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SECTION II: FGIDs: DIAGNOSTIC GROUPS

Esophageal Disorders

Qasim Aziz,[1] Ronnie Fass,[2] C. Prakash Gyawali,[3] Hiroto Miwa,[4] John E. Pandolfino,[5] and Frank Zerbib[6]

[1]Barts and The London School of Medicine and Dentistry, Wingate Institute of Neurogastroneterology, Centre for Neuroscience and Trauma, Blizard Institute Queen Mary University of London UK, London, United Kingdom; [2]MetroHalth Medical Center, The Esophageal and Swallowing Center, School of Medicine, Case Western Reserve University, Cleveland, Ohio; [3]Division of Gastroenterology, Washington University School of Medicine, St. Louis, Missouri; [4]Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; [5]Division of Medicine-Gastroenterology and Hepatology, Feinberg School of Medicine Center, Northwestern University, Chicago, Illinois; [6]CHU de Bordeaux, Gastroenterology Department, Université de Bordeaux, Bordeaux, France

Functional esophageal disorders consist of a disease category that presents with esophageal symptoms (heartburn, chest pain, dysphagia, globus) that are not explained by mechanical obstruction (stricture, tumor, eosinophilic esophagitis), major motor disorders (achalasia, esophagogastric junction outflow obstruction, absent contractility, distal esophageal spasm, jackhammer esophagus), or gastroesophageal reflux disease. Although mechanisms responsible are unclear, it is theorized that visceral hypersensitivity and hypervigilance play an important role in symptom generation, in the context of normal or borderline function. Treatments directed at improving borderline motor dysfunction or reducing reflux burden to subnormal levels have limited success in symptom improvement. In contrast, strategies focused on modulating peripheral triggering and central perception are mechanistically viable and clinically meaningful. However, outcome data from these treatment options are limited. Future research needs to focus on understanding mechanisms underlying visceral hypersensitivity and hypervigilance so that appropriate targets and therapies can be developed.

Keywords: Heartburn; Chest Pain; Dysphagia; Globus; Esophageal Motility Disorders; Gastroesophageal Reflux Disease; Rome IV.

Functional esophageal disorders present with typical esophageal symptoms that are not associated with structural, inflammatory, or a major motor abnormality[1] (Table 1). Thus, these patients typically present in the context of a normal endoscopy, and no evidence of mechanical obstruction or biopsy-confirmed eosinophilic esophagitis (EoE). In addition, there is no evidence of a major motor disorder (achalasia, esophagogastric junction [EGJ] outflow obstruction, absent contractility, distal esophageal spasm, jackhammer esophagus) and no pathologic esophageal acid exposure. The pathophysiology of these disorders focuses on alterations in neural processing between peripheral triggering and central perception of esophageal symptoms. These disorders do not progress along a tangible organic natural history, and, accordingly, a chronicity exists that reflects the underlying pathogenesis and disease burden. Thus, an arbitrary requirement of at least 3 months of symptoms with an onset at least 6 months before diagnosis is applied to each diagnosis to establish chronicity.

Recent advances in our understanding of esophageal motor disorders,[2] and the appreciation that EoE may be associated with diverse esophageal symptoms[3] (Figure 1) have led to more specific revisions of exclusionary criteria for functional esophageal disorders. Similar to ROME III, achalasia and absent contractility remain exclusion criteria.[1] However, the term *histopathology-based esophageal motor disorder* used in previous definitions (Rome III) is no longer accurate because these motor disorders are not diagnosed based on histology, but instead are defined by motor patterns. Furthermore, recent descriptions of spastic and hypercontractile motor phenotypes have expanded the exclusion criteria.[4] In contrast, borderline motor abnormalities, such as ineffective esophageal motility and fragmented peristalsis, are not exclusionary because these motor patterns can be seen in asymptomatic controls, and likely generate symptoms in the context of a secondary process, such as gastroesophageal reflux disease (GERD), visceral hypersensitivity, and hypervigilance.[2]

The current ROME IV criteria place a strong emphasis on ruling out mechanical obstruction as a mechanism of symptom generation. For instance, evidence of EGJ outflow obstruction would rule out a functional diagnosis because this can represent achalasia in evolution or a subtle mechanical obstruction. Further evaluation targeting structural EGJ processes (eg, endoscopic ultrasound, contrast radiography) should be considered once an EGJ outflow obstruction pattern is recognized.[2] Similarly, evidence of EoE on endoscopy or on mucosal biopsy also excludes a functional diagnosis because esophageal symptoms (heartburn, chest pain, dysphagia) can be related to the underlying inflammation and mechanical effects on the esophageal wall.[3]

Abbreviations used in this paper: **EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; NCCP, noncardiac chest pain; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; SSRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant.**

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Table 1. Functional Esophageal Disorders

Functional chest pain
Functional heartburn
Reflux hypersensitivity
Globus
Functional dysphagia

Another major change in the ROME IV classification is the more restrictive definition of GERD, accepting that sensitivity to a physiologic reflux burden may sit more firmly within the functional realm than true GERD, albeit within a spectrum allowing for overlap with GERD (Figure 2). The previous exclusion of patients with symptom–reflux correlation (based on response to proton pump inhibitor [PPI] therapy and symptom–reflux association with physiologic esophageal acid exposure) from functional esophageal disorders places undue emphasis on the strength of the PPI trial, and negates the underlying pathogenesis of visceral sensitivity in the reflux-hypersensitive esophagus. Thus, response to PPI as a criterion for defining GERD has been tempered by the high placebo response, low specificity, and limited predictive value.[5] Although patients with symptom–reflux correlation to physiologic reflux events may respond to PPI therapy, the most logical pathophysiologic explanation is consistent with the current understanding of visceral hypersensitivity and mechanisms of peripheral or central sensitization; thus, these should be included within the functional paradigm. However, care should be exercised in interpreting these designations because heavy emphasis is placed on the accuracy of ambulatory reflux monitoring, which can be falsely negative and subject to day-to-day variation in reflux burden.[6] The role of weakly acidic reflux events (reflux events with pH values between 4 and 7) in generating symptoms and end-organ damage remains controversial; one could argue that this, too, would be more consistent with hypersensitivity and abnormal perception in the context of heartburn and chest pain (Figure 2).

A1. Functional Chest Pain

Definition

Functional chest pain is defined as recurring, unexplained, retrosternal chest pain of presumed esophageal origin, not explained on the basis of reflux disease, other mucosal or motor processes, and representing pain different from heartburn. Functional chest pain is a subset within the broad umbrella of noncardiac chest pain (NCCP). History and physical examination do not reliably segregate esophageal from cardiac chest pain, stressing the need for an initial cardiac evaluation in appropriate clinical settings.

Epidemiology

The prevalence of functional chest pain is unknown and is based largely on inferential data from studies assessing NCCP. Population-based surveys assess the prevalence of NCCP at 19%–33%.[7,8] However, this includes chest pain from other esophageal processes including GERD, EoE, and esophageal motor disorders, and therefore likely overestimates the prevalence of true functional chest pain. For instance, Fass et al[9] estimated that within NCCP cohorts, 50%–60% have GERD, 15%–18% have esophageal dysmotility, and approximately 32%–35% have true functional chest pain. Within these limitations, the prevalence appears to be gender-equal, higher in patients younger than 45–55 years of age and lower in less-developed countries.

Clinical Evaluation

Initial exclusion of cardiac disease is a key step, and esophageal work-up should proceed only after confirmation (typically from the patient's cardiologist or primary care physician) that symptoms are unrelated to concurrent coronary artery disease. After exclusion of a cardiac cause, further work-up is guided by the prevalence of the underlying causes of NCCP, and potential clues from clinical

Table 2. Pain Modulators for the Treatment of Functional Esophageal Disorders

Class of drug	Dose	Disorder	RCT	Side effects	Response
TCAs					
Imipramine	50 mg/day	NCCP	+	+/-	57%
Amitriptyline	10–20 mg/day	NCCP, globus	+	+/-	52%
SSRIs					
Sertraline	50–200 mg/day	NCCP	+	+	57%
Paroxetine	50–75 mg/day	NCCP	+	+/-	Modest
Citalopram	20 mg/day	ES	+	+/-	Significant
Trazodone					
Vs clomipramine	50/25 mg/day	NCCP	-	+	Modest
Trazodone alone	100–150 mg/day	dysmotility	+	+/-	29%–41%
SNRIs					
Venlafaxine	75 mg/day	NCCP	+	++	52%
Other					
Theophylline	200 mg twice/day	NCCP	+	+/-	58%
Gabapentin	300 mg 3 times/day	globus	+	+/-	66%

ES, esophageal hypersensitivity; RCT, randomized control trial; SNRI, serotonin norepinephrine reuptake inhibitor.