Extra-esophageal manifestations of GERD

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INTRODUCTION

Atypical and extra-esophageal manifestations of gastroesophageal reflux disease remain an area of intense research. However, in many areas of extra-esophageal manifestations of GERD, there has been very limited progress in the understanding of the role of GERD in generating extra-esophageal symptoms. In addition, therapeutic trials directed toward gastroesophageal reflux disease in patients who are suspected to have extra-esophageal manifestations of GERD have demonstrated very limited efficacy. All suggest that our current understanding about the relationship between GERD and a variety of extra-esophageal manifestations remains very poor.

Noncardiac chest pain is one of the most common atypical manifestations of GERD. Based on the Montreal definition, chest pain is not considered an atypical manifestation of GERD, but rather one of the typical symptoms that may resolve from GERD.

The atypical presentations of GERD include chest pain, epigastric pain, and nausea. The extra-esophageal manifestations of GERD include dental erosions, hoarseness, globus sensation, sore throat, vocal cord irritation, vocal cord polyps and granulomas, posterior laryngitis,
chronic cough, asthma, aspiration, pulmonary fibrosis, recurrent pneumonia, sleep abnormalities, and cardiac angina. Studies have shown that about half of the patients with nonerosive reflux disease or erosive esophagitis report extra-esophageal and atypical manifestations of GERD (Table I).

When it comes to symptoms in patients with extra-esophageal manifestations of GERD, frequent heartburn is rare, infrequent heartburn is common, and absence of heartburn is not unusual. Endoscopy is commonly normal in these patients.

Noncardiac chest pain has been shown to be caused primarily by gastroesophageal reflux disease. Heartburn can be documented in 10% to 70% of the patients. However, it is well known that acid reflux may cause heartburn in some patients, chest pain in others, and both chest pain and heartburn in another subset of patients. Endoscopy and 24-hour esophageal pH monitoring have a limited a value in patients with noncardiac chest pain. The proton pump inhibitor test has been shown to be a highly sensitive, specific, simple and non-invasive modality for diagnosing GERD-related NCCP.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>EXTRA-ESOPHAGEAL MANIFESTATIONS OF GERD</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>Pharyngo-laryngeal</td>
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<tr>
<td>Asthma</td>
<td>Pharyngitis</td>
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<td>Aspiration pneumonia</td>
<td>Vocal cord granulomas</td>
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<td>Chronic bronchitis</td>
<td>Subglottic stenosis</td>
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<td>Bronchiectasis</td>
<td>Laryngitis</td>
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<td>Interstitial pulmonary fibrosis</td>
<td>Stridor</td>
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<td><strong>Oral</strong></td>
<td>Hoarseness</td>
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<td>Halitosis</td>
<td>Globus</td>
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<tr>
<td>Dental caries</td>
<td>Laryngeal cancer</td>
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<tr>
<td>Poor oral hygiene</td>
<td>Chronic cough</td>
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Symptoms of GERD have also been shown in patients with laryngeal symptoms. The more frequent the symptoms of GERD, the higher the prevalence of laryngeal symptoms. The role of pH testing in patients with laryngeal manifestations of GERD is unclear. Studies have shown that if the pH test is negative off therapy, it is unlikely that patients will respond to PPI treatment. However, if the test is positive prior to treatment, then there is only a 35% chance that patients will respond to therapy. Treatment for laryngeal presentations of GERD has been relatively disappointing. This was further supported by a large double blind, placebo-controlled, randomized, multicenter trial, suggesting that PPI twice daily was no better than placebo in treating patients with laryngopharyngeal reflux (LPR).

GERD AND SLEEP DISTURBANCES

There is some data supporting close association between nocturnal GERD and sleep disturbances. Sleep disturbances in patients with GERD are poorly recognized and rarely elicited during clinic visits. Despite the significant impact of these disturbances on patients’ quality of life and, probably, on their perception of the severity of their disease. Sleep disturbance is not usually asked about in the routine history taken from patients with reflux disease. When 759 patients with endoscopy-negative reflux disease, who were enrolled in the esomeprazole (Nexium) clinical trial program, were assessed by a quality of life tool for “sleep disturbances for at least some of the time” (score ≤ 4), 50% reported that symptoms of GERD were responsible for difficulties in getting a good night’s sleep. Other indicators of sleep disturbance were “feeling tired/worn out due to lack of sleep” (42%), “failure to wake up feeling fresh/rested” (41%), “having trouble falling asleep” (40%), and “heartburn/acid regurgitation waking the patient and preventing him/her from falling asleep” (35%).

In a national survey of 1,000 subjects with GERD, 75% of the participants reported that GERD symptoms affected their sleep, 63% believed that heartburn negatively affected their ability to sleep well. The prevalence of sleep disturbances among respondents increased with increase in frequency of the nighttime heartburn episodes dur-
ing the week. Additionally, 42% could not sleep through the night and 39% took naps whenever possible. Green et al. reported, in an abstract form, that GERD patients that sleep less during the night are more likely to have symptoms that correlate with acid reflux events. Additionally, the extent of distal esophageal acid exposure has a significant effect on patients’ reported sleep experience. The higher the acid exposure the lower the overall reported quality of sleep (supine) and the higher the number of nocturnal awakenings (total and supine). Dekel et al. demonstrated that the frequency and severity of GERD symptoms were correlated with patients’ quality of sleep. Patients with erosive esophagitis reported more nocturnal awakenings due to heartburn than those with non-erosive reflux disease, but otherwise reported similar sleep abnormalities and quality of sleep. Other investigators have demonstrated that nighttime gastroesophageal reflux may result in anamnestic short awakenings that lead to sleep fragmentation and feeling unrefreshed the next morning, dozing off and daytime sleepiness.

Obstructive sleep apnea (OSA) is a breathing disorder that occurs during sleep in which the patient experiences respiratory pauses lasting at least 10 seconds and occurring at least 5 times per hour of sleep. OSA is characterized by excessive daytime sleepiness, snoring, repeated episodes of upper airway obstruction during sleep, and nocturnal hypoxemia leading to memory problems, irritability, and depression. The exact association between OSA and GERD remains controversial. In one study, OSA was not influenced by severity of GERD. Additionally, objective measures of disordered sleep had stronger association with age, smoking and alcohol use than GERD in men and stronger association with age and body mass index than GERD in women. Kerr et al. have demonstrated that precipitous droops in pH were frequently preceded by arousal (98.4%), movement of the patient (71.9%), and swallowing (80.4%). In this case, arousal is theorized to be caused by increased ventilatory effort. Arousal and movement may trigger gastroesophageal reflux by causing transient alteration in the pressure gradient across the lower esophageal sphincter (LES). Additionally, the lowered intrathoracic pressure that accompanies OSA may itself predispose the patient to gastroesophageal reflux by exacerbating the LES pressure gradient.
Treatment with nasal continuous positive airway pressure (CPAP) showed dramatic reduction in the frequency of gastroesophageal reflux by elevating intrathoracic pressure.

Investigators have suggested that GERD causes OSA, and OSA has been linked to GERD. Other studies could not demonstrate a causal relationship between OSA and GERD. In a study by Penzel et al. 37 of 52 reflux events that occurred during sleep, involving either apnea or hypopnea, were found prior to the reflux event. The sequence in time did not prove a causal relationship between the respiratory and reflux events. Patients subjectively report that the quality of sleep is affected by the severity of GERD; however, objective correlation between OSA and GERD is lacking, which may suggest that both are common entities sharing similar risk factors but may not to be causally linked.

RECOMMENDED REFERENCES