REVIEW

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Functional heartburn: An underrecognized cause of PPI-refractory symptoms

ABSTRACT

Functional heartburn—persistent symptoms of esophageal reflux with no objective evidence of gastroesophageal reflux disease (GERD)—is the most common cause of failure of proton pump inhibitor (PPI) therapy, but it is often overlooked by internists and gastroenterologists.

KEY POINTS

Functional heartburn accounts for more than half of all referrals for PPI-refractory GERD.

Diagnostic criteria require at least 3 months of symptoms in the 6 months before presentation.

Results of upper endoscopy with biopsy, esophageal manometry, and esophageal pH monitoring must be normal.

Patient education is key, with reassurance that the risk of progression to malignancy is low in the absence of Barrett esophagus, and that the condition remits spontaneously in up to 40% of cases.

Neuromodulators to reduce pain perception are the mainstay of treatment for functional gastrointestinal disorders such as functional heartburn. Cognitive behavioral therapy and hypnotherapy are also used as first-line treatment.

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A 44-year-old woman presents with an 8-year history of intermittent heartburn, and in the past year she has been experiencing her symptoms daily. She says the heartburn is constant and is worse immediately after eating spicy or acidic foods. She says she has had no dysphagia, weight loss, or vomiting. Her symptoms have persisted despite taking a histamine $(H)_2$-receptor antagonist twice daily plus a proton pump inhibitor (PPI) before breakfast and dinner for more than 3 months.

She has undergone upper endoscopy 3 times in the past 8 years. Each time, the esophagus was normal with a regular Z-line and normal biopsy results from the proximal and distal esophagus.

The patient believes she has severe gastroesophageal reflux disease (GERD) and asks if she is a candidate for fundoplication surgery.

HEARTBURN IS A SYMPTOM; GERD IS A CONDITION

A distinction should be made between heartburn—the *symptom* of persistent retrosternal burning and discomfort—and gastroesophageal reflux disease—the *condition* in which reflux of stomach contents causes troublesome symptoms or complications.[1] While many clinicians initially diagnose patients who have heartburn as having GERD, there are many other potential causes of their symptoms.

For patients with persistent heartburn, an empiric trial of a once-daily PPI is usually effective, but one-third of patients continue to have heartburn.[2,3] The most common cause of this PPI-refractory heartburn is functional

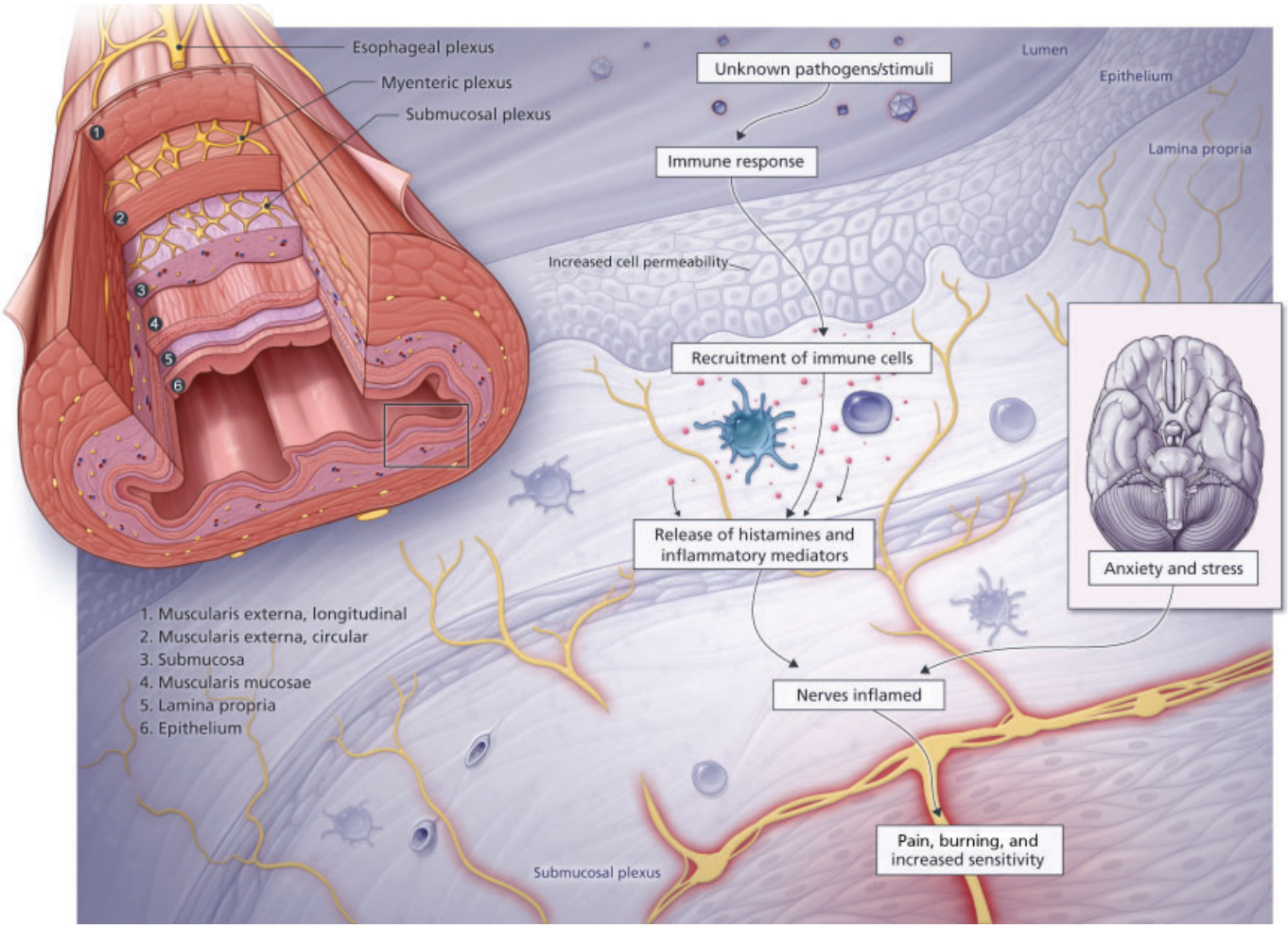


Figure 1. Conceptual pathophysiologic basis of functional heartburn.

heartburn, a functional or hypersensitivity disorder of the esophagus.[4]

PATHOPHYSIOLOGY IS POORLY UNDERSTOOD

Functional heartburn is defined as retrosternal burning in the absence of objective evidence of GERD, mucosal abnormality (ie, erosive esophagitis), or major motility disorder.[5] The symptoms are theorized to result from hypersensitivity of the visceral nerves of the esophagus, which may be exacerbated by central sensitization, hypervigilance, stress, and anxiety.[6] The pathogenesis is poorly understood, but it may involve activation of inflammatory mediators in the esophagus, alterations in esophageal mucosal integrity, increased chemical and pressure sensation in the esophagus, and both peripheral and central sensitization (**Figure 1**).[7]

DIAGNOSTIC EVALUATION

When evaluating patients with heartburn symptoms refractory to PPI therapy, the differential diagnosis is broad and includes GERD, eosinophilic esophagitis, infectious esophagitis, pill-induced esophagitis, esophageal motility disorder, and functional heartburn (**Table 1**). Of these, functional heartburn is the most common, accounting for more than 50% of cases of PPI-refractory heartburn.[8]

Clinicians have several tests available for diagnosing these conditions.

Upper endoscopy

Upper endoscopy is recommended for patients with heartburn that does not respond to a 3-month trial of a PPI.[9] Endoscopy is also indicated in any patient who has any of the following "alarm symptoms" that could be due to malignancy or peptic ulcer:

- Dysphagia
- Odynophagia
- Vomiting
- Unexplained weight loss or anemia
- Signs of gastrointestinal bleeding
- Anorexia
- New onset of dyspepsia in a patient over age 60.

During upper endoscopy, the esophagus is evaluated for reflux esophagitis, Barrett esophagus, and other inflammatory disorders such as infectious esophagitis. But even if the esophageal mucosa appears normal, the proximal and distal esophagus should be biopsied to rule out an inflammatory disorder such as eosinophilic or lymphocytic esophagitis.

Esophageal manometry

If endoscopic and esophageal biopsy results are inconclusive, a workup for an esophageal motility disorder is the next step. Dysphagia is the most common symptom of these disorders, although the initial presenting symptom may be heartburn or regurgitation that persists despite PPI therapy.

Manometry is used to test for motility disorders such as achalasia and esophageal spasm.[10] After applying a local anesthetic inside the nares, the clinician inserts a flexible catheter (about 4 mm in diameter) with 36 pressure sensors spaced at 1-cm intervals into the nares and passes it through the esophagus and lower esophageal sphincter. The patient then swallows liquid, and the sensors relay the esophageal response, creating a topographic plot that shows esophageal peristalsis and lower esophageal sphincter relaxation.

Achalasia is identified by incomplete lower esophageal sphincter relaxation combined with 100% failed peristalsis in the body of the esophagus. Esophageal spasms are identified by a shortened distal latency, which corresponds to premature contraction of the esophagus during peristalsis.[11]

Esophageal pH testing

Measuring esophageal pH levels is an important step to quantify gastroesophageal reflux and determine if symptoms occur during reflux events. According to the updated Porto GERD consensus group recommendations,[12] a pH test is positive if the acid exposure time is greater than 6% of the testing period. Testing the pH differentiates between GERD (abnormal acid exposure), reflux hypersensitivity (normal acid exposure, strong correlation between symptoms and reflux events), and functional heartburn (normal acid exposure, negative correlation between reflux events and symptoms).[5] For this test, a pH probe is placed in the esophagus transnasally or endoscopically. The probe records esophageal pH levels for 24 to 96 hours in an outpatient setting. Antisecretory therapy needs to be withheld for 7 to 10 days before the test.

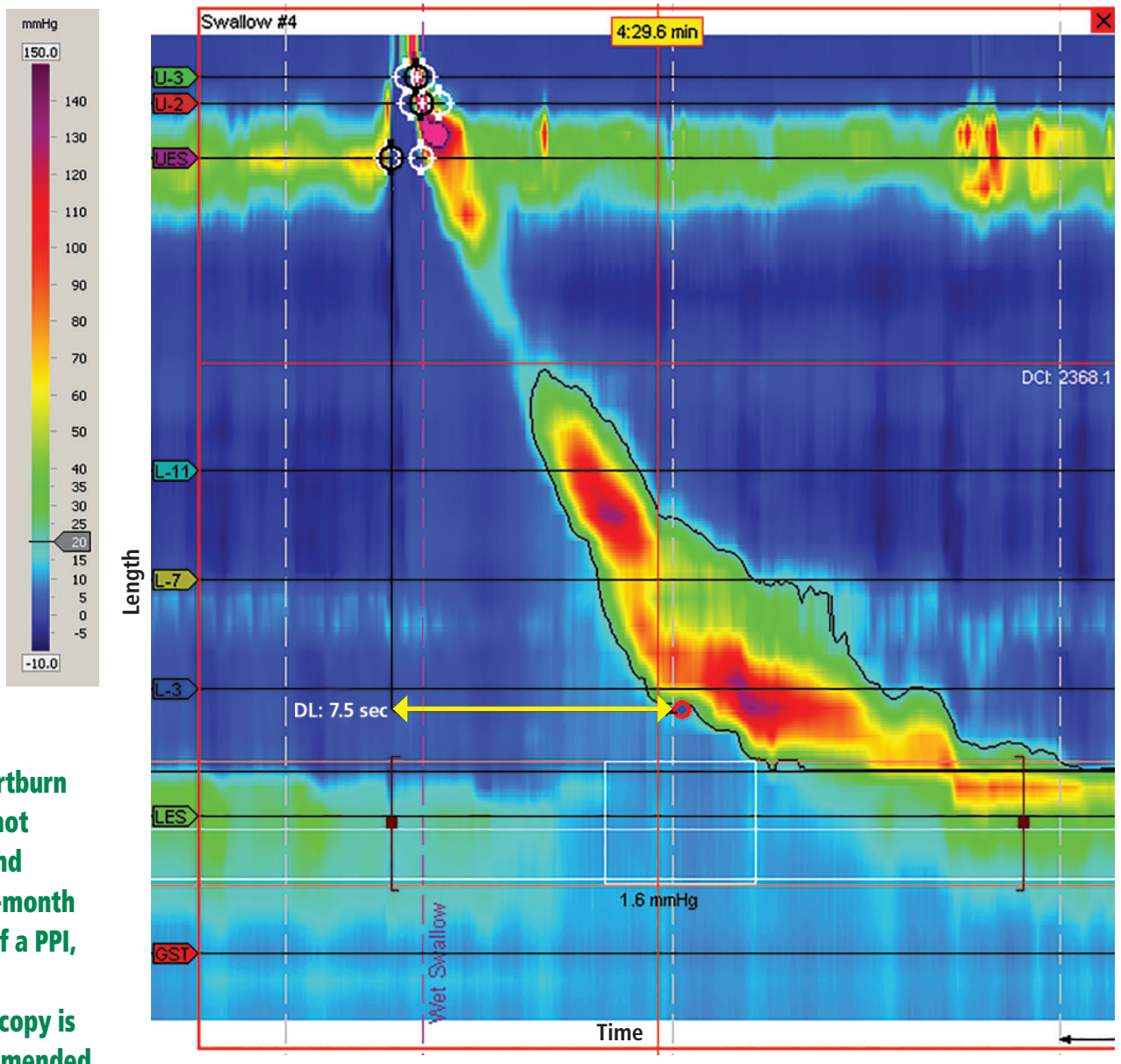
TABLE 1

Differential diagnosis of heartburn refractory to proton pump inhibitors

Erosive or reflux esophagitis
Nonerosive reflux disease
Eosinophilic esophagitis
Infectious esophagitis
Viral (cytomegalovirus, herpes simplex virus)
Fungal (*Candida*)
Pill-induced esophagitis
Antibiotics (doxycycline, tetracycline)
Nonsteroidal anti-inflammatory drugs and aspirin
Bisphosphonates
Potassium
Quinidine
Esophageal motility disorder
Achalasia
Esophageal spasm or "jackhammer" esophagus
Absent contractility, aperistalsis
Functional esophageal disorder
Functional heartburn
Reflux hypersensitivity

Functional heartburn accounts for > 50% of cases of PPI-refractory heartburn

Transnasal pH probe. For this approach, a thin catheter is inserted through the nares and advanced until the tip is 5 cm proximal to the lower esophageal sphincter. (The placement is guided by the results of esophageal manometry, which is done immediately before pH catheter placement.) The tube is secured with clear tape on the side of the patient's face, and the end is connected to a portable recorder that compiles the data. The patient pushes a button on the recorder when experiencing heartburn symptoms. (A nurse instructs the



If heartburn does not respond to a 3-month trial of a PPI, upper endoscopy is recommended

Figure 2. High-resolution esophageal manometry in our patient shows normal esophageal resting pressure and relaxation, and a distal latency of 7.5 seconds, indicating normal peristalsis. It also shows a distal contractile integral of 2,368 mm Hg-sec-cm, a measure of the pressure, duration, and vertical length of the distal esophageal contraction. The vertical axis shows the length along the esophagus from upper to lower, and the horizontal axis shows time. The color depicts pressure from low (blue) to high (red); note how the waves of contraction (high pressure) proceed from proximal (top) to distal (bottom).

DCI = distal contractile integral; DL = distal latency; GST = gastric sensor; LES = lower esophageal sphincter; UES = upper esophageal sphincter; U-3, U-2, L-11, L-7 = other specific sensors

patient on proper procedure.) After 24 hours, the patient either removes the catheter or has the clinic remove it. The pH and symptom data are downloaded and analyzed.

Transnasal pH testing can be combined with impedance measurement, which can detect nonacid reflux or weakly acid reflux. However, the clinical significance of this measurement is unclear, as multiple studies have found total acid exposure time to be a better

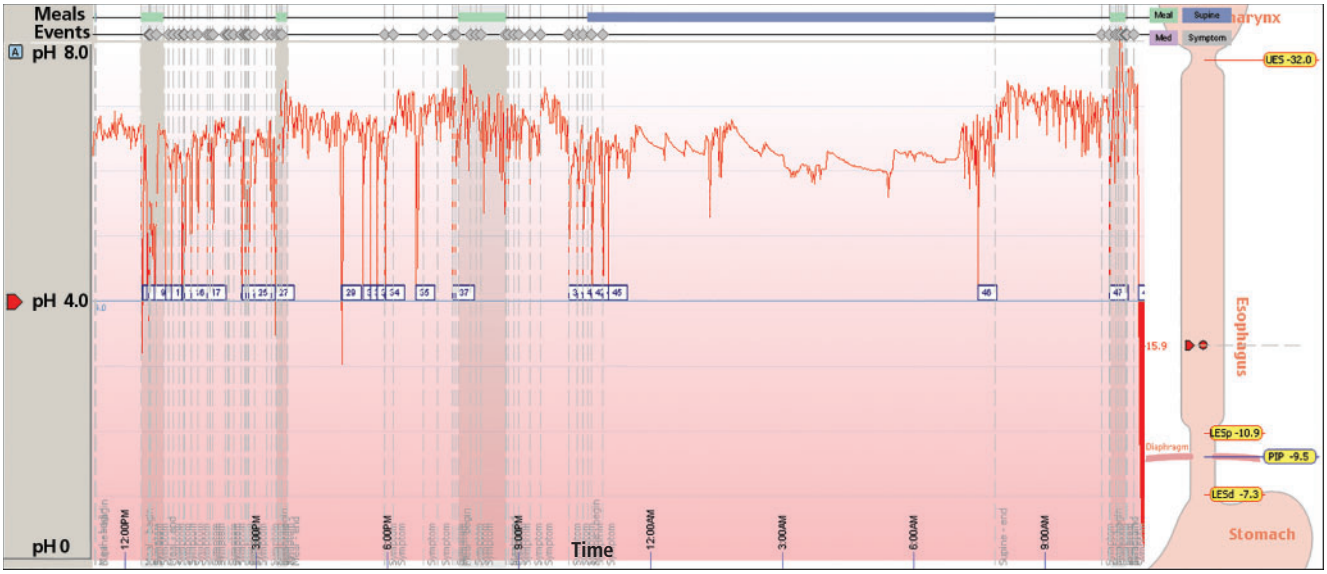


Figure 3. In our patient with functional heartburn, 24-hour wireless esophageal pH testing showed a pH greater than 4 (the conventional cutoff in esophageal pH testing) for most of the test. During the test, the patient recorded experiencing heartburn 67 times (gray diamonds); her esophageal pH was below 4 for just 3 of the 67 events. This pH test is consistent with a diagnosis of functional heartburn. The vertical axis shows the pH from 0 to 8, with a midline at 4. The horizontal axis shows a 24-hour period from noon to noon.

predictor of response to therapy than weakly acid or nonacid reflux.[12]

Wireless pH probe. This method uses a disposable, catheter-free, capsule device to measure esophageal pH. The capsule, about the size of a gel capsule or pencil eraser, is attached to the patient's esophageal lining, usually during upper endoscopy. The capsule records pH levels in the lower esophagus for 48 to 96 hours and transmits the data wirelessly to a receiver the patient wears. The patient pushes buttons on the receiver to record symptom-specific data when experiencing heartburn, chest pain, regurgitation, or cough. The capsule detaches from the esophagus spontaneously, generally within 7 days, and is passed out of the body through a bowel movement.

Diagnosing functional heartburn

The Rome IV diagnostic criteria for functional heartburn[5] require that a patient experience retrosternal burning, discomfort, or pain at least twice a week for at least 6 months. By definition, the symptoms have not responded to antisecretory drugs (an H_2-receptor antagonist or PPI) in optimal doses. Also, inflammatory disorders such as erosive esophagitis and eosinophilic esophagitis and motility disorders such as achalasia **(Table 1)** need to be ruled out.

CASE CONTINUED: NORMAL RESULTS ON TESTING

The patient undergoes esophageal manometry and esophagogastroduodenoscopy with placement of a wireless pH probe. Results of esophageal manometry are normal. She has normal lower esophageal resting pressure and relaxation and normal peristalsis in the esophagus body **(Figure 2)**. Wireless pH testing shows a total acid exposure time of 1.7% and a strongly negative symptom association with heartburn, chest pain, and regurgitation **(Figure 3)**.

Based on these results, her condition is diagnosed as functional heartburn, consistent with the Rome IV criteria.[5]

A pH test is positive if the acid exposure time is > 6%

TREATMENT

Patient education is key

Patient education about the pathogenesis, natural history, and treatment options is the most important aspect of treating any functional gastrointestinal disorder. This includes the "brain-gut connection" and potential mechanisms of dysregulation. Patient education along with assessment of symptoms should be part of every visit, especially before discussing treatment options.

TABLE 2

Neuromodulators to treat functional esophageal disorders

Tricyclic antidepressants
(in descending order of efficacy and descending order of anticholinergic effects)
Imipramine
Amitriptyline
Desipramine
Nortriptyline

Dosing: Start at 10 mg every night at bedtime; increase by 10 mg every 2–4 weeks

Selective serotonin reuptake inhibitors
Citalopram
Fluoxetine
Sertraline

Dosing: Start at lowest dose; increase after 4–6 weeks

Trazodone

Dosing: Start at 50 mg every night at bedtime; increase by 50 mg every 2–4 weeks

Serotonin and norepinephrine reuptake inhibitors
Venlafaxine
Duloxetine

Dosing: Start at lowest dose; increase every 4–6 weeks as needed

Antidepressants are used because of their effects on serotonin and norepinephrine in the gut

Patients whose condition is diagnosed as functional heartburn need reassurance that the condition is benign and, in particular, that the risk of progression to esophageal adenocarcinoma is minimal in the absence of Barrett esophagus.[13] Also important to point out is that the disorder may spontaneously resolve: resolution rates of up to 40% have been reported for other functional gastrointestinal disorders.[14]

Antisecretory medications may work for some

A PPI or H_2-receptor antagonist is the most common first-line treatment for heartburn symptoms. Although most patients with functional heartburn experience no improvement in symptoms with an antisecretory agent, a small number report some relief, which suggests that acid-suppression therapy may have an indirect impact on pain modulation in the esophagus.[15] In patients who report symptom relief with an antisecretory agent, we suggest continuing the medication tapered to the lowest effective dose, with repeated reassurance that the medication can be discontinued safely at any time.

Antireflux surgery should be avoided

Antireflux surgery should be avoided in patients with normal pH testing and no objective finding of reflux, as this is associated with worse subjective outcomes than in patients with abnormal pH test results.[16]

Neuromodulators

No drug has yet been approved by the US Food and Drug Administration to treat functional heartburn, and clinical evidence for treating this condition is minimal. Using neuromodulators to reduce pain perception is the mainstay of treatment for functional gastrointestinal disorders, including functional heartburn. **Table 2** lists neuromodulators used to treat functional esophageal disorders, with recommended dosing intervals.

It is important to discuss with patients the concept of neuromodulation, including the fact that antidepressants are often used because of their effects on serotonin and norepinephrine, which decrease visceral hypersensitivity.

The selective serotonin reuptake inhibitor citalopram has been shown to reduce esophageal hypersensitivity,[17] and a tricyclic antidepressant has been shown to improve quality of life.[18] These results have led experts to recommend a trial of a low dose of either type of medication.[19] The dose of tricyclic antidepressant often needs to be increased sequentially every 2 to 4 weeks.

Interestingly, melatonin 6 mg at bedtime has also shown efficacy for functional heartburn, potentially due to its antinociceptive properties.[20]

Alternative and complementary therapies

Many esophageal centers use cognitive behavioral therapy and hypnotherapy as first-line treatment for functional esophageal disorders. Here again, it is important for the patient to understand the rationale of therapy for functional gastrointestinal disorders, given the stigma in the general population regarding psychotherapy.

Cognitive behavioral therapy has been used for functional gastrointestinal disorders for many years, as it has been shown to modulate visceral

perception.[21] Although published studies are limited, research regarding other functional esophageal disorders suggests that patients who commit to long-term behavioral therapy have had a significant improvement in symptoms.[22]

The goal of esophageal-directed behavioral therapy is to promote focused relaxation using deep breathing techniques, which can help patients manage esophageal hypervigilance, especially if symptoms continue despite neuromodulator therapy. Specifically, hypnotherapy has been shown to modulate functional chest pain through the visceral sensory pathway and also to suppress gastric acid secretion.[21,23] A study of a 7-week hypnotherapy program reported significant benefits in heartburn relief and improved quality of life in patients with functional heartburn.[24] The data support the use of behavioral therapies as first-line therapy or as adjunctive therapy for patients already taking a neuromodulator.

CASE FOLLOW-UP: IMPROVEMENT WITH TREATMENT

During a follow-up visit, the patient is given several printed resources, including the Rome Foundation article on functional heartburn.[5] We again emphasize the benign nature of functional heartburn, noting the minimal risk of progression to esophageal adenocarcinoma, as she had no evidence of Barrett esophagus on endoscopy. And we discuss the natural course of functional heartburn, including the spontaneous resolution rate of about 40%.

For treatment, we present her the rationale for using neuromodulators and reassure her that these medications are for treatment of visceral hypersensitivity, not for anxiety or depression. After the discussion, the patient opts to start amitriptyline therapy at 10 mg every night at bedtime, increasing the dose by 10 mg every 2 weeks until symptoms improve, up to 75–100 mg every day.

After 3 months, the patient reports a 90% improvement in symptoms while on amitriptyline 30 mg every night. She is also able to taper her antisecretory medications once symptoms are controlled. We plan to continue amitriptyline at the current dose for 6 to 12 months, then discuss a slow taper to see if her symptoms spontaneously resolve. ■

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