

Do Proton Pump Inhibitor–refractory Laryngeal Symptoms Represent a True Acid-related Disease?

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Article: Proton pump inhibitor-unresponsive laryngeal symptoms are associated with psychological comorbidities and sleep disturbance: a manometry and impedance-pH monitoring study

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Gastroesophageal reflux disease (GERD) is a condition characterized by regurgitation of stomach contents into the esophagus or mouth, leading to troublesome symptoms or complications.¹ Globally, the overall burden of GERD has continued to worsen. The number of prevalent cases increased by 77.53% from 441.57 million in 1990 to 783.95 million in 2019.² A systematic review conducted in Asia in 2011 revealed an increasing prevalence of symptom-based GERD in Eastern Asia: 2.5–4.8% before 2005 and 5.2–8.5% between 2005 and 2010. Moreover, this study found that extraesophageal symptoms were more common in patients with GERD than in healthy individuals.³ Laryngopharyngeal reflux (LPR) is an extraesophageal manifestation of GERD. It refers to the reflux of gastric contents into the larynx, causing symptoms such as throat clearing, hoarseness, pain, globus sensation, coughing, excessive mucus in the throat, and dysphonia. However, no gold standard currently exists for the diagnosis and treatment of LPR, which presents a challenge to health-care systems.⁴

In a study published in this issue, Tseng et al⁵ focused on examining the physiological and clinical characteristics of patients who experienced laryngeal symptoms despite receiving empirical proton pump inhibitor (PPI) therapy for an adequate duration.

The authors not only investigated typical reflux symptoms but also considered comorbidities such as sleep disturbances and other psychological problems. According to several studies about the correlation between LPR and anxiety, depressive disorders, or insomnia, PPI-unresponsive laryngeal symptoms may be associated with psychological factors and sleep disturbances.⁶ In a study conducted in South Korea in 2022, the association between LPR and insomnia was investigated using multiple intraluminal impedance-pH (MII-pH) monitoring and a questionnaire survey (Insomnia Severity Index questionnaire). The results of that study are consistent with the findings of the current study.⁷ Tseng et al⁵ used various multidisciplinary assessment tools, including the 5-item Brief Symptom Rating Scale and the Pittsburgh Sleep Quality Index, to obtain objective information from patients and healthy asymptomatic individuals. However, it is difficult to generalize the study results because of the single-center design and lack of a cause-effect relationship. Moreover, a concern exists that endoscopy and MII-pH monitoring may not be adequate for evaluating patients with extraesophageal symptoms suggestive of LPR, as indicated in a previous study.⁸

LPR remains a challenging issue in clinical practice because

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of the lack of consensus regarding its diagnosis. Moreover, several factors are involved, including not only the reflux of gastric contents but also the patient's psychological factors, and the exact mechanisms remain unclear. Although empirical PPI trials are commonly used as a first-line therapeutic approach, they are no longer recommended because many patients are unresponsive to PPIs. Therefore, additional studies are needed to define patient characteristics and personalize the treatment options for LPR. This study provides valuable data supporting the existing hypothesis that PPI-refractory laryngeal symptoms are more strongly associated with psychological comorbidities and sleep disturbances than with reflux-related factors. These results are important because neuromodulator therapy and behavioral interventions are considered potential treatment options for LPR. However, the amount of available evidence regarding the effectiveness of neuromodulators and behavioral interventions in treating LPR is still limited. Thus, further large-scale studies are required to validate the relationships between PPI-unresponsive laryngeal symptoms and psychological problems, sleep disturbances, and other comorbidities.

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