Laryngopharyngeal Reflux

Laringofarengeal Reflü

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ABSTRACT

In patients with laryngopharyngeal reflux (LPR), gastric contents exhibit retrograde flow into the upper aero-digestive tract, causing extraesophageal symptoms. It is apparent that the pathophysiology of LPR is different from that of classical gastroesophageal reflux disease (GERD). Head and neck disorders associated with extraesophageal reflux are postulated to occur via direct mucosal damage or a direct effect on mucociliary clearance from exposure to gastric contents; gastroesophageal reflux (GER) related distal esophageal damage that results in vagally mediated, referred symptomatology; and laryngeal reflexes mediated by the stimulation of distal esophageal afferents. Alteration of pH has a direct effect on mucociliary transport and may lead to increased viscosity of the mucus. A reduction in mucociliary transport may decrease resistance to infection and has been theorized to contribute to the pathogenesis of subglottic stenosis. The diagnosis of LPR is difficult with the current understanding of the pathophysiology and available tests. Laryngoscopy does not dependably predict who will respond to treatment, due to high interobserver variability. A 2-month treatment course of PPI is typically safe in those without accompanying warning symptoms. A trial of twice-daily PPI for evaluation and management, in addition to dietary and behavioral changes, should be emphasized. All PPI therapy should be tapered to the minimum dose of acid suppression to control patient symptoms. Future studies with oropharyngeal pH monitoring and salivary pepsin assay need to provide controlled outcome data to better understand their role in cases with difficulty in the diagnosis. Overall, there is currently no clear evidence that an empiric PPI trial results in a significant reduction in LPR symptoms or laryngoscopic findings over placebo. Therefore, its use as a diagnostic or therapeutic tool in the management of patients with ENT symptoms remains controversial. However, on the basis of outcomes of LPR studies to date and earlier experience with treatment of GERD and erosive esophagitis, a trial of 2-3 months should be used, with dose tapering if a symptomatic response is achieved. Given the unreliability of laryngoscopic findings, therapy should be based on symptoms. *(JAREM 2014; 4: 85-7)*

Key Words: Reflux, laryngopharyngeal reflux, gastroesophageal reflux, pepsin, bile acid

ÖZET

Laringofarengeal reflüsü (LFR) olan olgularda gastrik içerik retrograd geçiş ile üst hava-sindirim kanalına doğru geçerek ekstraözofageal semptomlara yol açar. LFR'nin patofizyolojisi klasik gastroözofageal hastalığın (GFR) patofizyolojisinden farklıdır. Baş ve boyun rahatsızlıkları, ekstraözofageal reflü ile ilişkili mide içeriğine maruz kalmaya bağlı olarak doğrudan mukoza hasarı veya mukosilier klirens üzerine etki sonucu gelişir. Gastroözofageal reflü (GER) ile ilişkili vagal yol aracılığıyla distal özafagus hasarı semptomların ve distal özofageal afferentlerin stimülasyonu aracılığıyla larengeal reflekslerin ortaya çıkmasına yol açar. pH değişiklikleri mukosilier transportu doğrudan etkileyerek mukus vizkositesinde artışa yol açabilir. Mukosilier transporttaki azalmanın enfeksiyona karşı direnci azaltabileceği ve subglotik stenozun patogenezine katkıda bulunabileceği öne sürülmüştür. Çeşitli invazif diagnostik testler LFR'nin ayırıcı tanısında kullanılabilir. Ampirik proton pompa inhibitor (PPİ) tedavisini düzenlemede ve reflü içeriğinin safra asidi ile pepsin açısından değerlendirilmek üzere elde edilmesinde yararlı olabilecek bazı noninvazif yöntemler ve diagnostik amaçlı testler de tanıda yardımcı olabilir. Güncel bilgiler ışığında varolan testler ile LFR tanısının konulması zordur. Laringoskopi, değerlendirenler arasındaki yüksek değişkenlik nedeniyle tedaviye cevabı takipte tek başına güvenilir bir yöntem değildir. LFR açısından uyarıcı semptomları olan olgularda iki aylık bir proton pompa tedavisinin uygulanması belirgin koruyucu bir etki sağlayabilir. Uygulanan diyete ve değiştirilen alışkanlıklara ilaveten günde iki doz PPİ tedavisine cevap dikkatli bir şekilde takip edilip değerlendirilmelidir. Bütün PPI tedavileri minimum dozda asit supresyonu sağlayarak hastanın semptomlarını kontrol etmek üzere planlanmalıdır. Gelecekte orofarengeal pH'nın izlenmesi ve tükrükte pepsin tayini sonrasında elde edilecek kontrollü datalar tanısı zor olan olgularda bu yöntemlerin rolünü anlamada yardımcı olacaktır. Sonuç olarak, ampirik PPİ tedavisinin plaseboyla karşılaştırıldığında LFR semptomlarında veya laringoskopik bulguların anlamlı düzeyde azaltılmasında faydalı oldugunu gösteren belirgin bir kanıt yoktur. Bu nedenle kulak burun boğaz semptomları olan olguların değerlendirilmesinde PPİ lerinin tedavi veya tanı amaçlı kullanılması tartışmalıdır. Bununla birlikte günümüze kadar yapılan LFR çalışmalarının sonuçlarına dayanarak ve GER hastalığı ile erozif özofajitin tedavisinde elde edilen tecrübeler gözönüne alındığında iki-üç aylık bir PPİ kullanımı ile semptomatik bir iyileşme sağlanabilmektedir. Laringoskopik bulguların güvenilir olmaması nedeniyle tedavi semptomlar üzerinden planlanmalıdır. *(JAREM 2014; 4: 85-7)*

Anahtar Sözcükler: Reflü, laringofarengeal reflü, gastroözofageal reflü, pepsin, safra asidi

INTRODUCTION

Retrograde flow of gastric contents into the upper aero-digestive tract is defined as laryngopharyngeal reflux (LPR). In fact, LPR is different from classical gastroesophageal reflux in relation to pathophysiology.

Laryngeal manifestation of GERD (gastroesophageal reflux disease) is thought to be related to either direct acid peptic injury to the larynx by esophagopharyngeal reflux (the microaspiration theory) (1) or acidification of the distal esophagus through vagally mediated reflexes (the esophageal-bronchial reflex theory) (2, 3). Laryngeal tissue certainly lacks protective mechanisms of the esophagus, like production of bicarbonate, physical barriers, and intrinsic acid clearance mechanisms, like peristalsis, and is highly susceptible to any acid exposure. In addition to acidic pH levels, substances that can contribute to the noxious quality of the refluxate include pepsin, bile salts, and pancreatic enzymes. Previous studies suggested that pepsin may be the main cause

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of LPR symptoms (4, 5); however, recent studies suggested the coimportance of acid, pepsin, and bile acids (6). There is now a renewal of publications on the role of pepsin in LPR. It has been recommended that reflux of pepsin into the larynx with subsequent pepsin transfer into the cytoplasm of the laryngeal cells and later activation in cell organelles with lower pH ranges than the lumen may be an important contributor to LPR (7).

The pattern of reflux is different in LPR and GER (gastroesophageal reflux). LPR usually occurs during the daytime in the upright position, whereas GERD (GER disease) takes place more often in the supine position at night-time or during sleep.

Currently, the diagnosis of LPR still remains unclear. Measurement of pepsin in patients with LPR may be considered as a diagnostic test. Moreover, the determination of pepsin may be used to monitor clinical improvement of LPR after antireflux surgery. In vitro exposure of human hypopharyngeal and laryngeal cell cultures to pepsin in the presence of acidic and nonacidic conditions stimulates proinflammatory cytokines, and bile acids have been indicated as procarcinogenic by several studies, based on the increase in the prevalence of laryngeal cancer in subjects with gastrectomy. Despite this, it has not yet been relevant that reflux alone is a direct causative agent for carcinogenesis. On the other hand, pepsin and bile acids have a significant role in carcinogenesis, with greater toxicity at lower pH in a dose-dependent manner. It has been strongly recommended that continuous pepsin exposure will increase cell proliferation and by this way may contribute to oncogenesis by inducing tumor growth.

Gastroesophageal reflux always contains pepsin; on the other hand, not all reflux occurs below pH 4.0. This means that with the use of traditional gastroenterology standards for pH-metry, significant LPR may be underdiagnosed. Moreover, pepsin exhibits enzymatic activity at pH levels well above, and it is only irreversibly inactivated at a pH greater than 6.5. Thus, a patient could conceivably have a negative pH study (no reflux events pH ≤4) but might still have significant LPR-related disease. It has been previously reported that the laryngeal epithelium is far more sensitive to damage by pepsin in the presence of acid than esophageal epithelium, and this may help explain why the patterns of reflux, reflux mechanisms, and clinical manifestations of LPR and GERD are so different.

Pepsinogen is not detected in laryngeal tissue specimens, confirming that the laryngopharynx does not produce pepsin. Hence, the pepsin detected in patients with LPR was presumably deposited from a reflux event. The fact that pepsin is only produced in the stomach makes this parameter a specific marker for reflux when detected in the laryngopharynx. There are a range of techniques available to detect pepsin in refluxate, including enzymatic assays, immunohistochemistry, western blot, ELISA, and a new commercially available in vitro diagnostic test, the "peptest."

Additional recent tests in LPR include oropharyngeal pH monitoring and salivary pepsin assay. The Dx-pH measurement system (Respiratory Technology Corp, San Diego, CA) is a sensitive and minimally invasive device for the detection of acid reflux in the posterior oropharynx. It uses a nasopharyngeal catheter (the Restech pH catheter) to measure pH in either liquid or aerosolized droplets (8, 9). The measurement of esophageal acid exposure by ambulatory pH monitoring has long been considered a major tool in the diagnosis of GERD. The degree of esophageal mucosal injury seems to correlate with increased accuracy of pH monitoring, with decreasing sensitivity and specificity estimates, in patients without macroscopic esophageal mucosal injury (10). Introduction of multichannel intraluminal impedance (MII), in combination with double probe pH monitoring (pH-MII), permits the detection of all types of refluxate, irrespective of its acidity (11). Despite its utility in assessing the presence of GERD in patients with typical reflux syndromes, the accuracy of pH or pH-MII testing is much more variable in confirming the diagnosis of GERD in patients presenting with possible extraesophageal reflux (EER) syndrome. It has been estimated that half of otolaryngology patients with laryngeal and voice disorders have LPR. In fact, LPR is considered one of the most important and common factors causing inflammation in the upper airways. Tissue damage is demonstrated in both animals and humans. It may be caused by direct exposure to acid, pepsin, and bile and by vagally mediated reflexes.

Develioglu et al. (12) reported that acidified gastric pepsin causes hearing loss due to inner ear ototoxicity in a rat animal model. Moreover, inflammatory responses and metaplastic changes may play an important role in the etiology of middle ear pathologies due to exposure to pepsin and bile acid (13). Approximately 10% of all otolaryngology clinic patients and 50% of patients with voice complaints have been diagnosed with LPR.

Laryngopharyngeal reflux has a role in various laryngeal pathologies, including stenosis, malignancy, benign lesions, dysphagia, and functional disorders. Thus, LPR should be considered a chronic disease with a variety of presentations.

Otolaryngologists often overdiagnose LPR as the cause of laryngeal syndrome, which can lead patients and their referring physicians to anchor on this diagnosis as the underlying cause. Therefore, the first step in understanding the patient's problems is to deconstruct the diagnosis into the presenting syndrome and review the diagnostic steps taken to come to such a diagnosis, the therapies provided to date, and the response to such therapies (14, 15).

Empiric therapy with a PPI twice daily is considered to be the best diagnostic test in those with LPR. This initial therapy in the low-risk group (no serious symptoms), followed by diagnostic testing, is a reasonable approach in those initially suspected of having LPR. If the patient responds to therapy, then decreasing to once-daily PPI initially and then to minimal acid suppression to control symptoms is appropriate. In those with moderate to high risk (weight loss, dysphagia, anemia, odynophagia, hematemesis, or respiratory distress), an initial diagnostic tests is essential as well as esophagoscopy to exclude esophageal carcinoma. (16-18).

Actually, the diagnosis of LPR is difficult with the current understanding of the pathophysiology and available tests. Laryngoscopy does not dependably predict who will respond to treatment, due to high interassay variability. A 2-month treatment course of PPI is typically safe in those without accompanying warning symptoms. A trial of twice-daily PPI for evaluation and management, in addition to dietary and behavioral changes, should be emphasized. All PPI therapy should be tapered to the minimum dose of acid suppression to control patient symptoms. Future

studies with oropharyngeal pH monitoring and salivary pepsin assay need to provide controlled outcome data to better understand their role in cases with difficulty in the diagnosis (18-21).

Overall, there is currently no clear evidence that an empiric PPI trial results in a significant reduction in LPR symptoms or laryngoscopic findings over placebo. Therefore, its use as a diagnostic or therapeutic tool in the management of patients with ENT symptoms remains controversial. However, on the basis of outcomes of LPR studies to date and earlier experience with treatment of GERD and erosive esophagitis, a trial of 2-3 months should be used, with dose tapering if symptomatic response is achieved. Given the unreliability of laryngoscopic findings, therapy should be based on symptoms.

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