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REVIEW ARTICLE

The role of pepsin in the laryngopharyngeal reflux

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ABSTRACT: Laryngopharyngeal reflux (LPR) is a common defect among laryngological and phoniatric patients. Although LPR is categorized as a superficial gastroesophageal reflux disease (GERD), differential diagnosis should treat these two diseases separately. LPR symptoms can be assessed in the interview using as a tool the reflux symptom index (RSI). In addition, changes in the larynx that occur during LPR might be seen during laryngoscopy and classified according to the reflux finding score (RFS). One of the main mucosal irritants in LPR is pepsin which digests proteins and impairs the functions of the upper respiratory tract cells by affecting carbonate anhydrase (CAIII) and the Sep 70 protein. Pepsin initiates inflammatory changes within the larynx, nasopharynx and nasal cavity. The use of pepsin detection in upper and lower throat secretions is a new direction in LPR diagnostics.

KEYWORDS: pepsin, laryngopharyngeal reflux, reflux disease, hoarseness

Laryngopharyngeal reflux (LPR) is a supraesophageal form of gastroesophageal reflux disease (GERD). According to the statistics, LPR is diagnosed in about 10% of patients with laryngological problems and about 50% of patients with chronic hoarseness [1,2].

Literature also refers to the disorder in question as:

- Reflux laryngitis
- Laryngeal reflux
- Pharyngoesophageal reflux
- Supraesophageal reflux
- Extraesophageal reflux
- Atypical reflux

The definition of GERD as well as its classification into esophageal and extraesophageal syndromes has been established during the international conference in Montreal in 2005. Extraesophageal syndromes occurring in LPR include disorders with proven or likely association with reflux. The association between such syndromes as: reflux cough, reflux laryngitis, reflux asthma, or dental erosion has been demonstrated, while the syndromes that probably correlate with GERD include: pharyngitis, sinusitis, idiopathic lung fibrosis, and recurrent otitis media (Fig. 1) [3].

It is thought that the main mechanism in the pathophysiology of LPR involves direct irritation of mucus membranes of the upper airways by gastric juice consisting of hydrochloric acid, pepsin and, in some cases, bile acids and bile salts together with bacteria inhabiting the gastrointestinal tract. Depending on the pH of the gastric juice we may distinguish:

- Acid reflux (pH<4) – gastric contents consisting mainly of hydrochloric acid,
- Slightly acidic reflux (pH 4-7) – mixed gastric contents,
- Slightly alkaline reflux (pH<7) – gastric contents consisting mainly of pepsin and bile acids from the duodenum.

Vagal reflex is another mechanism involved in the development of LPR symptoms. Irritation of the epiglottis or distal esophagus may stimulate the vagal nerve and induce bronchospasm, cough, or stimulate throat clearing [2-6].

SYMPTOMS OF LPR

Symptoms of LPR vary. In order to systemize the symptoms reported by the patients, Belafsky et al. introduced the reflux symptom index (RSI), which facilitates gathering medical history from patients with reflux disease (Table 1)[2]. The questionnaire may be used after excluding vocal fold paresis and acute upper respiratory tract infection, which may falsify the result of RSI and lead to misdiagnosis. Each symptom mentioned in the RSI questionnaire is assessed on the scale from 0 (no symp-

toms) to 5 (severe symptoms). The maximum number of points possible to achieve using the RSI scale is 45. The score of 12 or more in the questionnaire indicates the diagnosis of LPR [3].

Belafsky et al. elaborated a scale for assessment of the severity of laryngeal changes in the course of LPR (*reflux finding score* – RFS). Similar to RSI, the assessment is made based on laryngoscopy (Table 2). The total RFS score of 7 or more gives a 95% certainty of LPR diagnosis [4].

The diagnosis of LPR may be established based on patient history and physical examination and therefore, both of the above-mentioned scales should be utilized during the visit in the laryngology office [5].

The differential diagnosis may involve indicating differences between LPR and GERD. Table 3 presents the main disparities between those disorders.

THE ROLE OF PEPSIN IN LPR

Pepsin is an active form of pepsinogen, a peptidase enzyme excreted by the glandular cells (chief cells) of the stomach. Pepsin digests proteins through hydrolysis of the peptide bonds. As it leaks out of the stomach together with other gastric contents, pepsin damages the mucosal membranes of the structures it comes in contact with. By digesting the intercellular connections (*gap-junctions*), pepsin impairs the epithelial barrier [5-7]. In the recent years, numerous studies have examined the defense mechanisms of the upper respiratory tract, demonstrating that carbonic anhydrase isoenzyme III (CAIII) may be of importance. This enzyme catalyzes the reversible hydration of carbon dioxide yielding, i.a. bicarbonate ions [8]. This process facilitates alkalization of the local environment, leading to CAIII-mediated deactivation of pepsin and protecting the upper airway mucosa [9, 10]. Another protective barrier of the upper airway epithelium involves the Sep70 protein (*squamous epithelium stress protein*), which regulates passage of other proteins through cells. Pepsin decreases levels of both CAIII and Sep 70, leading to impairment of the upper airway mucosal cell function [11].

Pepsin reaches peak activity in a low-pH environment (2-3,2). Successive episodes of reflux, especially acid reflux, activate pepsin located in the structures of the larynx and nasopharynx [12-15]. Some pepsin activity has also been observed at pH 6-7,2. Thus, mixed or slightly alkaline reflux may also activate pepsin. Moreover, pH of 6,4-7,2 is physiological for oral cavity and upper respiratory tract. Following penetration of pepsin into those structures, destruction of the upper airway mucosa may take place not only during the episodes of slightly alkaline reflux, but may persist due to the possibility of pepsin activation at that pH [12].

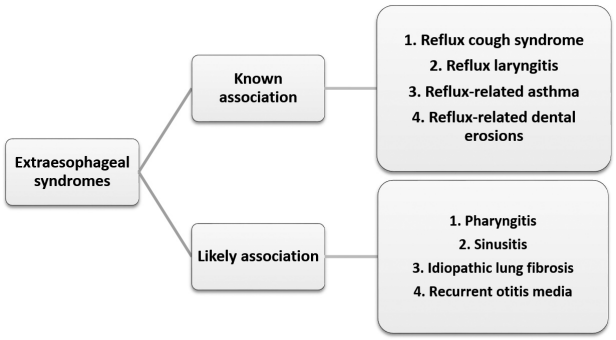

Fig. 1. Classification of extraesophageal syndromes occurring in GERD. Acc. to: Valkil N. et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol, 2006. 101(8): p. 1900-20 [1].

Tab. I. Reflux symptom index (RSI). wg: Belafsky P.C. et al Validity and reliability of the reflux symptom index (RSI). J Voice, 2002. 16(2): p. 274-7 [HYPERLINK \l „2].

WHICH ONE OF THOSE SYMPTOMS HAVE YOU EXPERIENCED DURING THE LAST MONTH? INDICATE THE APPROPRIATE NUMBER		0 - NO SYMPTOMS 5- SEVERE SYMPTOMS					
1.	Hoarseness or other voice problems	0	1	2	3	4	5
2.	Throat clearing	0	1	2	3	4	5
3.	Sensation of excess mucus or mucus flowing into nasopharynx	0	1	2	3	4	5
4.	Difficulty swallowing food, fluids or tablets	0	1	2	3	4	5
5.	Cough after eating or in supine position	0	1	2	3	4	5
6.	Difficulty breathing or dyspnea	0	1	2	3	4	5
7.	Cough (aggravating, irritating)	0	1	2	3	4	5
8.	Sensation of an obstacle in the throat, "tight throat" sensation	0	1	2	3	4	5
9.	Heartburn, chest pain, dyspepsia, acidic taste in the throat	0	1	2	3	4	5

Other than digestion of intercellular junctions, through endocytosis, pepsin is capable of:

- increasing oxidative stress and accumulation of reactive oxygen species (ROS),
- influencing the expression of genes involved in oxidative stress,
- interacting with receptors and inflammatory cytokines,
- influencing the expression of genes involved in inflammatory reactions,

- interacting with mitochondria and damaging mitochondrial DNA [9, 11].

Chronic exposure of laryngeal mucosa and adjacent tissues to pepsin results in inflammation (laryngitis). Laryngological examination will show:

- erythema of laryngeal mucosa, especially:
- aryepiglottic folds,
- epiglottis,
- retention of thick mucus in the larynx,
- tissue hypertrophy around the posterior commissure,
- granulomatous lesions in the posterior larynx,
- subepiglottal edema (*pseudosulcus*),
- vocal fold edema,
- closing of the laryngeal ventricle.

LPR resulting in the transfer of pepsin to the throat predisposes to chronic inflammation and may lead to development of a neoplastic process [16-18]. Gong et al. examined the concentration of pepsin in tissues collected from vocal folds with leukoplakia. Twenty-six patients were examined in the study group, while the control group consisted of healthy laryngeal preparations collected from the deceased 6 hours after death. The study showed elevated pepsin levels in tissues with leukoplakia, corroborating the effects of LPR on the development of precancerous lesions [19].

Johnston et al. conducted a study on the effect of pepsin on neoplastic progression in the larynx and surrounding structures. Epithelial cell lines from laryngeal mucosa and the lower throat were treated with pepsin and molecular changes were subsequently assessed. Results demonstrated significant effect of pepsin on 27 genes involved in carcinogenesis. Histopathological material collected from patients with laryngeal cancer and subjects without neoplastic disease was assessed for the presence of pepsin. Analysis of laryngeal sections revealed the presence of pepsin in 60% of patients with laryngeal cancer, while no pepsin was observed in specimens collected from healthy patients [20].

Sereg-Bahar et al. assessed lower throat secretions for the presence of pepsin in the group of patients with laryngeal cancer compared to healthy subjects. The investigators used ELISA to determine mean pepsin concentrations in the collected material. Study showed four-fold increase in the concentration of pepsin in throat secretions among cancer patients vs. controls [21].

Chronic irritation of the nasopharynx and surrounding structures by pepsin may result in tissue inflammation, pharyngeal tonsil hypertrophy or otitis media. Physical examination may reveal:

- erythema of mucous membranes,
- presence of thick mucus in the nasopharynx,

Tab. II. Reflux finding score (RFS). Acc. to: Belafsky P.C. et. al The validity and reliability of the reflux finding score (RFS). Laryngoscope, 2001. 111(8): p. 1313-7. [4].

STWIERDZANE ZMIANY W KRTANI (REFLUX FINDING SCORE; RFS)	
TYPE OF LESION	REFLUX FINDING SCORE (RFS)
Laryngeal atrium atrophy	0 – no changes 2 – changes present
Erythema/congestion	0 – no changes 2 - partial 4 - total
Vocal fold edema	0 – no changes 2 – aryepiglottic folds 4 - diffuse
Diffuse laryngeal edema	0 – no changes 1 – mild 2 – moderate 3 – severe 4 – polypous lesions
Posterior commissure hypertrophy	0 – no changes 1 – mild 2 – moderate 3 – severe 4 – constrictive
Laryngeal granuloma	0 – no changes 1 – mild 2 – moderate 3 – severe 4 – constrictive
Thickening of mucosal membrane of the larynx	0 – no changes 2 – changes present
Total score:	0 – no changes 2 – changes present
Suma:	..... / 26

Tab. III. The differential diagnosis of GERD and LPR.

SYMPTOM	GERD	LPR
DAYTIME SYMPTOMS	NO	YES
NOCTURNAL SYMPTOMS	YES	NO
HEARTBURN	YES	NO
ERUCTATION	YES	NO
HOARSENESS	NO	YES
SENSATION OF AN OBSTACLE IN THE THROAT	NO	YES
ASTHMA	NO	YES
COUGH	NO	YES
COUGH IN SUPINE POSITION	YES	NO
ESOPHAGITIS	YES	NO
ESOPHAGEAL MOTILITY DISORDER	YES	NO
OBESITY	YES	NO

- nasopharyngitis,
- pharyngeal tonsil hypertrophy,
- Eustachian tube edema,
- otitis media.

Luo et al. examined the presence of pepsinogen in hypertrophied pharyngeal tonsil in healthy subjects and patients with otitis media. Expression of pepsinogen in the epithelium covering pharyngeal tonsil was assessed by immunohistochemistry. There were greater concentrations of pepsinogen found in the group of patients with otitis media compared to the control group (Fig. 2 and 3.) Moreover, presence of pepsin was confirmed in the middle ear fluid in the study group [22].

Lieu et al. conducted a similar study, assessing the presence of pepsin in the fluid collected from the middle ear during paracentesis among pediatric patients with chronic or recurrent otitis media. Presence of pepsin in the collected material was confirmed in about 70% of patients regardless of the type of condition [23].

Tasker et al. also evaluated the presence of pepsin in the fluid collected from the middle ear during paracentesis among patients with exudative otitis media. From the group of 65 patients, pepsin was identified in the material collected from 59 (91%) subjects [24].

Chronic irritation of nasal mucus membranes may lead to development of an inflammatory process and tissue edema. Examination may reveal:

- erythema of mucus membranes,
- rentention of thick secretions,
- chronic sinusitis,
- inflammation of the nasolacrimal duct,
- dacryostenosis,
- Hasner valve insufficiency.

Iannella et al. demonstrated greater concentrations of pepsin in the tears of patients with laryngopharyngeal reflux in comparison to the group of subjects without the disorder (B). Results are shown in Figure 4 [25].

DIAGNOSIS OF LPR

The diagnosis of LPR is based on symptoms reported by the patient (RSI- Reflux Symptom Index) and laryngological examination (RFI- Reflux Finding Index). It may be confirmed through:

- pH-metry (a two-channel pH-meter used to measure pH in the esophagus and the throat is characterized by high sensitivity in LPR).

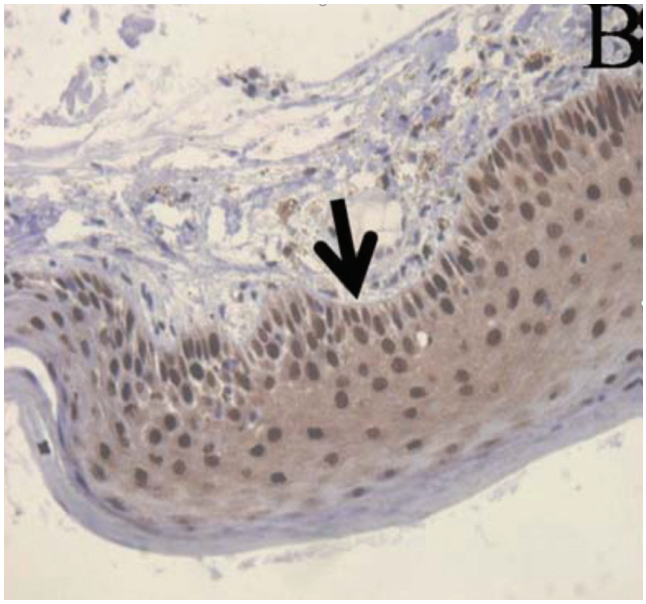

Fig. 2. Presence of pepsynogen in pharyngeal tonsil of a patient with otitis media. Intense staining of nuclei corresponds to increased protein concentrations in tissues. Z: Luo H.N. i wsp. Role of pepsin and pepsinogen: linking laryngopharyngeal reflux with otitis media with effusion in children. Laryngoscope, 2014. 124(7): p. E294-300.

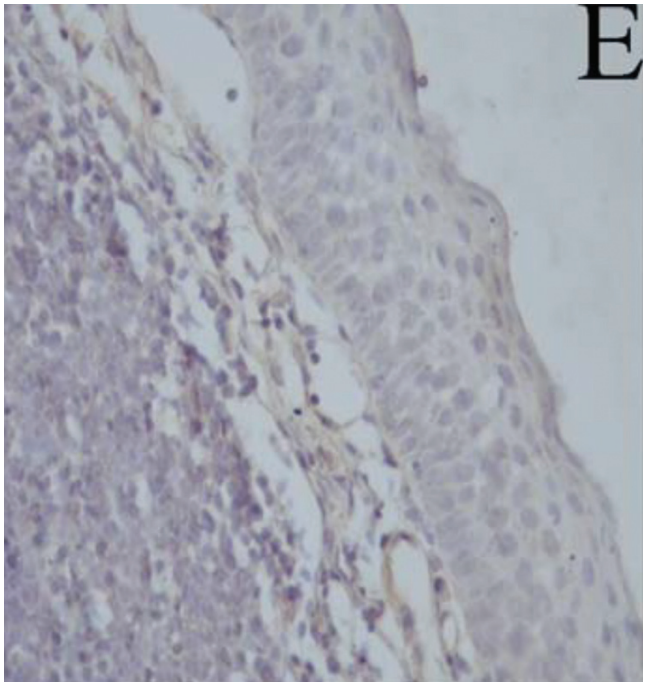

Fig. 3. Presence of pepsinogen in pharyngeal tonsil of a patient without otitis media. Less intense staining of nuclei corresponds lower protein concentrations in tissues. Z: Luo H.N. i wsp. Role of pepsin and pepsinogen: linking laryngopharyngeal reflux with otitis media with effusion in children. Laryngoscope, 2014. 124(7): p. E294-300.

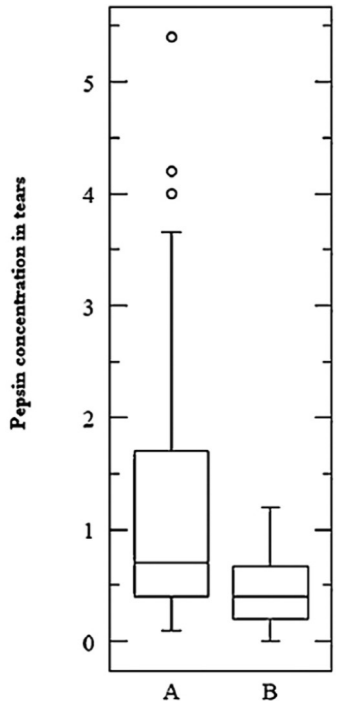

Fig. 4. Pepsin concentrations in the tears collected from: A- patients with LPR, B- patients without LPR. Z: Iannella G. i wsp. Investigation of pepsin in tears of children with laryngopharyngeal reflux disease. Int J Pediatr Otorhinolaryngol, 2015. 79(12): p. 2312-5.

- esophageal impedance, which measures the change in tissue impedance during reflux episodes detects both acidic and neutral reflux.
- testy for the presence of pepsin in the throat [26]:
- Immunohistochemistry (due to the decisive role of pepsin in the pathophysiology of LPR, methods have been developed to determine its presence in tissues exposed to its action. Literature describes methods to collect and assess tissue samples from nasopharynx and larynx in an immunohistochemical reaction [27]).
- Identification of pepsin in throat secretions [28]; two methods have been developed to date:

PEP-TEST requires transferring centrifuged secretions from the nasopharynx and the lower throat onto a pep-test. If pepsin is present in the secretions, it binds to the reagents and two lines appear on the strip (Fig. 5) [29].

Sensitive pepsin ELISA, i.e. immunoenzymatic test, that detects pepsin in examined secretions using antibodies conjugated with an appropriate enzyme.

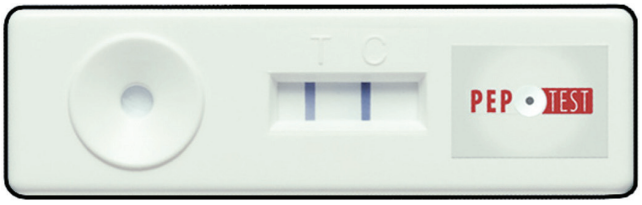

Fig. 5. PEP-TEST strip is used to assess for the presence of pepsin in nasopharyngeal and lower throat secretions. From: http://notash-tashkhis.com/index.php/component/tags/tag/3-peptest.

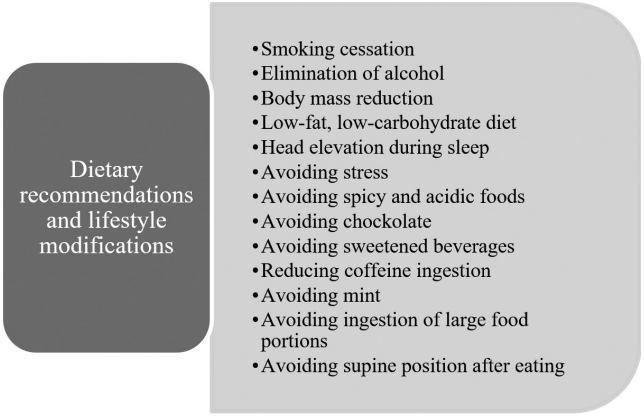

Fig. 6. Lifestyle modification as treatment of LPR. Acc. to: Pearson J.P. i wsp. Review article: reflux and its consequences--the laryngeal, pulmonary and oesophageal manifestations. Conference held in conjunction with the 9th International Symposium on Human Pepsin, Kingston-upon-Hull, UK, 21-23 April 2010. Aliment Pharmacol Ther, 2011. p. 1-71.

TREATMENT:

Lifestyle modification is the basis of treatment of LPR as well as GERD. It encompasses [30]:

Among the available pharmacotherapeutics, several groups of medications may be effective in treatment of LPR [30]:

- protein pump inhibitors, especially Dexilant, which contains dexlansoprasole with dual release,
- preparations inhibiting relaxation of lower esophageal sphincter: *Baclofen,*
- prokinetic drugs: *Metoklopramid,*
- alginic acid: *Gealcid, Gaviscon,*
- surgical treatment.

Literature reports that that measuring pepsin concentrations in saliva may be used to monitor effectiveness of surgical treatment of LPR [31].

SUMMARY:

LPR is a common problem, especially among patients with hoarseness. RFI and RSI scales should be used during history taking and laryngological examination. Proper diagnosis and disease severity are crucial for implementing appropriate treatment [2, 4].

It is thought that pepsin, a protein-digesting enzyme, is of significant importance for the pathophysiology of LPR. To date, we have been unable to elucidate all the mechanisms of action of pepsin. Based on literature data it may be concluded that pepsin impairs function of the upper airway mucosa and influences function of CDAIII and Sep70 proteins [9-11]. Moreover, there are studies on the use of pepsin inhibitors in the treatment of LPR. Further investigation of those issues will aid in expanding knowledge regarding pepsin function in LPR, but also contribute to expansion of the significance and utility of pepsin inhibitors [30].

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