

LITERATURE REVIEW

The impact of gastroesophageal reflux in the ENT pathology

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ABSTRACT

Frequently encountered in medical practice, the gastroesophageal reflux (GER) is a chronic condition characterized by the passage of gastric acid or gastric contents into the esophagus. In otorhinolaryngology, the diagnosis of pharyngo-laryngeal or rhinosinusal inflammatory conditions secondary to GER is one of exclusion and it is based on a detailed anamnesis in which we are interested in symptoms, behavioural and medical risk factors, on the ENT clinical examination, the laryngo-fibrosopic assessment, the phoniatic examination, the barite pharyngo-esogastric exam, the upper gastrointestinal endoscopy and the esophageal manometry.

The authors are making a systematization of the contribution of the gastroesophageal reflux has in the ENT pathology, emphasising the symptoms and the most frequent associated pathological entities.

KEYWORDS: gastroesophageal reflux, extraesophageal reflux, chronic laryngitis, rhinosinusitis, post nasal drip

INTRODUCTION

Frequently encountered in medical practice, the gastroesophageal reflux is a chronic condition characterized by the passage of gastric acid or gastric contents into the esophagus, without being accompanied by nausea or vomiting. In the literature, the term “laryngo-pharyngeal reflux” is also used, and the American Broncho-Esophagological Association introduced the term “extraesophageal reflux” for the extraesophageal manifestations of regurgitation of gastric contents¹.

THE INCIDENCE OF THE GASTROESOPHAGEAL REFLUX DISEASE

The gastroesophageal reflux is a pathology seen in all age groups, its incidence in adults constantly increasing, while in children it is recorded in 75%^{2,3}. A predilection of the gastroesophageal reflux disease according to gender has not been described, but an in-

crease in incidence in adults over 40 years can be noticed⁴.

Between 6 and 10% of patients presenting in an ENT service are diagnosed with gastroesophageal reflux. In 1995, Rival et al. found that 73% of patients with various complaints in the cervical region (n=216) suffered from the gastroesophageal reflux disease (GERD), symptomatology having improved in 84% of them by administration of antireflux treatment⁵. Five years later, Kouffman et al. showed that of the 113 patients with laryngeal pathology and dysphonia included in the study, 50% had extraesophageal reflux, the documentation being made by the esophageal pH test⁶.

CLINICAL FEATURES OF THE GASTROESOPHAGEAL REFLUX

The gastroesophageal reflux (GER) and the extraesophageal reflux (EER) are two different entities, differentiating, first of all, by symptoms they cause.

In the case of GERD, the main complaints of patients are heartburn, retrosternal pain and regurgitation. The extraesophageal reflux disease has less specific symptoms, being represented primarily by hemming, pharyngeal foreign body sensation, cough, hoarseness or pharyngeal dryness (retrosternal heartburn rarely appears). The signs of EER may or may not be accompanied by the typical symptoms of a reflux disease. It should be mentioned that the same amount of material discharged, which can be easily neutralized by the esophageal defence mechanisms, can cause hypo-pharyngo-laryngeal lesions⁷, which is why in EER esophageal lesions may be missing. The two diseases evolve differently in the long run too, GERD having a high risk of complicating with an esophageal adenocarcinoma, while EER presents a high risk of developing laryngeal or lung carcinoma, sinusitis and otitis^{8,9}.

In otorhinolaryngology, the diagnosis of pharyngo-laryngeal or rhinosinusal inflammatory conditions secondary to EER is one of exclusion and it is based on a detailed anamnesis in which we are interested in symptoms, behavioural and medical risk factors, on the ENT clinical examination, the laryngo-fibrosopic assessment (Figure 1), the phoniatic examination, the barite pharyngo-esogastric exam, the upper gastrointestinal endoscopy and the esophageal manometry. The examination for diagnostic certainty, both for GER and EER, is represented by monitoring of the esophageal pH test.

EER is characterized by extraesophageal manifestations of the gastric reflux. There are numerous diseases in the otorhinolaryngology which can be determined by this disorder, the most common being chronic reflux laryngitis¹⁰. Moreover, at the level of the larynx, vocal nodules, granulomas and contact ulcer, vocal cord polyp, sulcus glottidis, pharyngo-laryngeal cancer, laryngospasm, subglottic stenosis may also ap-

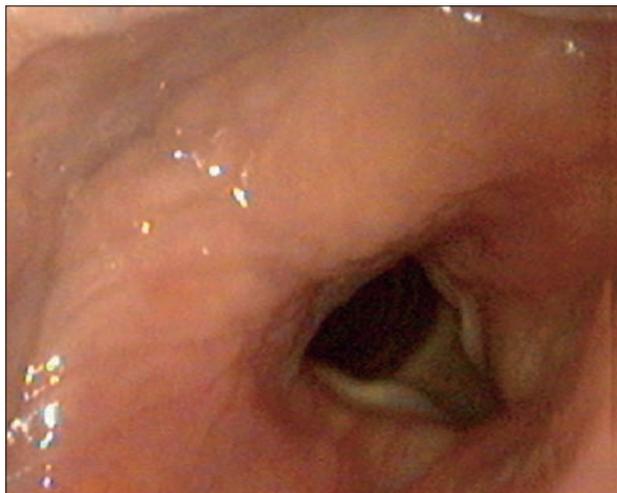


Figure 1 Fibro-laryngoscopy appearance of the larynx in a patient with GER

pear. Chronic rhinosinusitis, chronic hypertrophic rhinitis, postnasal drip, serous otitis media, sleep apnea, chronic cough or oropharyngeal mycosis can also be due to EER¹⁰⁻¹² (Table 1). Chronic recurrent pharyngitis occurs as a consequence of the gastric reflux in approximately 60% of the cases¹⁰.

Symptoms of the extraesophageal reflux can be divided into two categories: laryngeal and extralaryngeal. The most common symptoms associated with the laryngo-pharyngeal reflux are those signalling the involvement of the larynx and are represented by chronic cough, dysphonia (episodic or chronic), odynophagia, vocal fatigue, laryngospasm¹³. Regarding the extralaryngeal manifestations, feeling of "lump in the throat" (globus), dysphagia, chronic hemming, sore throat, mucus hypersecretion, postnasal drip, halitosis, nocturnal cough, pharynx burning sensation, otalgia may be representative¹⁰⁻¹².

Paraclinical explorations are especially used when we have an uncertain diagnosis, when symptoms are atypical, recurrent or associated with complications, if there is no adequate response to treatment or before the antireflux surgery. Carr et al.¹⁴ studied the changes specific to EER in a group of 77 patients, using direct laryngoscopy and bronchoscopy, and found that there were pharyngolaryngeal alterations consisting in lin-

Table 1
ENT manifestations of EER

Pharynx and larynx	Chronic Recurrent Pharyngitis
	Sore throat
	Chronic laryngitis
	Vocal cord granulomas, nodules, ulcer
	Laryngospasm
	Subglottic stenosis
	Cancer
	Sulcus glottides
	Dysphonia
Nasal and sinusal	Globus
	Chronic rhinosinusitis
	Chronic hypertrophic rhinitis
	Postnasal drip
Oral cavity	Halitosis
	Apthous ulcers
	Dental erosions
Middle ear	Serous otitis media
Tracheobronchopulmonary tree	Chronic cough
	Tracheobronchitis
Others	Sleep apnea syndrome

gual tonsil hypertrophy ($p<.001$), postglottic edema ($p<.001$), arytenoid edema ($p<.001$), vocal cord edema ($p=.003$) and cricotracheal changes ($p=0.003$) – carina inflammation ($p<0.001$). They have established severe arytenoid edema, postglottic edema and lingual tonsil hypertrophy as pathognomonic clinical signs of EER, 65% of the patients included in the study and diagnosed with GERD having at least one of these signs.

THE GASTROESOPHAGEAL REFLUX AND THE LARYNGEAL PATHOLOGY

1. Chronic laryngitis

Specific symptomatology of chronic laryngitis (Figure 2) is dysphonia compounded by vocal effort, persistent or relapsing hypopharyngeal burning sensation, without objectification of an infection, hemming or cough, in the absence of lower respiratory tract pathology. A study from 2000, conducted by Hanson and Jiang¹⁵, reveals that the posterior glottis is susceptible to EER, because of the cilia of the respiratory mucosa beating in its direction, resulting in prolonged contact with the acidic material. The authors included a total of 182 patients with EER and chronic laryngitis, for whom they have used various therapeutic methods in order to cure the pathology. Therefore, 51% of the patients included in the study were cured by nocturnal management of EER, 26% also associated H₂-receptor antagonists, 20% proton-pump inhibitors (PPIs) and diet, respectively the sleep position, and 3% combined all three therapeutic solutions (nocturnal management, H₂-receptor antagonists and PPIs). A year earlier, Habermann evaluated efficacy of the treatment with pantoprazole in 29 patients with chronic laryngitis and symptoms of gastroesophageal reflux¹⁶. At the end of six weeks of treatment, subjective and video-laryngo-stroboscopic improvement of symptoms were achieved ($p<0.05$).



Figure 2 Fibro-laryngoscopic examination - chronic laryngitis due to GERD

2. Contact ulcers and granulomas

Contact ulcers and granulomas (Figure 3) have as alleged etiology the gastroesophageal reflux, vocal misuse, intubation trauma, smoking, chronic infections and allergies. Havas¹⁷ conducted a retrospective study on the management of the vocal process granuloma; he established that in 76% of the 55 patients included in the study, the gastroesophageal reflux disease is the main etiological factor of this laryngeal pathology. He concluded that the therapy in case of granulomas requires antireflux and phoniatric treatment as well, surgical treatment being indicated only in selected cases. The authors obtained a degree of postoperative relapse of 50%, this percentage shrinking significantly in case of postoperative association of antireflux treatment. Two years later, in 2001, Hoffman reinforces by his results the observations and the treatment protocol previously suggested by Havas¹⁸.

3. Laryngeal cancer

Alcohol and cigarette smoke are the most frequent risk factors in laryngeal cancer (Figure 4). Regarding EER, it is well known that it can promote and maintain a chronic inflammatory process of the larynx, but its carcinogenic effect has not been proven. An important role in pharyngeal and esophageal carcinogenesis is also played by the biliary reflux, which increases the expression of cyclooxygenase 2¹⁹.

In 2002, Galli et al.²⁰ reports an incidence of 80.9% of EER in patients with hypopharyngolaryngeal squamous cell carcinoma, while Koufman and Burke⁶ detected, in a study conducted in 2000 on a group of 113 patients, EER in 88% of the patients with incipient glottic cancer. In both studies, the esophageal pH test was used for assessing patients.

Lewin and collaborators undertook a pilot study in 2003, which aimed to determine the incidence of the laryngopharyngeal reflux (LPR) in patients with laryn-

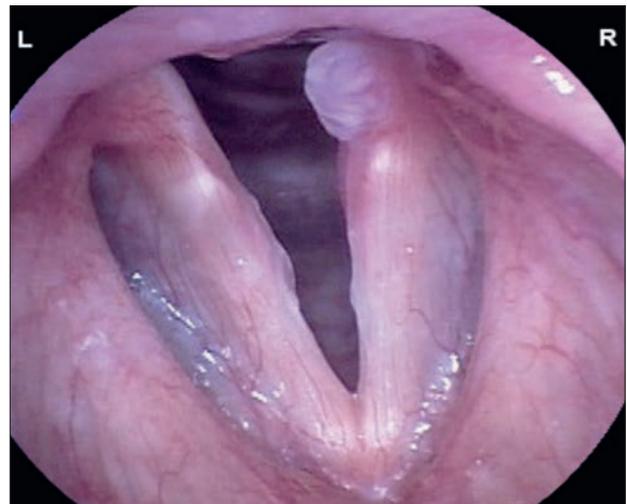


Figure 3 Left vocal process granuloma



Figure 4 Squamous cell carcinoma - left vocal cord

geal carcinoma or dysplasia, and also to highlight the existence of an association between the degree of the reflux and the histological type, smoking or body position. 85% of the patients with malignant and pre-malignant lesions have positive results in the esophageal

pH test, without being described a statistically significant association between the existence of LPR and the histological type²¹.

Our experience

Over a 4-year period, in the ENT Clinic of the "Sfanta Maria" Hospital, a prospective study was conducted on 164 patients with various laryngeal diseases, which aimed to reveal an association between the laryngeal pathology and the gastroesophageal reflux disease or the extraesophageal reflux. The patients included in the study had: chronic laryngitis, vocal cord polyps (Figure 5), myxomas (Figure 6), vocal cord nodules (Figure 7), granulomas (Figure 8), papillomas, carcinomas (Table 2).

All patients were assessed by barium radiological examination of the upper gastro-intestinal (GI) tract and upper gastrointestinal endoscopy. Following these investigations, out of the 164 patients included in the study, 83 were diagnosed with GER or EER, 58 of them being symptomatic and 25 asymptomatic.

Table 2
Laryngeal pathology associated to GER and EER

Lesion type	No. of patients	Barium radiological examination of the upper GI tract (+)	Gastrointestinal endoscopy (+)	Symptomatic	Asymptomatic
Chronic laryngitis	57	27	14	25	2
Granulomas	16	9	3	4	5
Polyps	19	18	6	8	10
Vocal nodules	16	10	6	4	6
Myxomas	14	2	12	1	1
Papillomas	10	1	7	1	0
Carcinomas	32	16	4	15	1



Figure 5 Polyp of the left vocal cord



Figure 6 Laryngeal myxoma



Figure 7 Left vocal cord nodule

From a clinical point of view, the presence of a local inflammatory appearance of the laryngeal mucosa superimposed on the vocal cord injury was found. For the evaluation of the 83 patients, the laryngopharyngeal reflux index was used, its average being significantly higher in patients with laryngeal pathology and reflux, than in patients with the same disorder but without reflux (9.50 vs. 2.92). These values were significantly improved after the administration of antireflux treatment (7.35 vs. 9.50). The most important elements of the index were edema and interarytenoid and endolaryngeal hyperemia, as well as interarytenoid pachydermia.

Laryngeal pathology is characterized by voice alteration; that is why, the Voice Handicap Index (VHI) was measured before and after treatment of the background disorder and of the gastroesophageal reflux (Table 3). A significant decrease in the VHI after treatment was noticed, especially in patients with gastroe-



Figure 8 Left vocal cord granuloma

sophageal reflux. To the surgical and drug treatment, voice therapy was added, carried out 3 times a week.

THE GASTROESOPHAGEAL REFLUX AND THE SLEEP APNEA SYNDROME

In the literature, there are obvious correlations between the gastroesophageal reflux and the obstructive sleep apnea syndrome (OSAS)²²⁻²⁵.

In a study conducted in 1997, Locke et al.²⁶ discovered an incidence of the gastroesophageal reflux of 59% among people with sleep apnea. Moreover, Kerr reported the existence of a significant gastroesophageal reflux in 5 out of 6 patients with OSAS²³.

In 2002, Valipour found the existence of a symptomatic gastroesophageal reflux in 160 out of 228 patients with obstructive sleep disorders included in the study (73%; 135 diagnosed with OSAS and 93 with

Table 3
Evolution of VHI in the group of patients included in the study

Lesion	VHI before T		VHI after T	
	GER+	GER-	GER+	GER-
Vocal nodules	42.1	39.8	29.1	27.2
Polyps	54.3	49.2	25.2	23.1
Chronic laryngitis - Reinke's edema	47.5	41.1	26.3	22.2
Myxoma	57.2	53.3	37.9	34.3
Granuloma	45.7	–	36.2	–
Chronic laryngitis - Sulcus	37.2	36.1	31.2	29.1
Papilloma	65.5	65.3	48.3	47.9

chronic snoring), with no statistically significant difference between the two groups²⁷.

THE GASTROESOPHAGEAL REFLUX AND THE RHINOSINUSAL PATHOLOGY

The involvement of the gastroesophageal reflux in the rhinosinusal pathology is still a controversial topic.

Various studies conducted over time have tried to prove that the gastroesophageal reflux is a predisposing factor in the development of rhinosinusitis both in adults and children²⁸⁻³². The action mechanism is still incompletely known and there are two hypotheses: either by direct damage of the rhinosinusal mucosa, or by determination of vagally mediated neuroinflammatory modifications. Jacker et al.²⁸, in a study regarding the relation between GERD, EER and chronic recurrent rhinosinusitis, emphasized that patients with recurrent CRS experienced a significantly increased number of events of acid reflux into the esophagus, and the period of time with pH<4 and RAI (reflux area index) were 10 times higher than in the control group. At the same time, modifications in the hypopharynx were not detected in the two groups of patients included in the study.

Dental impairment in EER is suggested by several studies. Dental erosion with enamel loss is determined by peptic aggression (5-53.41% in patients with EER). It is known that complicated dental caries can favour odontogenic rhinosinusitis³³.

Phipps et al.³⁴ studied the contribution of the gastroesophageal reflux in chronic rhinosinusitis, using a group of 30 paediatric patients, aged between 2 and 18 years. All patients were monitored by esophageal pH test for 24 hours, 19/30 (63%) being diagnosed with gastroesophageal reflux. In 6 out of the 19 patients (32%), the existence of a nasopharyngeal reflux was revealed. The response to the antireflux treatment was positive, 15/19 patients (79%) showing improvement in the rhinosinusal symptomatology.



Figure 9 Right maxillary rhinosinusitis

Besides rhinosinusitis (Figure 9), GERD seems to be also involved in the occurrence of the postnasal drip syndrome (Figure 10)^{35,36}.

THE GASTROESOPHAGEAL REFLUX IN THE PEDIATRIC PATHOLOGY

First described as a pathological entity in pediatrics in 1950, with a predominance of 3:1 for males, the gastroesophageal reflux has a high incidence, until the age of 3-4 months, 60-70% of children being symptomatic³⁷. The most common causes of occurrence of the gastroesophageal reflux in children are represented by: esophageal atresias, diaphragmatic hernias, prematurity (70% of newborns under 1700 g), neurological diseases, gastrointestinal dyskinesias of different causes, feeding probes (for a long time).

The respiratory pathology is the most frequently associated with GERD in children, the trigger mechanism being inflammation and bronchospasm³⁸. ENT diseases associated to EER in children are chronic laryngitis, laryngomalacia, subglottic stenosis, stridor, vocal cord granulomas, dysphagia, and also rhinitis, chronic rhinosinusitis, otalgia/ otitis media³⁷⁻³⁹.

Bouchard⁴⁰ recommends the pH test in children with stridor, laryngomalacia and laryngitis, when the usual means of diagnosis do not clarify the diagnosis. At the same time, he also claims that the pH test does not bring the same diagnosing benefits in children with papillomatosis or dysphonia. The incidence of laryngomalacia complications is directly correlated with the degree of GER/ EER.

Regarding the involvement of the gastroesophageal reflux in the adenoid hypertrophy, it still remains nowadays a controversial topic. Some authors, such as Phipps et al.³⁴, argue that the action mechanism of the gastroesophageal reflux in rhino-adenoiditis is maintaining local inflammation, by delaying infection healing. In the study carried out in 2000, they identified a



Figure 10 Post nasal drip

significantly higher incidence of the reflux among children under the age of two with symptomatic adenoid hypertrophy³⁴. On the other hand, there are authors hypothesizing that adenoids would influence the occurrence of reflux by modifying intrathoracic inspiratory and expiratory pressure, thus favouring the retrograde movement of gastric acid in the esophagus⁴¹.

Another pathology in which the gastroesophageal reflux is identified as a potential risk factor is the otic one. The favouring element of these disorders in children is the particular position of the Eustachian tube. This is almost horizontal and less angulated, thus allowing the penetration of secretions from the pharynx, especially in the supine position. Penetration of the acid reflux and epithelial damage in the Eustachian tube may cause otalgia in the absence of other auricular symptoms. In the case of otitis media with effusion that require tympanotomy, the presence of pepsin has been demonstrated in fluid extracted post-tympanotomy, in concentrations 1,000 times higher than normal⁴².

CONCLUSIONS

The gastroesophageal reflux is an important factor in the otorhinolaryngological pathology, being a major etiologic factor in the inflammatory and tumor pathology in the nose, throat and ears region. Moreover, it delays healing and recovery from certain diseases.

In order to be effective, drug therapy requires a prolonged period of administration, but it may be insufficient. In this case, it is required to complete it with surgical treatment.

Conflicts of interests: None

Contribution of authors: All authors have equally contributed to this work.

REFERENCES

- Vakil N., van Zanten S.V., Kahrilas P., Dent J., Jones R.; Global Consensus Group. - The Montreal definition and classification of gastroesophageal reflux disease. *Am J Gastroenterol.*, 2006;101(8):1900-1920.
- Barnhart D.C. - Gastroesophageal reflux disease in children. *Seminars In Pediatric Surgery.* <http://dx.doi.org/10.1053/j.sempedsurg.2016.05.009>.
- El-Serag H.B. - Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol.*, 2007;5(1):17-26. Epub 2006 Dec 4.
- Patti MG. - Gastroesophageal reflux disease. Available at: emedicine.medscape.com/article/176595-overview.
- Rival R., Wong R., Mendelsohn M., Rosgen S., Goldberg M., Freeman J. - Role of gastroesophageal reflux disease in patients with cervical symptoms. *Otolaryngol Head Neck Surg.*, 1995;113(4):364-369.
- Koufman J.A., Amin M.R., Panetti M. - Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. *Otolaryngol Head Neck Surg.*, 2000;123(4):385-388.
- Ho K.Y., Kang J.Y., Seow A. - Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. *Am J Gastroenterol.*, 1998;93(10):1816-1822.
- Ruigomez A., Garcia Rodriguez L.A., Wallander M.A., Johansson S., Graffner H., Dent J. - Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther.*, 2004;20(7):751-760.
- Lagergren J., Bergstrom R., Lindgren A., Nyrén O. - Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.*, 1999;340(11):825-831.
- Vaezi M.F. - Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. *Am J Med.*, 2003;115 Suppl 3A:97S-104S.
- Richter J.E. - Extraesophageal presentations of gastroesophageal reflux disease. *Semin Gastrointest Dis.*, 1997;8(2):75-89.
- Wong R.K., Hanson D.G., Waring P.J., Shaw G. - ENT manifestations of gastroesophageal reflux. *Am J Gastroenterol.*, 2000;95(8 Suppl):S15-S22.
- Vaezi M.F. - Laryngeal manifestations of gastroesophageal reflux disease. *Curr Gastroenterol Rep.*, 2008;10(3):271-277.
- Carr M.M., Nagy M.L., Pizzuto M.P., Poje C.P., Brodsky L.S. - Correlation of findings at direct laryngoscopy and bronchoscopy with gastroesophageal reflux disease in children: a prospective study. *Arch Otolaryngol Head Neck Surg.*, 2001;127(4):369-374.
- Hanson D.G., Jiang J.J. - Diagnosis and management of chronic laryngitis associated with reflux. *Am J Med.*, 2000;108 Suppl 4a:112S-119S.
- Habermann W., Eherer A., Lindbichler F., Raith J., Friedrich G. - Ex juvantibus approach for chronic posterior laryngitis: results of short-term pantoprazole therapy. *J Laryngol Otol.*, 1999;113(8):734-739.
- Havas T.E., Priestley J., Lowinger D.S. - A management strategy for vocal process granuloma. *Laryngoscope*, 1999;109(2 Pt 1):301-306.
- Hoffman H.T., Overholt E., Karnell M., McCulloch T.M. - Vocal process granuloma. *Head Neck*, 2001;23(12):1061-1074.
- Chan G., Boyle J.O., Yang E.K., Zhang F., Sacks P.G., Shah J.P., Edelstein D., Soslow R.A., Koki A.T., Woerner B.M., Masferrer J.L., Dannenberg A.J. - Cyclooxygenase-2 Expression Is Up-Regulated in Squamous Cell Carcinoma of the Head and Neck. *Cancer Res.*, 1999;59(5):991-994.
- Galli J., Cammarota G., Calò L., Agostino S., D'Ugo D., Cianci R., Almadori G. - The role of acid and alkaline reflux in laryngeal squamous cell carcinoma. *Laryngoscope*, 2002;112(10):1861-1865.
- Lewin J.S., Gillenwater A.M., Garrett J.D., Bishop-Leine J.K., Nguyen D.D., Callender D.L., Ayers G.D., Myers J.N. - Characterization of laryngopharyngeal reflux in patients with premalignant or early carcinoma of the larynx. *Cancer*, 2003;97(4):1010-1014.
- Samuelson C.F. - Gastroesophageal reflux and obstructive sleep apnea. *Sleep*, 1989;5:475-476.
- Kerr P., Shoenuit J.P., Millar T., Buckle P., Kryger M.H. - Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. *Chest*, 1992;101(6):1539-1544.
- Graf K.I., Karaus M., Heinemann S., Korber S., Dorow P., Hampel K.E. - Gastroesophageal reflux in patients with sleep apnea syndrome. *Z Gastroenterol.*, 1995;33(12):689-693.
- Ing A.J., Ngu M.C., Breslin A.B. - Obstructive sleep apnea and gastroesophageal reflux. *Am J Med.*, 2000;108 Suppl 4a:120S-125S.
- Locke G.R. 3rd, Talley N.J., Fett S.L., Zinsmeister A.R., Melton L.J. 3rd - Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*, 1997;112(5):1448-1456.

27. Valipour A., Makker H.K., Hard R., Emegbo S., Toma T., Spiro S.G. - Symptomatic gastroesophageal reflux in subjects with a breathing sleep disorder. *Chest*, 2002;121(6):1748-1753.
28. Jecker P., Orloff L.A., Wohlfeil M., Mann W.J. - Gastroesophageal reflux disease (GERD), extraesophageal reflux (EER) and recurrent chronic rhinosinusitis. *Eur Arch Otorhinolaryngol.*, 2006;263(7):664-667. Epub 2006 Mar 9.
29. Delehaye E., Dore M.P., Bozzo C., Mameli L., Delitala G., Meloni F. - Correlation between nasal mucociliary clearance time and gastroesophageal reflux disease: our experience on 50 patients. *Auris Nasus Larynx*, 2009;36(2):157-161. doi: 10.1016/j.anl.2008.06.004. Epub 2008 Sep 5.
30. Katle E.J., Hart H., Kjaergaard T., Kvaloy J.T., Steinsvag S.K. - Nose- and sinus-related quality of life and GERD. *Eur Arch Otorhinolaryngol.*, 2012;269(1):121-125. doi: 10.1007/s00405-011-1675-y. Epub 2011 Jun 26.
31. Temnikova I.V., Onuchina E.V., Subbotina M.V., Kozlova N.A. - Especially chronic rhinosinusitis associated with gastroesophageal reflux disease. *Eksp Klin Gastroenterol.*, 2015;(3):21-25.
32. Dibaise J.K., Sharma V.K. - Does gastroesophageal reflux contribute to the development of chronic sinusitis? A review of the evidence. *Dis Esophagus.*, 2006;19(6):419-424.
33. Roesch-Ramos L., Roesch-Dietlen F., Remes-Troche J.M., Romero-Sierra G., Mata-Tovar Cde J., Azamar-Jacome A.A., Barranca-Enríquez A. - Dental erosion, an extraesophageal manifestation of gastroesophageal reflux disease. The experience of a center for digestive physiology in Southeastern Mexico. *Rev Esp Enferm Dig.*, 2014;106(2):92-97.
34. Phipps C.D., Wood W.E., Gibson W.S., Cochran W.J. - Gastroesophageal reflux contributing to chronic sinus disease in children. *Arch Otolaryngol Head Neck Surg.*, 2000;126(7):831-836.
35. Sylvester D.C., Karkos P.D., Vaughan C., Johnston J., Dwivedi R.C., Atkinson H., Korteque S. - Chronic Cough, Reflux, Postnasal Drip Syndrome, and the Otolaryngologist. *International Journal of Otolaryngology*, 2012;vol. 2012, Article ID 564852, 5 pages
36. doi:10.1155/2012/564852.
37. De Benedetto M., Monaco G., Marra F. - Extra-laryngeal manifestations of gastro-oesophageal reflux. *Acta Otorhinolaryngol Ital.*, 2006;26(5):256-259.
38. Schwarz S.M. - Pediatric gastroesophageal reflux. Available at: <http://emedicine.medscape.com/article/930029-overview#a5>.
39. Rudolph C.D. - Supraesophageal complications of gastroesophageal reflux in children: challenges in diagnosis and treatment. *Am J Med.*, 2003;115 Suppl 3A:150S-156S.
40. Weaver E.M. - Association between gastroesophageal reflux and sinusitis, otitis media and laryngeal malignancy: a systemic review of the evidence. *Am J Med.*, 2003;115 Suppl 3A:81S-89S.
41. Bouchard S., Lallier M., Yazbeck S., Bensoussan A. - The otolaryngologic manifestations of gastroesophageal reflux: when is a pH study indicated? *J Pediatr Surg.*, 1999;34(7):1053-1056.
42. Caruso G., Passali F.M. - ENT manifestations of gastro-oesophageal reflux in children. *Acta Otorhinolaryngol Ital.*, 2006;26(5):252-255.
43. Tasker A., Dettmar P.W., Panetti M., Koufman J.A., Birchall J.P., Pearson J.P. - Reflux of gastric juice and glue ear in children. *Lancet*, 2002;359(9305):493.