Laryngopharyngeal Reflux and Voice Disorders: A Multifactorial Model of Etiology and Pathophysiology

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Summary: Objective. The aim of this paper is to shed light on the pathogenesis and pathophysiological mechanisms underlying the development of hoarseness related to laryngopharyngeal reflux disease (LPRD).
Material and methods. PubMed, Embase, and The Cochrane Library were searched for the terms reflux, laryngopharyngeal, laryngitis, voice, and hoarseness. Experimental and clinical studies providing substantial information about the occurrence of voice disorders, laryngeal histologic changes, or any pathophysiological processes related to LPRD were included by two independent investigators.
Results. Of the 104 studies reviewed, 47 studies that met our inclusion criteria were analyzed. LPRD leads to significant macroscopic and microscopic histopathologic changes in the mucosa of the vibratory margin of the vocal folds. More and more studies suspect that epithelial cell dehiscence, microtraumas, inflammatory infiltrates, Reinke space dryness, mucosal drying, and epithelial thickening are probably responsible for the hoarseness related to reflux and the impairment of the subjective and objective voice quality evaluations.
Conclusion. Future clinical studies examining the pathophysiology of hoarseness related to LPRD should take into consideration all potential mechanisms involved in the development of hoarseness.
Key Words: Voice–Laryngopharyngeal–Reflux–Hoarseness–Pathophysiology.

INTRODUCTION

Laryngopharyngeal reflux disease (LPRD) is an inflammatory condition defined as the backflow of gastric contents into the laryngopharynx, where it comes in contact with the tissues of the upper aerodigestive tract.[1] LPRD occurs in 4%–30% of patients who visit otolaryngology departments and up to 55% of patients with hoarseness.[2–4] LPRD is characterized by chronic inflammation of the laryngopharynx and, more broadly, the tissues of the upper aerodigestive tract.[5] Patients with LPRD usually complain of a myriad of nonspecific symptoms including throat clearing, persistent cough, heartburn, globus sensation, or hoarseness, with hoarseness accounting for 71%–79% of the symptoms reported.[6,7] Historically, LPRD has often been given as a default diagnosis for hoarseness. However, current beliefs would suggest that although LPR may coexist with other vocal fold disorders, other vocal fold pathologies are often diagnosed via laryngovideostroboscopy, which might explain the hoarseness. In addition, some data showed that the major etiologic factor for hoarseness more than 3 months in duration is LPRD, because LPR occurs in 55%%–79% of patients with resistant hoarseness.[8,9] Among the laryngostroboscopic findings, vocal fold edema has often been suggested as the main factor affecting the vocal fold vibrations, leading to hoarseness,[10,11] but recent data call this assumption into question, especially for mild and moderate LPRD where there is no or mild edema.[3,12,13] To date, the precise mechanisms of voice disorders related to LPRD remain incompletely understood.

This systematic review was designed to shed light on the etiology, pathogenesis, and pathophysiological mechanisms underlying the development of hoarseness related to LPRD and to identify the laryngostroboscopic findings associated with hoarseness related to LPRD.

MATERIALS AND METHODS

Literature search

We conducted a systematic literature research on PubMed, Embase, and The Cochrane Library databases to identify experimental and clinical studies directly or indirectly related to the development of hoarseness associated with LPRD. This research covers different aspects of LPRD and hoarseness including pathogenesis, basic science, pathophysiology, genetic, and biomolecular studies. The keywords used were "reflux," "laryngopharyngeal," "laryngitis," "voice," and "hoarseness." When data were found in more than one publication, we used the data reported in the largest and most recent publications. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for reviews and meta-analysis[14] and the Participant, Intervention, Comparison, Outcome, and Study design criteria for the clinical studies (Table 1). The local ethics committee approved this review.

Types of studies

The following inclusion criteria were used: prospective, controlled or uncontrolled, clinical, or experimental studies published since 1996, which was the year of the first paper that identified LPRD as a different entity from gastroesophageal reflux disease.[16]

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TABLE 1.
Participant, Intervention, Comparison, Outcome, and Study Design (PICOS) Criteria Used for the Clinical Studies Composing This Systematic Review[15]

Parameters	Inclusion Criteria	Exclusion Criteria
Patients	Adults ≥18 years with suspected LPRD The confirmation of the diagnosis required at least: (1) signs and symptoms± (2) pH metry confirmation± (3) Peptest confirmation± (4) a 3- or 6-month empirical therapeutic response	Patients under 18 years of age
Intervention	Medical± Diet and behavioral advice± Surgery	
Comparator	(1) pre- to post-treatment comparisons ± controlled group or (2) case-controlled studies (at baseline) with healthy subjects (control group)	
Outcomes	(1) laryngostroboscopic findings± (2) aerodynamic measurements± (3) acoustic parameters± (4) electroglottography findings	
Study design	Randomized controlled trials Nonrandomized controlled trials Prospective or retrospective studies Cross-sectional studies	Case reports

Only the probative findings were extracted from the included studies, especially those that conveyed direct or indirect information on vocal fold mucosa function. We determined the grade of recommendation for each clinical study following the Oxford Centre for Evidence-Based Medicine evidence levels.[17] We classified the experimental research according to the topic of the study, which was the involvement of LPRD in the defense mechanisms of the mucosa or in the inflammatory reaction.

Data extraction

All references were sorted manually to extract all descriptions of subjects meeting the diagnosis of laryngopharyngeal reflux by the first author (JRL). Each study was identified based on PubMed abstracts, available full text, title, or keywords that made reference to LPRD. The author (JRL) was not blinded to the papers' authors, their institutions, or the journal of publication.

RESULTS

Experimental studies

The database search yielded 34 articles. A total of 24 papers were included and represented 17 controlled and seven uncontrolled studies. Fifteen studies used human laryngeal samples, and nine were based on animal models (Tables 2 and 3). The studies that examined the inflammatory reactions of the laryngeal mucosa (N = 14) are shown in Table 2. The studies that focused mainly on the defense mechanisms of the laryngeal mucosa (N = 7) are described in Table 3.

Clinical studies

Our initial PubMed, Cochrane Library, and Embase searches identified 70 articles. From these, we included 23 relevant papers for a total of 1342 patients (Tables 4 and 5). Of these studies, we reported five controlled studies that assessed objective voice quality at baseline for a total of 485 patients (Table 5). Of the prospective trials, we selected 10 uncontrolled, 6 controlled, and 2 randomized placebo-controlled trials, which accounted for 857 patients with LPRD (Table 5). The flowchart showing the process of article selection is described in Figure 1.

DISCUSSION AND EVIDENCE SYNTHESIS

Experimental studies

Etiology, pathogenesis, and chronic inflammatory reaction

Previous studies have shown that irritation of the laryngeal mucosa in LPRD is due to two mechanisms. The main mechanism concerns the direct effect of the gastric content reflux (ie, acid, pepsin, trypsin, bile salts, and some gastroduodenal proteins) on the laryngeal mucosa (Table 2)[32,54,65,66]; the second mechanism (indirect effect), which remains controversial, involves the mucosa chemoreceptor stimulation resulting from refluxate from the stomach in the distal portion of the esophagus, with vagal reflexes followed by coughing and throat clearing.[67–69] The current literature tends to confirm with high prevalence the direct effect of gastric content, but to date, the existence of an indirect effect has not been excluded and could add to the first theory.

Indeed, most human and animal studies have demonstrated the presence of pepsin in extra-[30,70] and intracellular[20,21,24,32] laryngeal structures, which suggests a key role in the inflammatory process (Table 2). Pepsin may be active to some degree at any pH between 1.5 and 6.0, although a longer exposure time may be necessary at pH 5 to produce lesions.[22,37,71] Interestingly, the inactivated pepsin molecules in the laryngeal epithelium have