ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

Esophageal Hypersensitivity

C. Prakash Gyawali, MD
Associate Professor of Medicine
Division of Gastroenterology
Washington University School of Medicine
St. Louis, Missouri

G&H What is meant by esophageal hypersensitivity, and why is it a problem?

CPG A hypersensitive esophagus has a lowered threshold for symptom perception and reporting. Therefore, patients with esophageal hypersensitivity have more frequent and intense esophageal perceptive symptoms (such as heartburn and chest pain) for the same degree of esophageal stimulation as compared to patients without a hypersensitive esophagus. Stimuli that trigger symptoms could be mechanical, chemical, emotional, or combinations thereof; in some instances, triggering stimuli may not be identified. Mechanical stimuli include distension of the esophagus, typically from refluxed gastric contents or air (belch), or from swallowed bolus or air. Chemical stimulation can occur from acid and, possibly, from other contents in refluxates, including bile; inflammatory mediators in other forms of esophagitis such as eosinophilic esophagitis can also induce symptoms in certain patients. Emotions and stress tend to potentiate symptom reporting; for instance, anxiety and panic disorder can be associated with esophageal symptoms even in the absence of direct physiologic or pathologic esophageal stimulation.

Esophageal hypersensitivity is a problem because it can coexist with organic esophageal disorders such as gastroesophageal reflux disease (GERD) and eosinophilic esophagitis, and recognition requires clinical judgment and test evidence that the organic disorder is adequately treated. Furthermore, patients may continue to believe that they have an undiagnosed disorder or heart disease despite evidence to the contrary. Unless this condition is recognized and adequately addressed with the patient, healthcare utilization in the form of hospital visits and testing can be high and the quality of health can be poor.

G&H Could you further discuss the causes of this condition?

CPG Sensitization of the esophagus can occur in certain individuals with exposure to noxious triggers such as reflux events. Qasim Aziz and associates have shown that the esophagus and its central connections respond to noxious triggers by lowering thresholds for sensation perception, not only at the level of stimulation, but also at sites distant or proximal to the site of stimulation. Although this phenomenon has been described even in normal individuals, it is more pronounced in predisposed individuals, particularly in the presence of noxious triggers such as acid reflux events. While we do not know why or how some patients are predisposed to hypersensitivity, we do know that patients with affective disorders (depression, anxiety), nonspecific spastic disorders of the esophagus, somatization disorders, and fibromyalgia tend to have a higher prevalence of esophageal hypersensitivity. Additionally, central triggers such as stress, anxiety, and other affective conditions tend to increase symptom perception and reporting.

G&H Can esophageal hypersensitivity be classified as a subgroup of GERD? Is it possible for a patient to have esophageal hypersensitivity in the absence of GERD?

CPG Esophageal hypersensitivity can overlap with GERD, and presentation can be exactly the same. On

ambulatory pH monitoring, a subcategory of patients with GERD symptoms have normal esophageal acid exposure times but have significant symptom-reflux correlations, in that many of their reported symptoms are triggered by physiologic acid reflux events. This category of patients, sometimes designated acid-sensitive, are now considered part of the GERD spectrum, as they frequently respond, at least partially, to proton pump inhibitor (PPI) therapy. However, even within categories of GERD with elevated esophageal acid exposure times, esophageal sensitization to acid can occur. Therefore, a proportion of patients with GERD or GERD-like symptoms very likely have esophageal hypersensitivity contributing to their symptoms. There is evidence that hypersensitivity to acid has a higher prevalence in patients with nonerosive reflux disease when compared to erosive GERD.

On the other hand, esophageal hypersensitivity can also exist without GERD. Other organic esophageal disorders such as eosinophilic esophagitis can be associated with esophageal hypersensitivity. Furthermore, triggers for symptom generation could be physiologic or emotional; in the absence of reflux-triggered symptoms and normal esophageal histopathology, the terms functional heartburn, functional chest pain, functional dysphagia, and globus are often used in describing symptoms from esophageal hypersensitivity.

G&H How often does esophageal hypersensitivity occur in patients with GERD symptoms or eosinophilic esophagitis?

CPG The true prevalence of esophageal hypersensitivity is difficult to estimate, as this is a heterogeneous state that can overlap with any esophageal disorder or symptom that a practitioner encounters. In the setting of ambulatory pH monitoring for GERD-like symptoms, approximately 5–12% will have normal acid exposure with positive symptom-reflux association indicating acid sensitivity in the purest sense; 20–25% will have a nonspecific spastic disorder of the esophageal body on concurrent manometric testing, which could be considered an indirect marker for esophageal hypersensitivity. In many of these situations, true GERD overlaps with, and likely triggers, esophageal hypersensitivity, and symptoms may improve when GERD is adequately managed. Prevalence is likely similar across most perceptive esophageal symptoms.

The prevalence of esophageal hypersensitivity in eosinophilic esophagitis is unknown.

G&H What are the presenting symptoms of a hypersensitive esophagus?

CPG Esophageal hypersensitivity can present with symptoms similar to GERD, including heartburn and chest pain. Some patients have globus sensation, which is a constant discomfort or sensation in the region of the neck that does not impair swallowing. Other patients report a sensation of food dragging down, and triggering of more intense retrosternal symptoms with certain acidic or spicy items of diet. A true dysphagia type sensation can also be functional and related to esophageal hypersensitivity, but other obstructive structural or motor processes need to be excluded. Sometimes, reflux events can trigger more proximal symptoms such as throat clearing or cough.

G&H How is esophageal hypersensitivity diagnosed?

CPG Esophageal hypersensitivity can be suspected in the setting of esophageal symptoms that do not respond to seemingly adequate GERD treatment. Esophageal pH monitoring may reveal normal acid exposure times but statistically significant symptom reflux associations in patients with acid sensitivity. Patients with sensitivity to esophageal distension may have symptom correlation with reflux events irrespective of pH, as detected by pH impedance testing. Esophageal motility studies could reveal spastic patterns, which tend to be associated with esophageal hypersensitivity. Other patients may have esophageal symptoms with completely normal tests, when functional heartburn, functional chest pain, functional dysphagia, or globus may be diagnosed—these may all be related to esophageal hypersensitivity. Patients with esophageal hypersensitivity tend to have a higher predilection for affective disorders (anxiety and depression), somatization, and fibromyalgia, and panic disorder appears to be particularly associated with symptoms of esophageal hypersensitivity. The female gender is represented to a higher degree. There may be overlaps with other functional syndromes, including irritable bowel syndrome and functional dyspepsia.

For a conclusive diagnosis, 2 types of tests are available in the research setting. First, acid perfusion studies, where hydrochloric acid and saline are infused into the distal esophagus, can detect acid sensitivity when patients report symptoms with acid infusion but not saline infusion. Balloon distension studies involve distending small balloons in the esophagus and assessing volumes of distension at the first perception of symptoms as well as the degree of discomfort with distension. In the late 1980s, Richter and colleagues showed that smaller volumes of distension cause a higher degree of discomfort in patients with esophageal hypersensitivity when compared to normal individuals. Acid perfusion and balloon distension studies are not typically performed in the clinical setting; therefore, recognition involves clinical suspicion and assessment of the lack of response to typical symptom management.

G&H How is esophageal hypersensitivity treated? Does it always require treatment?

CPG In the presence of GERD, acid suppressive regimens are usually part of the initial treatment regimen and can provide partial or short-term symptom relief. Noxious triggers such as reflux events can be decreased effectively by standard GERD therapies (including antireflux surgery or endoscopic GERD procedures), which could consequently reduce symptom frequency and intensity. Inhibitors of transient lower esophageal sphincter relaxation such as baclofen or its analogs can also be tried, but there are no data on the use of these agents specifically in esophageal hypersensitivity. The diagnosis of a hypersensitive esophagus is not a contraindication for antireflux surgery, but may predict a higher likelihood of residual symptoms despite successful antireflux therapy.

Symptom management can be further augmented with the use of neuromodulators, typically low-dose antidepressants used with the intention to suppress symptoms rather than manage concurrent affective disorders. Among the antidepressants, tricyclics have the best track record of success. Other contemporary antidepressants have also demonstrated a benefit if tricyclics are not tolerated or contraindicated. Treatment with neuromodulators does not need to be lifelong; if adequate desensitization is achieved, the antidepressants can be slowly weaned off. Symptom recurrence on medication withdrawal may be an indication that chronic suppressive therapy is needed.

Concurrent affective disorders, stress, and anxiety can potentiate symptoms, and these conditions need appropriate attention. Theophylline, a nonspecific adenosine receptor antagonist, has also been used in functional chest pain with some benefit. In the event that symptoms do not adequately respond to medication regimens, other supplementary options include cognitive and behavioral therapy, hypnosis, and stress relaxation. Nontraditional therapies such as acupuncture and transcutaneous electrical nerve stimulation have also been utilized with partial success.

Continuing esophageal symptoms can be bothersome and can affect quality of life. Therefore, it is beneficial to attempt symptom suppression. This decision is easy for patients with frequent and intense symptoms, who will usually accept daily medication regimens if the indication is clearly explained to them. However, if symptoms are few and infrequent, a chronic daily medication regimen may not be required, and intermittent use of acid suppressive regimens may be adequate.

G&H Are there any particular challenges or concerns when treating these patients?

CPG A high index of suspicion helps the practitioner suspect esophageal hypersensitivity in the appropriate patient; there are no simple or easy tests to identify this condition. Conclusive diagnostic tests are not typically performed in the clinical setting. This can be a challenge and requires detailed symptom evaluation and good clinical judgment. Patients may be reluctant to accept the concept of esophageal hypersensitivity and may be unwilling to take antidepressants. In these patients, it is important to explain that their threshold for symptom perception is lower than that of other patients and that the antidepressants are specifically for altering symptom perception and not for management of affective disorders. Patients should not be told that their symptoms are just in their minds, as this may be counterproductive in terms of patient management.

Another challenge with managing these patients stems from the tendency in the gastroenterology community to designate anyone with esophageal GERD-like symptoms not related to eosinophilic esophagitis that do not improve with PPIs as having refractory GERD, implying that it is the treatment of the condition that is inadequate. If objective documentation of GERD is not available, esophageal pH (or pH impedance) monitoring performed off antireflux therapy will help determine whether abnormal acid or reflux exposure is present. In this setting, if reflux parameters are normal but symptoms correlate with reflux events, acid sensitivity can be diagnosed; if symptoms do not correlate with reflux events, a functional basis for symptoms can be suspected. In both of these instances, treatments for esophageal hypersensitivity may be appropriate. It is worthwhile to use an algorithmic approach to refractory symptoms in this fashion and utilize neuromodulators to suppress symptoms prior to considering a surgical approach to management.

With persisting esophageal symptoms, patients and physicians alike often continue to worry about a cardiac etiology for symptoms, leading to emergency room visits, hospitalizations, and invasive cardiac testing that results in increased healthcare utilization. These are good indications to document whether reflux events trigger symptoms using pH or pH impedance monitoring and to assess esophageal motor patterns that are associated with visceral hypersensitivity with esophageal manometry. Explanation of symptom generation, when supported by objective test results, may reduce patient (and referring-physician) anxiety and, consequently, reduce healthcare utilization and improve quality of life in these patients.

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

CPG Using high-resolution manometry, my colleagues and I have identified a shift in contraction vigor to the distal of 2 smooth muscle contraction segments in the esophagus in the presence of esophageal hypersensitiv-

ity. Others have described a correlation between higher esophageal contraction amplitudes and esophageal symptom reporting using balloon distension studies, and sustained esophageal smooth muscle thickening (potentially related to longitudinal muscle contraction) has been identified as a potential correlate on high-frequency esophageal ultrasound. Further studies are needed to determine whether these patterns of smooth muscle contraction have a physiologic or pathophysiologic basis in symptom generation. Identification of patient phenotypes that predispose patients to visceral hypersensitivity will allow better prediction of functional syndromes. Functional imaging studies may help identify whether abnormal central mechanisms are more prevalent in patients with such hypersensitivity and, consequently, whether central abnormalities, if any, predate the development of esophageal symptoms.

Suggested Reading

Galmiche JP, Clouse RE, Balint A, et al. Functional esophageal disorders. In: Drossman DA, ed. *Rome III: The Functional Gastrointestinal Disorders*. 3rd ed. McLean, VA: Degnon Associates, Inc; 2006:369-418.

Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. *Gut.* 2009;58:295-309.

Richter JE. How to manage refractory GERD. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4:658-664.

Kushnir VM, Sayuk GS, Gyawali CP. Abnormal GERD parameters on ambulatory pH monitoring predict therapeutic success in noncardiac chest pain. *Am J Gastroenterol*. 2010;105:1032-1038.

Broeders JA, Draaisma WA, Bredenoord AJ, et al. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication. *Br J Surg*. 2009;96:1023-1030.

Gyawali CP, Clouse RE. Approach to dysphagia, odynophagia or noncardiac chest pain. In: Yamada T, Alpers DH, Kaplowitz N, Owyang C, Powell DW, eds. *Principles of Gastroenterology.* Oxford, UK: Blackwell Publishing; 2008:62-82.

Prakash C, Clouse RE. Long-term outcome from tricyclic antidepressant treatment of functional chest pain. *Dig Dis Sci.* 1999;44:2373-2379.

Winslow ER, Clouse RE, Desai KM, et al. Influence of spastic motor disorders of the esophageal body on outcomes from laparoscopic antireflux surgery. *Surg Endosc.* 2003;17:738-745.

Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology*. 1986;91:845-852.

Borjesson M, Pilhall M, Eliasson T, et al. Esophageal visceral pain sensitivity: effects of TENS and correlation with manometric findings. *Dig Dis Sci.* 1998;43:1621-1628.