ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Management of GERD-Related Chronic Cough

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G&H What are the most common causes of chronic cough? How often is chronic cough associated with gastroesophageal reflux disease?

RM The most common causes of chronic cough (ie, cough that does not improve after 8 weeks) have traditionally been postnasal drip, asthma, and gastroesophageal reflux disease (GERD). It is frequently thought that GERD plays a big role in chronic cough; there are reports that 25% or more of chronic cough cases are associated with GERD. However, this does not necessarily mean that GERD is the cause of chronic cough in many of these individuals. GERD occurs in approximately 20% of Americans, and chronic cough is a very common problem, which patients with GERD are not immune to developing. Due to the baseline GERD rate of 20%, it is difficult to separate the presence of the disorder from the causative effect of the disorder.

G&H What then is the current understanding of the relationship between chronic cough and GERD?

RM Two mechanisms have been proposed to explain why people with GERD develop chronic cough. The most intuitive theory is called the reflux theory, whereby reflux rises above the esophagus and upper esophageal sphincter, resulting in microaspiration as microdroplets land in the larynx or occasionally enter the bronchial tree, directly causing cough as a protective mechanism against reflux. The other theory is known as the reflex theory. Because of the common embryologic origin of the respiratory tract and the digestive tract, a little bit of reflux in the esophagus can lead to an esophagobronchial reflex that causes cough.

In addition, some investigators have found that cough can lead to reflux, which then leads to a cycle of cough (the cough-reflux-cough cycle).

G&H Is there an association between chronic cough and nonacidic reflux or weakly acidic reflux?

RM Although there has been some research on this issue, there is no clear consensus on whether the refluxate has to be acidic or whether it can be weakly acidic/nonacidic (pH >4). Many doctors who believe that reflux can lead to chronic cough also believe that it is possible for the reflux to have a pH above 4. Pepsin can be found in the bronchial tree of people with laryngopharyngeal reflux, and it might cause injury even at a pH above 4.

G&H Do patients with GERD-related chronic cough always present with standard GERD symptoms in addition to their cough?

RM These patients fall into 2 groups. One group consists of individuals with cough who also have the typical GERD symptoms of heartburn and regurgitation. In these individuals, the main problems are usually heartburn and regurgitation; cough is usually a secondary issue. The other group consists of individuals who present only with cough—which, by definition, means that they do not have GERD symptoms. Physicians are trained to consider GERD as a potential cause for cough despite the lack of GERD symptoms. Unfortunately, this group of patients tends not to respond well to standard GERD therapy (ie, acid suppressive therapy). Thus, when treating a patient with chronic cough, it is very important to consider both

the likelihood that the patient has GERD and that the patient will respond to acid suppression.

G&H How, specifically, is GERD-related chronic cough differentiated from non–GERD-related chronic cough?

RM Currently, it is very difficult to differentiate between the 2 types of cough. pH testing, pH impedance testing, and/or an upper endoscopy can be performed to look for evidence of GERD. The difficulty is that the presence of an abnormal finding on any of these studies does not prove causality; a positive finding just shows that there are abnormalities suggesting the presence of GERD. In patients with idiopathic cough, an upper endoscopy is very commonly (up to 90%) negative for any signs of significant GERD, such as esophagitis or Barrett esophagus. On pH testing and pH impedance testing, the likelihood of finding significant GERD can range from approximately 10–50%, depending on the study.

Another way that doctors have tried to prove that cough is caused by GERD is by performing a trial of proton pump inhibitor (PPI) therapy; the patient is given high doses of PPIs and is monitored for several weeks up to 3 months to see if his or her cough improves. It is thought that it takes approximately 3 months for true GERD-related cough to improve because the nerves involved in the cough reflex take time to return to normal function.

There are also clues that chronic cough could be related to GERD (eg, cough that occurs at night and/or postprandially, when the patient reclines, not in association with activity, and/or without the presence of postnasal drip).

G&H According to the data currently available, how effective is standard GERD medical therapy for treating cough in these patients?

RM Older studies of standard GERD therapy (PPIs) for patients with chronic cough were predominantly small observational studies. Some of these studies found that up to 70% of patients with chronic cough responded to PPIs. However, data from more recent randomized controlled trials suggest that PPIs for patients with chronic cough are not as effective as we initially believed. The most recent review from the Cochrane group found a lack of strong data supporting the practice of empiric PPI therapy for patients with chronic cough. The subgroup of patients who may respond best to PPIs are those with concomitant GERD symptoms such as heartburn and regurgitation or a positive pH study, but even within this subgroup, only approximately one third of patients will respond to PPIs. In one study of patients with chronic idiopathic cough and no heartburn, there was no difference in outcomes between the group that received high-dose PPIs and the group that received placebo.

G&H How are these patients usually treated?

RM Unfortunately, there are currently no standards of care for patients with suspected GERD-related cough. These patients should first undergo evaluation for pulmonary etiologies, such as asthma, as well as otolaryngologic etiologies, such as rhinitis or postnasal drip, prior to starting a trial of PPIs, since these etiologies are more commonly the cause of the patient's chronic cough. Often, patients receive empiric trials of various agents for other conditions, such as asthma medications (eg, bronchodilators and inhaled steroids), allergy medications, and postnasal drip medications. To adequately perform a trial of empiric PPI therapy for these patients, high doses of twice-daily PPIs for 2–3 months should be provided. Nonetheless, even this regimen fails to resolve cough in 50–75% of patients.

G&H Have there been any recent developments in the treatment of GERD-related chronic cough?

RM Some interesting findings have recently been reported regarding the use of gabapentin for patients with chronic cough, whether or not it is related to GERD. Thus far, there have only been a small number of studies of this medication, only one of which addressed the management of patients with cough and GERD. In a study presented at last year's American College of Gastroenterology meeting, my colleagues and I retrospectively reviewed our experience using gabapentin to treat patients referred to our tertiary care esophageal center for chronic cough. In this study, we used gabapentin starting at low doses (usually 100 mg at night) and titrating up to 300 mg in most patients and as high as 900 mg or more in a few patients. Approximately 75% of patients experienced at least a 50% subjective improvement in cough, irrespective of their pH findings. Although this was a small retrospective study without a control group, it indicated that even patients with documentation of GERD on a pH impedance study could respond to treatment targeted toward the abnormal cough reflex instead of simply treating GERD.

Around the same time as our data were presented, an article was published in *Lancet* in which researchers conducted a randomized, double-blind, placebo-controlled study of patients with idiopathic cough who were treated with gabapentin or placebo. Similar to our study, these investigators found significant improvement in their patients' cough-related quality of life, with a number needed to treat of 4. However, in contrast to our study, these patients received higher doses of gabapentin with a

different titration protocol up to 1,800 mg if tolerated, which led to a 31% rate of adverse effects.

The use of gabapentin to treat chronic cough is a novel concept; as far as I know, most pulmonologists, otolaryngologists, and gastroenterologists are not familiar with this treatment option, as it has not been extensively reported in the literature. However, some pediatricians have been using gabapentin for some time to treat patients with chronic cough.

G&H What are the next steps for research in this area?

RM The first step is to prospectively demonstrate whether or not there is a difference in response to gabapentin based on the presence or absence of GERD or an abnormal pH impedance study. It might turn out that GERD alone is not causing the cough; GERD may merely be one of the stimuli evoking cough in a patient with an abnormal cough reflex. Treating GERD without treating the abnormal reflex may not necessarily improve the cough; the abnormal reflex has to be treated as well. Thus, future research needs to determine whether a pH study or pH impedance study is worth performing or whether doctors should simply initiate treatment with an agent such as gabapentin. We have started doing this in our practice in some patients; after doing a basic gastroenterology workup (upper endoscopy and PPI trial), we empirically use gabapentin to treat patients with chronic cough, with very similar beneficial results.

Another important step in future research is to find a drug that is similar to gabapentin but with fewer adverse effects. (Gabapentin has been associated with fatigue, drowsiness, and occasionally nausea.) Pregabalin may have promise in this regard.

Finally, it would be important to figure out why the abnormal cough reflex develops. It may be a pharyngeal neuropathy caused by an infection, an underlying inflammatory condition, or GERD that rises into the pharyngeal region. We will have to determine the etiology of the neuropathy as well as develop diagnostic and treatment algorithms for it.

Suggested Reading

Madanick RD, Sigmon L, Ferrell K, Shaheen NJ, Dellon ES. Gabapentin for the treatment of chronic cough: a novel approach to treating a challenging clinical problem in gastroenterology. *Am J Gastroenterol*. 2012;107(suppl 1): S27-S28.

Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev.* 2011;(1):CD004823.

Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2011;33:225-234.

Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380:1583-1589.

Sifrim D, Barnes N. GERD-related chronic cough: how to identify patients who will respond to antireflux therapy? *J Clin Gastroenterol*. 2010;44:234-236.

Hersh MJ, Sayuk GS, Gyawali CP. Long-term therapeutic outcome of patients undergoing ambulatory pH monitoring for chronic unexplained cough. *J Clin Gastroenterol*. 2010;44:254-260.