

Endoscopy
Endoscopy is the best single test to document mucosal abnormalities and establish a diagnosis of erosive oesophagitis or Barrett's oesophagus in patients with suspected GOR disease. Macroscopic lesions of the oesophageal mucosa have been detected in up to 60% of patients with heartburn or regurgitation, while the remainder have a normal oesophagus or minimal non-erosive alterations.[39] In patients with GOR related cough the test can confirm the presence of mucosal damage by reflux but, similarly to barium swallow, cannot prove that cough is due to reflux.

Pharyngeal pH monitoring
It has recently been proposed that pharyngeal pH monitoring with a pH catheter placed 2 cm above the upper oesophageal sphincter is an accurate method to identify patients in whom abnormal reflux causes airway problems,[40] and that pharyngeal reflux is present in 70% of patients with airway symptoms including cough.[41] At variance with GOR, pharyngeal reflux is uncommon in normal subjects.[41] The clinical usefulness of pharyngeal pH monitoring in the study of GOR related cough remains to be established.

24 hour oesophageal pH monitoring
The bulk of the literature (reviewed by Irwin et al[1]) indicates that the most sensitive and specific test for diagnosing cough due to GOR is 24 hour oesophageal pH monitoring. Abnormal pH profiles on oesophageal pH monitoring that may be used in the diagnosis of GOR related cough have been reported.[42 43] The recording of cough events by means of a diary or event marker during oesophageal pH monitoring is also useful, since patients with normal standard reflux parameters may still have acid related cough if a temporal relationship between GOR episodes and cough can be established.[2] Prospective studies in which the causes of chronic cough were determined in ~90% of patients also showed that the positive and negative predictive value of reflux indexes derived from oesophageal pH monitoring were 89% and 100%, respectively.[4] Similar outcomes have recently been obtained by McGarvey et al.[42] In contrast, Ours et al[31] reported that only 35% of patients with chronic cough and abnormal pH profiles responded favourably to proton pump inhibitor therapy, and concluded that oesophageal pH monitoring is not a reliable predictor of acid related cough. Resistance to acid suppression,[35] short treatment duration,[4 5] cough mediated by non-acid reflux events,[44] and co-existence of other causes of cough can all account for the discrepancy.

It is now well established that reflux can be acid, non-acid, pure liquid, and a mixture of gas and liquid. Intraoesophageal impedance recording is therefore emerging as a useful tool to diagnose the presence of non-acid reflux in patients whose symptoms persist despite adequate acid suppression.[44–46]

Empirical trial
When oesophageal pH monitoring is not available or the results obtained with this technique are controversial, an empirical trial of antireflux therapy may represent a useful and reasonable diagnostic alternative. Recent lines of evidence suggest that cough relief following empirical treatment with high doses of proton pump inhibitors identifies patients with GOR related chronic cough in which other common causes have been excluded.[31] If an empirical trial is chosen, treatment must be continued for up to 3–4 months before GOR can reasonably be excluded as a cause of cough.[4 7] Confirmation of GOR, preferably by pH

monitoring, may be useful to increase the patient's compliance with prolonged treatment. When empirical treatment fails, pH monitoring should be performed to identify patients with a poor response to treatment and to verify the adequacy of drug dosing.

TREATMENT

Treatment of GOR related cough should be carefully tailored to the specific needs of each patient.[1 47 48] Treatment should be directed to both reduce the number of reflux events and change the chemical characteristics of the refluxing material. Since many factors may combine in the genesis of cough,[1] treatments for other established causes of chronic cough (such as asthma and rhinitis) should be added, especially when the response to antireflux treatment has been partial. Finally, treatment failure does not rule out GOR as the cause of chronic cough.[49] Reassessment of lifestyle measures, drug selection, dosage regimen, and length of treatment should be considered, together with the possibility of cough induced by non-acid reflux.[50] In some patients insensitive to any form of medical treatment,[31] surgery may be the most appropriate therapeutic option.

Conservative and lifestyle measures

Sleeping with an elevated head in patients with documented night time reflux episodes, smoking cessation, weight reduction, and a low fat diet (<45 g/day) have all been found to be useful measures.[2 6] Avoidance of food and beverages with a pH of <5 and/or capable of relaxing the LOS—such as alcohol, chocolate, mint, onions, coffee, tea, cola, citrus fruits—is also highly recommended, and patients should avoid food and beverages 2–3 hours before going to bed.[2 6]

Pharmacological treatment

H_2 receptor antagonists, whose action is based on the reduction of gastric volume and acid secretion, have been widely used in the treatment of GOR related cough. Response rates of 80%, usually in association with conservative measures, have been observed with both cimetidine and ranitidine.[1] The positive effect persists 6 weeks after discontinuing treatment. Prokinetic agents such as metoclopramide, cisapride, and domperidone exert their effects mainly by facilitating gastric emptying. They are usually used in association with H_2 antagonists or proton pump inhibitors. When used as monotherapy in children, prokinetic agents have been shown to produce high response rates in the suppression of cough.[1] However, the risk of fatal arrhythmia with cisapride outweighs the benefit for which the drug is prescribed, and this has led to its discontinuation in most countries.[51] Similar adverse effects have been described for domperidone.[52] Proton pump inhibitors, whose effect is based on the inhibition of acid secretion, have recently emerged as the most effective treatment for GOR disease. A recent randomised, double blind, crossover, placebo controlled study showed that omeprazole in a daily dose of 40 mg for 8 weeks produced a significant reduction in GOR induced cough and the effect continued after cessation of treatment.[53] In a few patients, however, gastric acidity persisted despite treatment with doses up to 80 mg daily.[49]

New agents related to γ-aminobutyric acid-B ($GABA_B$) agonists have been shown to reduce the rate of transient lower oesophageal relaxation.[54] Baclofen is the most potent inhibitor of transient lower oesophageal relaxation identified to date.[54] Drowsiness, nausea, and lowering of the threshold for seizures are presently the main challenge to the use of baclofen and other $GABA_B$ agonists for the treatment of GOR related disorders. Notably, intraventricular administration of baclofen inhibits the cough evoked by capsaicin inhalation in cats and guinea pigs,[55] which suggests that this drug or similar compounds may be particularly suitable for treating GOR related cough.

Surgery

Surgery (open or laparoscopic fundoplication) is the treatment of choice in patients with signs of recurrent aspiration, and is indicated also in those patients with GOR related cough which persists after appropriate medical treatment, including high doses of proton pump inhibitors.[56] Notably, it has been reported[6] that, in a selected group of patients with chronic cough that persisted after total or near total acid suppression who met the clinical profile for GOR related cough, the symptoms disappeared or were greatly improved by antireflux surgery. A prospective trial has shown that 51% of patients who had not responded to maximal medical treatment with omeprazole were free of cough and 31% experienced a significant improvement 6 months after fundoplication.[57] In a study of 118 patients with GOR, 53% of whom had additional respiratory symptoms, surgery resulted in relief of respiratory symptoms in 76% of patients. Interestingly, oesophageal dysmotility was significantly more common in patients whose condition failed to improve with surgery.[58] Although this finding would suggest that surgical management of GOR should be restricted to patients who have normal oesophageal motility, this possibility has been denied by Fibbe et al[59] who reported similar postoperative outcomes in patients with and without dysmotility.

CONCLUSIONS

Given the complex pathogenesis and the protean clinical features of GOR related cough and the limited reliability of the available diagnostic tests, the procedures for assessing and managing the condition need to be more accurately defined. In general, treatment needs to be tailored to meet the specific needs of each patient, and the possible presence of other causes of chronic cough must be ascertained. Failure of treatment should be considered only when cough persists after administration of proton pump inhibitors at an adequate dosage and for a sufficiently long period of time.

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