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EDITORIAL

Psychological Comorbidity and Chronic Heartburn: Which Is the Chicken and Which Is the Egg?

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During the last two decades, it has been recognized that patients reporting heartburn may not necessarily have gastroesophageal reflux disease (GERD) as the underlying cause of their symptoms [1]. Heartburn does not appear to be stimulus-specific, since numerous stimuli may provoke this symptom [2]. For example, either mechanical (intraesophageal balloon distension) or chemical (mucosal acidification) can cause heartburn [3]. This scientific breakthrough enabled research groups to identify new disorders in which heartburn was the predominant symptom, such as functional heartburn and reflux hypersensitivity, which are not GERD-related but instead are included in the category of functional esophageal disorders [4]. Importantly, within the GERD group, there are 3 phenotypic presentations, all with heartburn as the predominant symptom: nonerosive reflux disease (NERD), erosive esophagitis, and Barrett's esophagus [5]. Thus, there are currently 5 accepted disorders (3 GERD-related and 2 functional esophageal disorders) in which heartburn is the principal symptom.

Several studies have demonstrated that patients carrying a psychiatric diagnosis are more likely to report heartburn, exercise-induced heartburn, and dysphagia as compared with those who are without psychiatric disorder [6]. Additionally, 42% of psychiatric patients compared with 5% of normal controls reported gastroesophageal reflux-related symptoms [7]. Furthermore, according to several studies of psychological comorbidities in GERD patients, anxiety, depression, and somatization are significantly more common as compared with normal controls [8, 9]. There is evidence that increased severity of GERD, as determined by frequency and duration of symptoms, is more likely to be associated with psychological distress [10]. Interestingly, no relationship has been established between psychological comorbidity and pH testing or mucosal pathology; furthermore, the presence or absence of psychological comorbidity is not predictive of any of the GERD phenotypes [10–12].

In this issue of *Digestive Diseases and Sciences*, Bilgi et al. [13] assessed the prevalence of psychiatric comorbidity in patients with heartburn. While the authors considered erosive esophagitis, nonerosive reflux disease, hypersensitive esophagus, and functional heartburn as different GERD phenotypes, as mentioned above, the two former are GERD subgroups and the latter two are not related to GERD but rather to functional esophageal disorders. Moreover, the authors used the term "hypersensitive esophagus," which was changed to "reflux hypersensitivity" according to the Rome IV criteria [4].

The impetus behind this research project is the paucity of systematic evaluations of psychological comorbidity in patients with heartburn, including GERD and nonGERD groups. Stratification of patients with heartburn to the different groups was carried out using a battery of tests, including upper endoscopy, esophageal manometry, impedance + pH, and a GERD questionnaire. Subsequently, psychological comorbidity was determined using several evaluation tools including a structured clinical interview according to the Diagnostic and Statistical Manual (DSM)-IV, the somatosensory amplification scale,

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the Beck depression inventory, and the state-trait anxiety inventory. The short form 36 (SF 36) was used to assess the reported general health-related quality-of-life. The authors demonstrated that depression was significantly more common in all heartburn groups whether GERD-related or functional, as compared with healthy controls. When the prevalence of psychological comorbidity was compared among the different patient groups, major depression was significantly more common in the functional heartburn patients and anxiety in the hypersensitive esophagus and erosive esophagitis groups.

The study confirmed the findings of previous trials that depression and anxiety are common in patients with GERD and those with functional esophageal disorders. Interestingly, anxiety was specifically more common in those with erosive esophagitis and the hypersensitive esophagus. It is possible that the small number of participants in each group of patients may have skewed the results of the anxiety assessment. The study should serve as the impetus of a much larger trial, with hundreds of patients in each group.

The study, though well designed, leaves several unanswered questions that whether addressed would have increased the understanding of the nature of the relationship between heartburn and psychological comorbidity. Importantly, it still remains to be elucidated which factor is causative. Several studies have demonstrated that patients exposed to prolonged life stressors are more likely to complain of symptoms of GERD [14]. Vital exhaustion, a measure of sustained stress, is the most common parameter that correlates with heartburn [15]. Furthermore, prolonged stress can lead to hypervigilance and thus the over-reporting of symptoms [16]. Acute stress can exacerbate heartburn symptoms by enhancing perceptive responses to intra-esophageal acid [15]. Thus, it appears from the aforementioned studies that psychological comorbidity is a central factor that can modulate perception of intra-esophageal stimuli, increasing complaints of symptoms such as heartburn in these patients [17].

More important is the question about the impact of psychological comorbidity on the response of GERD patients to anti-reflux treatment. While the data are limited, several studies have suggested that the presence of psychological comorbidity adversely affects the response of patients to proton pump inhibitor (PPI) treatment. High levels of anxiety and depression reduce the likelihood of achieving complete heartburn relief [18, 19]. Moreover, the level of psychological distress is an independent predictor for poor response to PPI treatment [20].

In summary, psychological comorbidity is common among heartburn patients, either those with GERD or patients with functional esophageal disorders. More importantly, psychological comorbidity profoundly affects disease presentation, by altering the perception of disease severity. The presence of psychological comorbidity reduces the likelihood of achieving complete heartburn resolution while being treated for reflux. All data suggest the need to identify the presence of psychological comorbidity in patients with heartburn symptoms. Timely psychological intervention concomitant with pharmacologic anti-reflux treatment in GERD patients and neuromodulators in those with functional esophageal disorders carry the highest probability of achieving therapeutic success.

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