

Laryngopharyngeal Reflux and Eye: More Than a Hypothesis

Valerio Damiani¹, Antonio Schindler², Vitaliana Luccarelli³, Giorgio Ciprandi⁴

¹Department of Medicine, D.M.G. Group, Pomezia, Italy

²Department of Biomedical and Clinical Sciences, Luigi Sacco Università Degli Studi Di Milano, Milan, Italy

³Department of ENT, University of Milan, Milano, Italy

⁴Department of Allergy, Casa di cura Villa Montallegro, Genova, Italy

Abstract

Objective: Laryngopharyngeal reflux is a frequent medical condition affecting about 1/3 of the general population. Also, laryngopharyngeal reflux may involve the ocular surface. Dry eye disease is also a common disorder affecting any age. Dry eye disease is a multifactorial disease sustained by different causes.

Methods: We reviewed the most recent evidence about the relationship between laryngopharyngeal reflux and eye.

Results: There is documentation that pepsin may be detectable in the tears of laryngopharyngeal reflux patients. Notably, pepsin is produced only in the stomach, so it is a biomarker of gastric reflux. There is also the demonstration that patients with dry eye disease may have frequent laryngopharyngeal reflux comorbidity, and dry eye disease severity is associated with high odds of laryngopharyngeal reflux comorbidity. In addition, a preliminary trial suggested that treating also laryngopharyngeal reflux in dry eye disease patients with gastric reflux could be a promising strategy. As a result, it is conceivable to imagine that eye reflux could be a new nosologic entity. It seems reasonable to recommend that the management of laryngopharyngeal reflux patients should include the investigation of possible ocular comorbidity.

Conclusions: Laryngopharyngeal reflux and dry eye disease are 2 common diseases that not rarely can be associated together. Thus, careful attention to these disorders should be paid to in clinical practice by otolaryngologists visiting patients with laryngopharyngeal reflux.

Keywords: Laryngopharyngeal reflux, eye reflux, symptoms, comorbidity, treatment

INTRODUCTION

Gastric reflux is usually a physiological event that repeatedly occurs in a day. It consists of the overflow of gastric contents (refluxate) from the cardias. It may be gaseous, most commonly, liquid, or mixed. Notably, gastric reflux is often asymptomatic or associated with mild burping. However, when gastric reflux causes tissue damage, mainly concerning the esophagus, gastroesophageal reflux disease (GERD) takes place.¹ Usually, mucosal damage results from impaired defense mechanisms, caused by multifactorial agents, including incorrect diet and lifestyle, drugs, smoking, alcoholic beverage, and mechanical dysfunction.

Regurgitation and heartburn are typical GERD symptoms; they depend on the esophageal exposure to refluxate, containing hydrochloric acid, pepsin, and bile. However, in some subjects, the refluxate may overflow outside the esophagus, involving airways, mainly the larynx and pharynx: the laryngopharyngeal reflux (LPR). Laryngopharyngeal reflux is an extra-esophageal manifestation of gastric reflux that depends on the aggressive refluxate exposure on the upper airways, namely the larynx and pharynx. Laryngopharyngeal reflux has been described for the first time 30 years ago.² The typical LPR symptoms include hoarseness, sore throat, globus sensation, and throat clearing but may also be asymptomatic, the so-called "silent LPR."³ Laryngopharyngeal reflux is common as it may affect up to 30% of the general population and represents a relevant burden concerning social and personal costs and impaired quality of life.^{4,5} It has been underlined that GERD and LPR are 2 distinct diseases characterized by different symptoms, pathophysiology, and response to treatments. In general, LPR symptoms occur daytime and in the upper position, whereas GERD symptoms occur at night and in the supine position.

The refluxate with low and pepsin lead to chronic inflammation of mucosae.^{6,7} Pepsinogen is the precursor of pepsin, such as a proteolytic enzyme. The pepsin activation requires low pH (at least <4). It has to be remarked that pepsin

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Corresponding author:

Giorgio Ciprandi

E-mail:

gio.cip@libero.it

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production occurs only in the stomach. As a result, pepsin detection outside the gastric area has to be envisaged as a marker for gastric reflux.⁸ Some studies documented the presence of pepsin in the larynx, hypopharynx, oral cavity, teeth, nose, paranasal sinuses, Eustachian tube, and middle ear.⁸⁻¹⁵ Noticeably, pepsin is produced only by the stomach, so its presence in an organ documents its gastric provenience.^{16,17} As a result, pepsin may be considered a reliable biomarker of LPR.¹⁹

On the other hand, dry eye disease (DED) is a common medical condition as it may affect up to 35% of the general population worldwide.¹⁹ The Dry Eye Workshop, promoted by Tear Film and Ocular Surface Society, stated that "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."²⁰ Dry eye disease may include 2 main phenotypes: (i) hyper-evaporative phenotype (caused by an impaired lipid film for meibomian gland dysfunction) and (ii) aqueous-defective phenotype (due to a reduced tear volume), with a broad spectrum of overlapping presentations.²¹ Namely, DED is an umbrella term including a cluster of signs and symptoms which may depend on impaired ocular hydration, lubrication, and protection caused by defective tear quality and/or quantity. Different pathogenic mechanisms are involved in DED. Some risk factors may worsen the clinical feature, including ocular surgery, electronic device use, cosmetics, preservatives and systemic medications, contact lens wearing, and environmental factors (dry and cold air, pollution, smoke, and irritants). In particular, the use of computers and smartphone significantly affects the ocular surface.^{22,23} As a result, a functional vision impairment occurs, mainly in reading, seeing, and driving.²⁴ Recently, a pathogenic role has also been ascribed to ocular dysbiosis.²⁵

The main symptoms include redness, itching, burning, foreign body sensation, and photophobia. The DED diagnosis relies on a thorough history, examination, and ophthalmological assessment.²⁶ Careful attention should be given to age and gender, as these factors significantly affect ocular surface parameters and could be associated with the so-called "inflammaging" in older subjects, such as a chronic mild inflammatory state.²⁷ Moreover, DED is frequently associated with autoimmune diseases, mainly with Sjogren syndrome. Interestingly, many patients with Sjogren syndrome may also have gastric reflux associated with a drop in salivary volume.²⁸

An intriguing link between the LPR and the eye, mainly concerning the anterior segment, has also been argued in these last years.

METHODS

This paper presents and discusses the data reported in literature that support the potential pathogenic role of LPR in patients with dry eye. The research selected all articles that appeared on PubMed using laryngopharyngeal reflux and dry eye as keywords.

RESULTS

The evidence body consists of 3 primary sources: demonstration of pepsin in tears, epidemiological studies, and therapeutic trial.

Pepsin Assay in Tears

To document the presence of pepsin in tears constituted the first step for demonstrating a link between DED and LPR. A preliminary study

hypothesized the presence of pepsin in the tears of patients with gastric reflux.²⁹ Three studies were therefore performed to confirm this hypothesis. The first study enrolled 20 children with LPR, documented by 24-h pH monitoring, and 20 healthy children as control.³⁰ Four (20%) children with LPR showed a concentration level of pepsin ranging between 3.5 and 5.4 ng/mL, whereas all control children showed no pepsin in tears. The same authors conducted another study that enrolled 70 adult patients: 50 with documented LPR and 20 as control.³¹ Thirty-two (64%) patients with LPR had pepsin in tears; the mean concentration of pepsin was 86.6 ng/mL with a range between 20.5 and 247.6 ng/mL. Notably, no control subject presented pepsin in tears. The last study included 50 patients with LPR, documented by endoscopic findings and positive questionnaires, and 20 healthy subjects; 48% of LPR patients showed conjunctival damage, and 72% had impairment of lacrimal function.³² Tear pepsin was demonstrated in 64% of patients; the mean concentration was 55.4 ng/mL. However, no control subject showed pepsin in tears. Also, many LPR patients reported ocular symptoms, including itching in 38%, redness in 56%, and foreign body perception in 40%. Remarkably, the levels of tear pepsin were significantly and positively correlated with LPR severity and ocular scores.

Epidemiological Studies

Three studies have been conducted until today. The first study recruited 290 patients with ocular surface disease.³³ The ocular surface disease index (OSDI) and the reflux symptom index (RSI) questionnaires were administered. The findings showed that 34% of patients with ocular surface disease had LPR. Notably, there was a moderate ($r=0.58$) correlation between OSDI scores and RSI scores. Consistently, a total OSDI score cut-off > 42 was able to discriminate patients with LPR. Therefore, this study demonstrated that LPR was common in patients with ocular surface disease, and the OSDI severity predicted LPR. As a consequence, the authors coined the term "Eye reflux." A recent 5-year case series of patients with LPR reported an ocular involvement, such as tearing.³⁴ A further study included 245 patients with ocular disorders: 152 patients had DED and 93 other ophthalmological conditions.³⁵ Considered parameters were RSI, OSDI, symptom assessment in dry eye for frequency and severity, Schirmer test, tear break-up time (BUT), and Oxford grading. Eighty (32.6%) patients had a pathological RSI (score > 13): 68 (85%) with DED and 12 (15%) control patients. In particular, 68 (44.7%) DED patients had pathological RSI (score > 13), whereas only 12 (12.9%) control patients had pathological RSI. The probability of having a positive RSI was 8 times higher (odds ratio (OR)=8) in DED patients. Consistently, a positive RSI was associated with higher OSDI scores in DED patients. In other words, LPR in DED patients may be predictive (OR=8.75) of severe ocular symptoms. As a result, the authors concluded that LPR deserves adequate attention in the workup of DED patients.

Therapeutical Trials

To date, only 1 study has been published on the treatment of LPR in patients with DED. This preliminary study compared 2 treatments: the first included 2 products administered topically and systemically, and the second consisted of hyaluronic acid eye drops.³⁶ The first therapeutic option consisted of eye drops containing hyaluronic acid, magnesium alginate, *Camellia sinensis* extract, and oral tablets containing magnesium alginate and simethicone. This combined treatment aimed to treat at the same time DED and LPR, whereas the second option treated only DED. The treatments lasted for 3 months. The findings showed that patients treated with eye drops alone had only a significant reduction of OSDI. On the contrary,

patients treated with combined therapy reported a significant improvement in OSDI, RSI, Schirmer test, T-BUT, and the reflux finding score documented by fiberoptic laryngoscopy. Thus, even though this study was preliminary and requires adequate confirmation, it seems promising to manage patients with DED and LPR using a combined strategy.

Pathophysiological Considerations

An inflammatory response characterizes LPR; it originates from exposure to gastric contents that flow back from the stomach and may spread to the airways. It has to be noted that the pathophysiological link between LPR and DED is still unknown. Nevertheless, some hypotheses have been proposed. The first considers the retrograde backflow of the refluxate into the nasal cavity and the nasolacrimal duct that leads to chronic ocular inflammation over time.³⁷ Another theory considers the dysbiosis of the nasolacrimal duct caused by acid reflux.³⁸ Finally, a third supposition envisages a genetic predisposition to an excessive immune reaction.³⁹

The mucosal exposure to refluxate promotes, amplifies, and maintains a cascade of inflammatory events resulting in derangement of epithelial architecture and function.⁴⁰ Mucus changes characterize LPR and determine an impairment of protective and lubricant functioning.⁴¹ Alterations of mucin composition, secretory IgA, and antimicrobial proteins have been reported in patients with LPR.⁴⁰ Inflammasomes, such as interleukin (IL)-1, IL-6, and tumor necrosis factor- α , promote mucosal inflammation. As a result, dysfunction of epithelial intercellular junctions occurs.⁶ Refluxate disrupts the cohesion between epithelial cells by digesting the intercellular junctions. Namely, acid and pepsin concur to damage the mucosal surface.

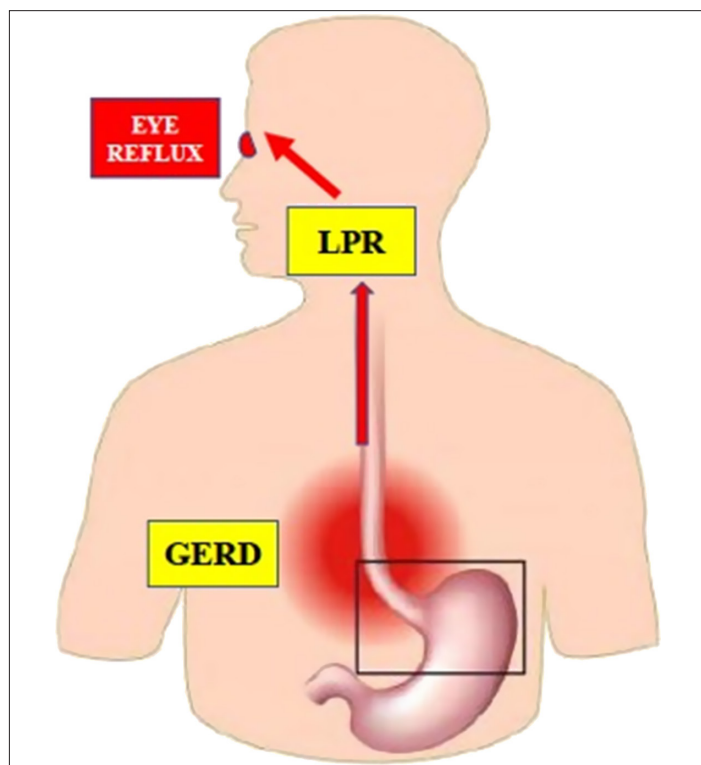


Figure 1. Schematic representation of refluxate overflow from the stomach to the esophagus (GERD) or to upper airways (LPR) or to the eye (eye reflux).

CONCLUSIONS

Although LPR is widespread, its diagnosis remains difficult because it lacks a well-defined criterion.⁴² The RSI questionnaire has been reported to be useful for suspecting LPR in clinical practice.⁴³ In addition, accurate workup and appropriate therapeutical management should be performed in patients with LPR.^{44,45}

At present, LPR plays an important pathogenetic role in inducing an inflammatory reaction in several organs, besides the larynx and pharynx, such as the nose, paranasal sinuses, and middle ear.⁴⁶ This evidence formed the logical premise to investigate a possible involvement of the eye as well. In fact, the presence of pepsin has been demonstrated at the ocular level.³⁰⁻³² Consistently, patients with ocular surface disease frequently have also LPR.^{33,36} Moreover, a preliminary trial demonstrated that LPR treatment could improve also DED complaints.³⁶ The LPR comorbidity may also aggravate the severity of DED.

Consequently, a new nosological entity could be identified: the eye reflux, as schematically reported in Figure 1.

However, it must be remembered that conclusive evidence of the existence of a link between LPR and DED necessitates mechanistic studies and randomized controlled trials. However, it may be convenient to assess in subjects with LPR also the possible presence of ocular involvement.

Implication for Practice

Laryngopharyngeal reflux and DED are 2 common diseases that not rarely can be associated together. In this regard, the refluxate could arrive up to the eye causing inflammation and consequently symptoms. Thus, careful attention to these disorders should be paid to in clinical practice by otolaryngologists visiting patients with LPR.

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