Review

Atypical Clinical Presentation of Laryngopharyngeal Reflux: A 5-year Case-Series

Jerome R. Lechien, MD, PhD, MS[1-4], Stéphane Hans, MD, PhD, MS[2,3], Francois Bobin, MD[5], Christian Calvo-Henriquez, MD[6], Sven Saussez, MD, PhD[1,4,7*], Petros D. Karkos, MD, PhD, MPhil[8*]

1. Department of Human Anatomy and Experimental Oncology, Mons School of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), B7000 Mons, Belgium.
2. Department of Otolaryngology-Head & Neck Surgery, Foch Hospital, School of Medicine, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), 92150 Paris, France.
3. Department of Otolaryngology-Head & Neck Surgery, Ambroise Paré Hospital, APHP, Paris Saclay University, 92150 Paris, France.
4. Department of Otolaryngology-Head & Neck Surgery, CHU Saint-Pierre, Faculty of Medicine, University Libre de Bruxelles, 1000 Brussels, Belgium.
5. Elsan polyclinic of Poitiers, Poitiers, France.
6. Department of Otolaryngology, Hospital Complex of Santiago de Compostela, Santiago de Compostela, Spain.
7. Department of Otolaryngology-Head & Neck Surgery, EpiCURA Hospital, Mons, Belgium.
8. Department of Otorhinolaryngology and Head and Neck Surgery, AHEPA University Hospital, Thessaloniki Medical School, 54621 Thessaloniki, Greece.

*Dr Saussez & Dr Karkos equally contributed to the paper and have to be co-senior authors.

Correspondence to: Dr. Jerome R. Lechien, M.D., Ph.D., M.S.; Department of Otolaryngology-Head & Neck Surgery, Foch Hospital, School of Medicine, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France. Email: Jerome.Lechien@umons.ac.be
Telephone: +32 65 37 35 84

Abstract:

Background: Laryngopharyngeal reflux (LPR) is a common disease in otolaryngology characterized by an inflammatory reaction of the mucosa of the upper aerodigestive tract caused by digestive refluxate enzymes. LPR has been identified as etiological or favoring factor of laryngeal, oral, sinonasal or otological diseases. In this case-series, we reported atypical clinical presentation of LPR in patients presenting in our clinic with reflux.

Methods: A retrospective medical chart review of 351 patients with LPR treated in the European Reflux Clinic in Brussels, Poitiers and Paris was performed. In order to be included, patients had to report atypical clinical presentation of LPR, consisting of symptoms or findings that are not described in reflux symptom score and reflux sign assessment. The LPR diagnosis was confirmed with 24-hour hypopharyngeal-esophageal impedance pH-study and patients were treated with a combination of diet, proton pump inhibitors and alginates. The atypical symptoms or findings had to be resolved from pre- to posttreatment

Results: From 2017 to 2021, 21 patients with atypical LPR were treated in our center. The clinical presentation consisted of recurrent aphthosis or burning mouth (N=9), recurrent burps and abdominal disorders (N=2), posterior nasal obstruction (N=2), recurrent acute suppurative otitis media (N=2), severe vocal fold dysplasia (N=2), and recurrent acute rhinopharyngitis (N=1), tearing (N=1), aspirations (N=1) or tracheobronchitis (N=1). Abnormal upper aerodigestive tract reflux events were identified in all of these patients. Atypical clinical findings resolved and did not recur after an adequate anti-reflux treatment.

Conclusion: LPR may present with various clinical presentations including mouth, eye, tracheobronchial, nasal or laryngeal findings, which may all regress with an adequate treatment.

 doi:10.20944/preprints202104.0409.v1

Future studies are needed to better specify the relationship between LPR and these atypical findings through analyses identifying gastroduodenal enzyme in the enflamed tissue.

Keywords: Reflux; Laryngopharyngeal; Clinical; Atypical; Nasal; Otological; Respiratory; Management; Treatment; Diagnosis.

Introduction

Laryngopharyngeal reflux (LPR) may be defined as an inflammatory condition of the upper aerodigestive tract tissues related to the direct and indirect effect of gastric or duodenal content reflux, inducing morphological changes in the upper aerodigestive tract [1]. Many basic science studies demonstrated that the mucosal lesions are mainly due to the extra- or intracell pepsin activity into the upper aerodigestive tract mucosa [2,3]. Pepsin was found in nasal mucosa of patients with resistant chronic rhinosinusitis and LPR [4]. Others identified LPR as a key condition responsible of nasal symptoms in patients who do not report sinonasal infection [5]. In the same way, pepsin and LPR were identified as important factors in the development of chronic media otitis in children and adults [6], laryngeal disorders [7], or bronchial irritation in patients with asthma [8]. The involvement of LPR in many respiratory and digestive conditions may lead to atypical clinical presentation of the disease, which may be difficult to detect in clinical practice.

This paper aims to present a case-series of patients with atypical clinical presentation of LPR diagnosed in our reflux clinic.

Methods

Design, data collection, and setting.

A retrospective medical chart review of patients who were diagnosed with LPR from 2017 to 2021 at the European Reflux Clinics (Brussels, Paris, Poitiers) [9] was performed. The LPR diagnosis was made through 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) respecting predefined criteria in patient who initially reported LPR-related symptoms, e.g. hoarseness, dysphagia, throat pain, throat clearing, halitosis or globus sensation [10]. The atypical LPR was defined as a clinical presentation with symptoms or findings that are not reported in reflux symptom score (RSS) [11] or reflux sign assessment (RSA) [12]. RSS is 22-item patient-reported outcome questionnaire that report the most prevalent otolaryngological, digestive and respiratory symptoms associated with LPR. The score was developed after a systematic review of the most prevalent LPR symptoms and signs reported in the literature [13] and may be considered as a complete and reliable patient-reported outcome questionnaire [11]. The association between atypical finding and LPR was confirmed if the LPR diagnosis was confirmed with HEMII-pH, if the finding resolved posttreatment and if the atypical finding of patient was not explained by another condition. Rigorous exclusion criteria were subsequently used to select well-matched samples, to minimize bias and to eliminate confounding factors. Patients with other comorbidities different from LPR or gastroesophageal reflux disease (GERD) such as smoking, drinking, or active allergy at the time of the evaluations were excluded. Incomplete medical records were also excluded.

The epidemiological, medical and therapeutic data of each patient who consulted in our center were all recorded, electronically available in our system and were easily extracted for the purpose of the study using the following key word: “atypical”, “unusual”, “uncommon”, “nasal”, “respiratory”, “bronchial”, “ear”, and “eye”.

24-hour HEMII-pH

The HEMII-pH catheter was composed of 8 impedance ring pairs and 2 pH electrodes (Versaflex Z®, LPR ZNID22+8R FGS 9000-17; Digitrapper pH-Z testing System, Medtronic, Hauts-de-France, France, supplementary file). The catheter model used was introduced transnasally and chosen based

on the esophageal length of patient. Six impedance segments were placed along the esophagus zones (Z1 to Z6) below the upper esophagus sphincter (UES). Two additional impedance segments were placed 1 and 2 cm above the UES in the hypopharyngeal cavity. The configuration of this catheter enabled the recording of changes in intraluminal impedance at each point. The two pH electrodes were placed 5 cm above LES and 1-2 cm above UES. The HEMII-pH probe was placed in the morning before breakfast (8:00 AM). A hypopharyngeal reflux event (HRE) was defined as an episode that reached two hypopharyngeal impedance sensors. A LPR diagnosis was given if there was ≥1 acid or nonacid HRE [14]. Acid reflux was defined as an episode with pH≤4.0. Nonacid reflux consisted of an episode with pH>4.0. The HEMII-pH tracing was electronically analyzed by the software and the result was verified by two senior physicians. LPR was defined as acid when the ratio of number of hypopharyngeal acid reflux episodes/number of nonacid reflux episodes was >2. LPR was defined as nonacid when the ratio of number of acid reflux episodes/number of nonacid reflux episodes <0.5. Mixed reflux consisted of a ratio ranged from 0.51 to 2.0. GERD was defined as a DeMeester score >14.72 or a length of time >4.0% of the 24-hour recording spent below pH 4.0.

Finding evolution, treatment and management of atypical clinical presentations

The management of patients in our reflux clinics is summarized in Figure 1. In practice, after the HEMII-pH diagnosis, the laryngologists started a treatment depending on the HEMII-pH features. The treatment scheme included diet, behavioral changes, and use of proton pump inhibitors (PPIs), alginate or magaldrate for 3 months. PPIs were taken once or twice daily before meals depending on the pattern of reflux events (daytime, nighttime reflux events). Alginates were taken twice or thrice daily after the main meals in case of weakly acid (mixed) or nonacid LPR. Diet recommendations were based on a validated European diet scheme [15]. Treatment of patient was tailored at 3- and 6-month regarding the evolution of RSS.

Nonresponders or those presenting with unusual clinical presentation benefited from additional general and specific (related to the anatomical findings) examinations in order to identify differential diagnosis or comorbidities associated with LPR (Figure 2).

Results

From the 351 patients who had a positive HEMII-pH diagnosis, 24 patients met our inclusion criteria. Three patients were excluded because there were no posttreatment data in the medical record. The atypical findings consisted of recurrent aphthosis or burning mouth (N=9), recurrent burps and abdominal disorders (N=2), posterior nasal obstruction (N=2), recurrent acute suppurative media otitis (N=2), severe vocal fold dysplasia (N=2), recurrent acute rhinopharyngitis (N=1), chronic tearing (N=1), recurrent aspirations (N=1) and tracheobronchitis (N=1). The patient features are reported in Tables 1 to 3.

Oral atypical manifestations.

Eleven patients reported oral atypical manifestations. From them, two patients had recurrent aphthosis and burning mouth syndrome, while seven individuals had severe isolated burning tongue/mouth. Before the realization of HEMII-pH, the patients benefited from a complete dental and maxillofacial examinations, excluding the following lesions or conditions associated with secondary burning mouth syndrome: atrophic glossitis, geographical tongue, other aphthosis causes, dysplasia, lichen, mycosis, Sjogren, autoimmune disease, vitamin disorders, or hypersensitivity to dental materials. After the exclusion of these causative factors, they benefited from a reflux consultation and a 24-hour HEMII-pH. As exhibited in Table 1, LPR was identified in all patients, consisting of acid (N=7), weakly acid (N=1) and alkaline (N=1) LPR. Regarding the HEMII-pH features, patients received a personalized treatment, and the disorders/lesions regressed after 3- to 6-month therapy. There was no recurrence of the disorder at the last follow-up time, ranging from 6 months to 3 years. Note that the patient number 6 also developed fissured tongue (Figure 3 (2)), which did not change after treatment.

Patient number 3 was living abroad and was referred to our clinic with severe anorexia related to burning mouth syndrome resistant to 3- to 6-month anti-reflux therapy (i.e. the use of PPIs, alginate, antireflux diet). The patient lost 15 kg over the previous 6 months. The HEMII-pH revealed alkaline LPR, and patient were treated with magaldrate (four times daily) for 6 months. Because the symptoms did not improve, an additional check-up was proposed to patient and a histamine intolerance was detected. The symptoms and findings disappeared after 2 months of a histamine-free diet.

Among the patients with oral findings, two patients complained of recurrent burps, halitosis and abdominal pain. Because they were resistant to PPI therapy, patients were addressed to our clinics. The LPR diagnosis was confirmed with the HEMII-pH and the digestive work-up (biology and lactose hydrogen breath test) revealed gluten (patient n10) and lactose (patient n11) intolerance. The gluten-free and lactose-free diets were sufficient to significantly improve laryngopharyngeal and digestive symptoms in these patients over the long-term follow-up (4 years).

Otological and nasal atypical manifestations.

Six patients had otological or nasal atypical LPR presentations (Table 2). Among them, three individuals reported resistant chronic nasal obstruction, which was not related to nasal or rhinopharyngeal tumor, polyposis, chronic rhinosinusitis, septal deviation, allergic rhinitis, inflammatory nasal disease, cartilage hypotonia, infection, chemical or drug-induced rhinitis. CT-scan of nose and sinuses was unremarkable. There was no history of nasal surgery and they did not respond to a 3-month topical treatment including saline solution irrigation and two different corticosteroids (mometasone furoate and budesonide). The patients benefited from acoustic rhinomanometry to confirm the nasal obstruction, which was related to inferior turbinate hypertrophy. In patient number 13, the turbinate edema was located in the back of the turbinate. The RSS and the nasal obstruction of patients significantly improved after 3- to 6-month antireflux therapy. Two patients were weaned from the antireflux medication and were clinically controlled with the antireflux diet over the long-term. One patient was not weaned from the alginate-based treatment because she continued to have laryngopharyngeal symptoms (LPR chronic course). At baseline, this patient also had chronic tearing related to an inferior meatus edema. Although the laryngopharyngeal symptoms persisted, the inferior meatus edema and the related tearing disorder disappeared.

Three patients had otological clinical presentation associated with LPR (Table 2). Patient number 15 had 3 to 4 times yearly acute suppurative otitis throughout the last decade. During the last episode, otolaryngologist observed bulging and erythema of both tympanic membranes and patients benefited from antibiotic/anti-inflammatory treatment. The favoring factors of recurrent otitis media were all excluded (e.g. immunological disorders, nasal disorder, rhinitis, chemical exposure). Patient number 16 also reported otological disorder (retraction pocket) without history or favoring factors. These two patients were addressed to the reflux clinics by general otolaryngologists who observed LPR-related signs and erythema of the nasopharyngeal cavity (Figure 3 (3)). Acid gaseous upright and daytime LPR was confirmed in both cases. The personalized treatments led to a complete resolution of recurrent acute otitis media history and retraction pocket after treatment. There was no recurrence at one year posttreatment. The last patient had a chronic course of rhinopharyngitis with severe rhinorrhea, postnasal drip, nasal obstruction, face and ear pressure. Nasal fibreoptic endosopy revealed important nasopharyngeal sticky mucus and erythema (Figure 3 (4)). CT-scan and otological examinations (i.e. otoscopy, tympanometry and audiometry) were unremarkable. There was also a dust allergy that was controlled by antihistamines. As for the other patients, the HEMII-pH confirmed the diagnosis and the rhinopharyngitis-related symptoms disappeared after a personalized treatment.

 doi:10.20944/preprints202104.0409.v1

Table 1: Data of patients with oral manifestations.

			Baseline features			Post-treatment features		
PN	**G**	**Age**	**Atypical presentation**	**HEMII-pH/RSS**	**Treatment**	**RSS/RSA**	**Presentation evolution**	**Long-term follow-up**
1	M	36	**Recurrent aphthosis & burning mouth** Dental check-up: normal	Upright acid reflux GI: normal RSS: 48 - RSA: 26	Strict diet PPIs Magaldrate	RSS: 13 RSA: 10	Resolution of aphthosis & burning mouth	Long-term diet No recurrence (3-y)
2	F	55	**Recurrent aphthosis & burning mouth** Dental check-up: normal	Upright acid reflux GI: not performed RSS: 50 - RSA: 26	Strict diet PPIs Alginate	RSS: 5 RSA: NP	Resolution of aphthosis & burning mouth	Long-term diet No recurrence (6-m)
3	M	31	**Mouth burning & severe anorexia** GI/dental check-up: normal Nutritionist: Histamine intolerance	Upright nonacid reflux GI: normal RSS: 148 - RSA: 14	Histamine-free Diet	RSS: 64 RSA: NP	Resolution of pain & weight gain	Long-term histamine-free diet. No recurrence (1-y)
4	M	38	**Tongue burning** Dental check-up: normal	Upright weakly acid reflux GI: normal RSS: 131 - RSA: 37	Strict diet PPIs Alginate	RSS: 16 RSA: 23	Resolution of tongue burning	Long-term diet No recurrence (1-y)
5	M	55	**Tongue burning** Dental check-up: normal	Upright acid reflux GI: GERD, hiatal hernia RSS: 76 - RSA: 24	Strict diet PPIs Magaldrate	RSS: 48 RSA: 21	Reduction of tongue burning	Long-term diet Long-term PPIs & Magaldrate (1-y)
6	F	53	**Tongue burning & fissured tongue** Dental check-up: normal	Upright acid reflux GI: GERD, esophagitis RSS: 247 - RSA: 28	Strict diet PPIs Magaldrate	RSS: 135 RSA: 22	Reduction of tongue Burning but no change of fissured tongue	Long-term diet Long-term intermittent Magaldrate (9-m)
7	F	54	**Tongue & mouth burning** Dental check-up: normal	Upright acid reflux GI: GERD RSS: 88 - RSA: 26	Strict diet PPIs Magaldrate	RSS: 19 RSA: 13	Resolution of tongue burning	Long-term diet No recurrence (3-y)
8	F	62	**Tongue & mouth burning** Dental check-up: normal	Upright acid reflux GI: GERD, esophagitis	Strict diet PPIs	RSS: 19 RSA: 32	Resolution of tongue burning	Long-term diet One recurrence controlled

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 April 2021 doi:10.20944/preprints202104.0409.v1

				RSS: 203 - RSA: 22	Alginate			with alginate (3-y)
9	F	64	**Tongue & mouth burning** Dental check-up: normal	Upright acid reflux GI: normal RSS: 124 - RSA: 32	Strict alcaline Diet	RSS: 12 RSA: NP	Resolution of tongue burning	Long-term diet No recurrence (6-m)
10	F	31	**Recurrent burps & abdominal pain** GI check-up: gluten intolerance	Upright acid reflux GI: bulbitis RSS: 167 - RSA: 20	Gluten-free Diet	RSS: 40 RSA: 17	Resolution of burps & Abdominal pain	Long-term gluten-free diet. No recurrence (4-y)
11	F	36	**Recurrent burps & abdominal pain** GI check-up: lactose intolerance	Upright nonacid reflux GI: normal RSS: 111 - RSA: 31	Lactose-free Diet	RSS: 16 RSA: 21	Resolution of burps & Abdominal pain	Long-term lactosis-free diet. No recurrence (4-y)

Table 1 footnotes: Abbreviations: G=gender; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HEMII-pH=hypopharyngeal-esophageal multichannel intraluminal impedance pH-monitoring; m=month; NP=not provided; PN=patient number; PPI=proton pump inhibitor; RSA=reflux sign assessment; RSS=reflux symptom score; y=year.

 doi:10.20944/preprints202104.0409.v1

Table 2: Data of patients with oral manifestations.

			Baseline features			Post-treatment features		
PN	**G**	**Age**	**Atypical presentation**	**HEMII-pH/RSS**	**Treatment**	**RSS/RSA**	**Presentation evolution**	**Long-term follow-up**
12	F	64	**Resistant chronic nasal obstruction*** Nasosinusal check-up: hypertrophy of the posterior part of the inferior turbine	Upright weakly acid reflux GI: normal RSS: 250 - RSA: 29	Strict diet PPIs Alginate	RSS: 67 RSA: NP	Resolution of nasal obstruction	Long-term diet No recurrence (6 months)
13	F	50	**Resistant chronic nasal obstruction*** Nasosinusal check-up: hypertrophy of the posterior part of the inferior turbine	Upright acid reflux GI: not performed RSS: 58 - RSA: 12	Strict diet PPIs Alginate	RSS: 43 RSA: NP	Resolution of nasal obstruction Septoplasty not required	Long-term diet No recurrence (6 months)
14	F	66	**Resistant chronic nasal obstruction and tearing** Nasosinusal check-up: hypertrophy of the posterior part of the inferior turbine	Upright weakly acid reflux GI: not performed RSS: 210 - RSA: 32	Strict alcaline Diet	RSS: 184 RSA: NP	Resolution of nasal obstruction & tearing Resolution of edema of inferior & middle meatus	Long-term diet & alginate No recurrence (6-m) of tear & nasal symptoms Chronic throat symptoms
15	F	35	**Recurrent suppurative media otitis & Ear pressure and pain** Nasosinusal check-up: normal Otological check-up: retraction pocket	Upright acid reflux GI: not performed RSS: 11 - RSA: 20	Strict alcaline Diet	RSS: 2 RSA: 7	Resolution of media otitis	Long-term diet No recurrence (1-y) of symptoms or tympanic membrane findings.
16	M	37	**Chronic media otitis** Nasosinusal check-up: obstruction and erythema of the Eustachian tube.**	Upright acid reflux GI: not performed RSS: 73 - RSA: 36	Strict alcaline Diet	RSS: 48 RSA: NP	Improvement of nasal obstruction	Long-term diet & short period of alginate No recurrence (1-y)
17	M	36	**Recurrent rhinopharyngitis/otitis** Otological check-up: normal Nasal check-up: controlled dust allergy	Upright weakly acid reflux GI: not performed RSS: 107 - RSA: 29	Strict diet PPIs Alginate	RSS: 52 RSA: 20	Resolution of rhino-pharyngitis posttreatment	Long-term diet No recurrence (6 months)

Table 2 footnotes: *Resistant chronic nasal obstruction=resistant to two type of nasal sprays (mometasone furoate and budesonide). **Eustachian tube disorder highlighted with abnormal tympanometry and audiometry reporting retrotympanic membrane liquid. Abbreviations: F/M=female/male; G=gender; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HEMII-pH=hypopharyngeal-esophageal multichannel intraluminal impedance pH-monitoring; m=month; NP=not provided; PN=patient number; PPI=proton pump inhibitor; RSA=reflux sign assessment; RSS=reflux symptom score ; y=year.

 doi:10.20944/preprints202104.0409.v1

Broncho-laryngeal atypical manifestations.

The third patient group included two individuals with severe dysplasia of the vocal fold, one with recurrent aspirations and related lung infections, and another with recurrent tracheobronchitis. No patient smoked or had tobacco or chemical exposure history. Prior to the reflux consultation, patients with vocal fold leukoplakia underwent direct laryngobronchoscopy with biopsy confirming severe dysplasia (Figure 3 (1)). Patients with aspiration and tracheobronchitis benefited from pulmonologist work-up, including lung spirometry, bronchoscopy and chest CT-scan, which were normal. Patient with aspiration had no neurological disorder and videofluoroscopy and bronchoscopy were unremarkable. HEMII-pH identified acid or weakly acid LPR in these patients. The patient disorders disappeared with the personalized treatment and there was no recurrence over the follow-up period.

Figure 3: Some Atypical Findings associated with Reflux.

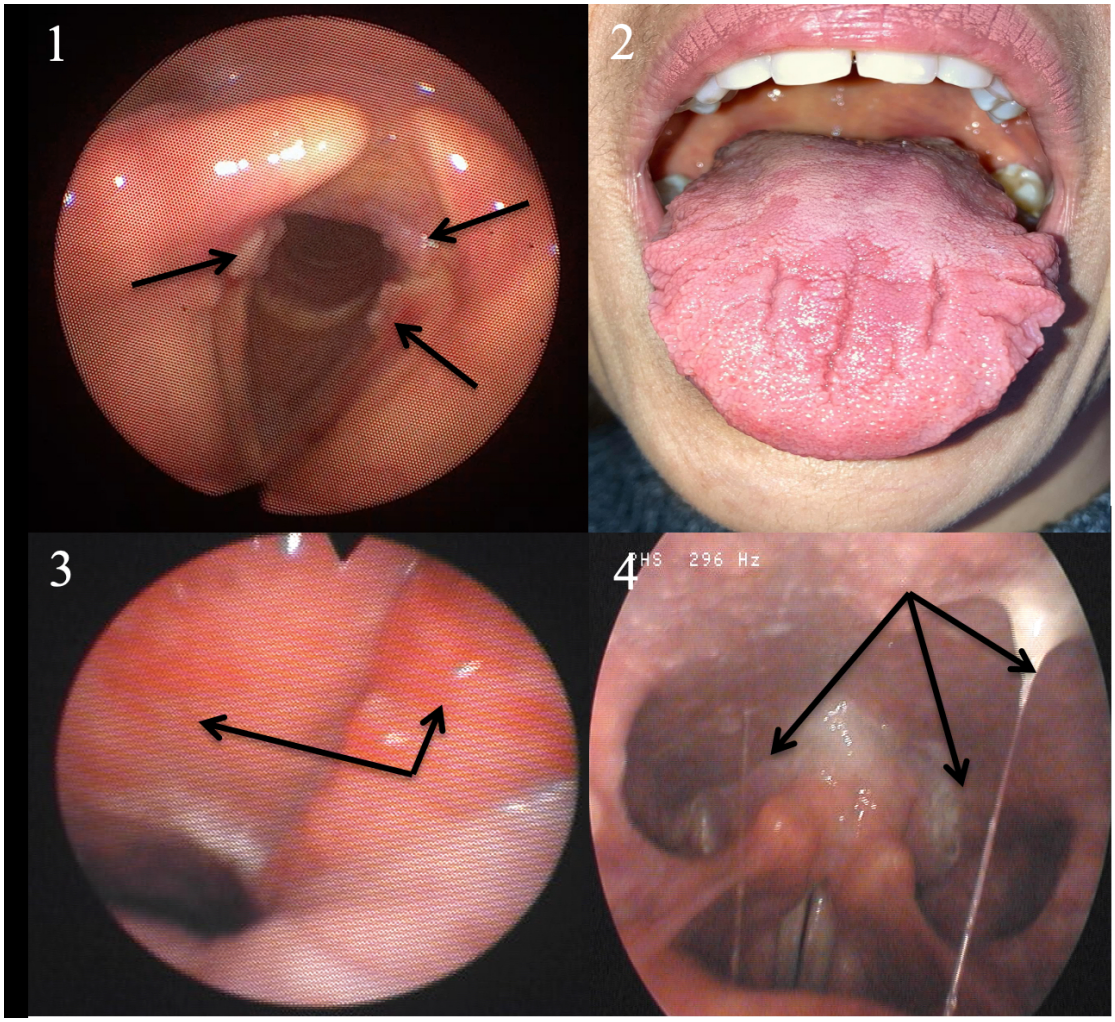

Figure 3 footnote: Leukoplakia (1), fissured tongue (2), erythema of the nasopharynx and Eustachian meatus (3), and sticky mucus from nasopharynx to oropharynx (4).

 doi:10.20944/preprints202104.0409.v1

Table 3: Broncho-laryngeal manifestations of reflux.

			Baseline features			Post-treatment features		
PN	**G**	**Age**	**Atypical presentation**	**HEMII-pH/RSS**	**Treatment**	**RSS/RSA**	**Presentation evolution**	**Long-term follow-up**
18	F	34	**Severe idiopathic vocal fold dysplasia** Laryngeal check-up: normal No tobacco/toxic exposition history	Upright acid reflux GI: not performed RSS: 34 - RSA: 39	Strict alcaline Alginate Diet	RSS: 9 RSA: 20	Resolution of dysplasia within 6 months	Long-term diet No recurrence (6 months)
19	M	45	**Severe idiopathic vocal fold dysplasia** Laryngeal check-up: normal No tobacco/toxic exposition history	Upright acid reflux GI: not performed RSS: 73 - RSA: 23	Strict alcaline Diet	RSS: 16 RSA: 18	Resolution of dysplasia within 6 months	Long-term diet No recurrence (9 months)
20	M	38	**Daily aspirations & pneumonia** Lung/Swallowing check-up: normal	Upright acid reflux GI: esophagitis RSS: 156 - RSA: 27	Strict alcaline Diet Alginate	RSS: 81 RSA: 18	Resolution of dysplasia within 6 months	Long-term diet No recurrence (6 months)
21	F	65	**Recurrent tracheobronchitis** Lung check-up: normal No tobacco/asthma history	Upright weakly acid reflux GI: LES insuffisiency RSS: 415 - RSA: 24	Strict diet Magaldrate	RSS: 110 RSA: 19	Resolution of tracheo- bronchitis within 6 months	Long-term diet Magaldrate (sometimes) No recurrence (6 months)

Table 3 footnotes: Abbreviations: F/M=female/male; G=gender; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HEMII-pH=hypopharyngeal-esophageal multichannel intraluminal impedance pH-monitoring; LES=lower esophageal sphincter; m=month; NP=not provided; PN=patient number; RSA=reflux sign assessment; RSS=reflux symptom score; y=year.

Discussion

Laryngopharyngeal reflux is occasionally associated with nonspecific symptoms and findings, which make diagnosis challenging for unaware physicians [16]. The involvement of LPR in the development of several inflammatory conditions of the upper aerodigestive tract was increasingly studied over the past decades, reporting potential involvement in rhinological, otological and laryngological diseases [5-8]. In this study, our team shared some clinical observations where the diagnosis and the treatment of LPR disease had a significant impact of the resolution of specific conditions that are currently not or poorly known to be associated with reflux.

The involvement of LPR in the development of oral disorders was suspected for a long time, the first reports dating from the seventies [17]. In the present study, we reported several patients with primary burning mouth syndrome that was not attributed to any dental or general condition. Interestingly, we observed that symptoms significantly improved or resolved with an adequate treatment and a long-term antireflux diet. A few studies investigated the involvement of reflux in dental lesions [18], or primary burning mouth syndrome [19-21] but authors reported conflicting results, which may be related to methodological discrepancies across studies [22]. Indeed, the majority of authors studied the association between burning mouth syndrome and reflux considering GERD and not LPR diagnostic criteria [19-21]. To date, it has been demonstrated that patients with LPR may not have GERD and vice versa [1]. The development of burning or pain mouth may be related to mucosal injury related to pepsin, which may be easily detected in saliva samples with peptest. Thus, the saliva pepsin detection could be useful to investigate the potential involvement of LPR in primary burning mouth syndrome, 'idiopathic' aphtosis or fissured tongue could require.

Several studies demonstrated that reflux events may reach nasopharyngeal and nasal regions [23,24]. In this study, we identified patients who had nasal or otological findings associated with LPR, i.e. nasal obstruction, excessive nasopharyngeal mucus or recurrent acute media otitis. The pharyngeal reflux events are known to be mainly gaseous, occurring upright and daytime [25]. The occurrence of rhinopharyngeal reflux episodes may easily support the development of a reflux-related nasopharyngeal inflammation and the local production of sticky nasopharyngeal mucus, the obstruction of the Eustachian tube and the development of otitis media disorders. Furthermore, pepsin has been identified in secretion of otitis media in several studies [6,26,27]. According to nasal obstruction, two recent studies supported that LPR may lead to edema of the nasal mucosa, including the posterior part of the inferior turbinate as observed in this study [28,29]. Interestingly, XX *et al.* found pepsin in the tears [30], which may support the occurrence of a relationship between laryngopharyngeal reflux and tear disorders through the injury of the nasal mucosa of the inferior meatus.

The pepsin-related mucosal injury was initially studied in vocal fold tissues [3,31]. Pepsin may induce macroscopic and microscopic changes in the vocal fold mucosa, including epithelial cell dehiscence, microtraumas, inflammatory infiltrates, Reinke space dryness, mucosal drying, and epithelial thickening [32]. The development of severe dysplasia and its resolution after LPR treatment may probably support the potential impact of LPR in the development of some vocal fold morphological changes in non-smoker patients. Clinically, LPR may have an impact on the clinical presentation and the therapeutic response of patients with asthma [8], which supports that the LPR-related inflammation may reach the bronchi. The observation of patients with LPR and chronic bronchitis that was not attributed to another disease supports the importance to keep in mind that LPR may be an irritative factor of the lower airway. In the same way, pepsin was found in trachea and bronchi of patients with idiopathic stenosis [33].

In this case-series, the association between LPR and atypical findings is possible but not proven. The detection of pepsin and other gastroduodenal enzymes in saliva, nasal or bronchial secretions may form the basis for a future study and perhaps demonstrate the impact of LPR in the development of many unusual conditions. Gastroduodenal enzymes may irritate the upper aerodigestive tract mucosa but they may have an additional role on the local microbiota [34]. In the digestive area, many researches demonstrated the importance of gut bacteria in the mucosa homeostasis, protection, recovery, or renewal [35,36]. Similarly, the critical role of microbiota was reported in respiratory tract diseases, such as tracheal stenosis or asthma [37,38]. Thus, it seems conceivable that LPR may impact the upper aerodigestive tract microbiota leading to the development of some disorders.

The primary limitation of the present clinical study is the lack of tissue-related demonstration of the involvement of reflux in the development of the atypical disorders. However, the occurrence of LPR at the HEMII-pH study and the complete resolution after treatment strongly support a clinical association. The retrospective design, the low number of included patients and the short follow-up time of some patients are additional limitation of the study.

Conclusion

LPR may present with various clinical presentations including mouth, eye, tracheobronchial, nasal or laryngeal findings, which may all regress with an adequate treatment. Future studies are needed to better specify the relationship between LPR and these atypical findings through analyses identifying gastroduodenal enzyme in the enflamed tissue.

Author Contributions: Acknowledgments:

Author Contributions: Conceptualization, JRL, SH, PK and SS; Methodology/Organization, FB, CC; Writing – Original Draft Preparation, JRL, PK; Writing – Review & Editing, PK, SS, SH; Supervision, SS, SH, PK.

Conflicts of interest: The authors declare no conflict of interest.

References:

1.Lechien JR, Akst LM, Hamdan AL, Schindler A, Karkos PD, Barillari MR, Calvo-Henriquez C, Crevier-Buchman L, Finck C, Eun YG, Saussez S, Vaezi MF. Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. *Otolaryngol Head Neck Surg*. **2019**; 160(5):762-782. doi: 10.1177/0194599819827488.

2. Klimara MJ, Randall DR, Allen J, Figueredo E, Johnston N. Proximal reflux: biochemical mediators, markers, therapeutic targets, and clinical correlations. *Ann N Y Acad Sci*. **2020**; 1481(1):127-138. doi: 10.1111/nyas.14366.

3.Samuels TL, Johnston N. Pepsin as a marker of extraesophageal reflux. *Ann Otol Rhinol Laryngol*. **2010**; 119(3):203-8. doi: 10.1177/000348941011900310.

4. Ren JJ, Zhao Y, Wang J, Ren X, Xu Y, Tang W, He Z. PepsinA as a Marker of Laryngopharyngeal Reflux Detected in Chronic Rhinosinusitis Patients. *Otolaryngol Head Neck Surg*. **2017**; 156(5):893-900. doi: 10.1177/0194599817697055.

5. Pawar S, Lim HJ, Gill M, Smith TL, Merati A, Toohill RJ, Loehrl TA. Treatment of postnasal drip with proton pump inhibitors: a prospective, randomized, placebo-controlled study. *Am J Rhinol*. **2007**; 21(6):695-701. doi: 10.2500/ajr.2007.21.3098.

6. Lechien JR, Hans S, Simon F, Horoi M, Calvo-Henriquez C, Chiesa-Estomba CM, Mayo-Yáñez M, Bartel R, Piersiala K, Nguyen Y, Saussez S. Association Between Laryngopharyngeal Reflux and Media Otitis: A Systematic Review. *Otol Neurotol*. **2021**. doi: 10.1097/MAO.0000000000003123.

7. Lechien JR, Akst LM, Saussez S, Crevier-Buchman L, Hans S, Barillari MR, Calvo-Henriquez C, Bock JM, Carroll TL. Involvement of Laryngopharyngeal Reflux in Select Nonfunctional Laryngeal Diseases: A Systematic Review. *Otolaryngol Head Neck Surg*. **2020**: 194599820933209. doi: 10.1177/0194599820933209.

8. Pearson JP, Parikh S, Orlando RC, Johnston N, Allen J, Tinling SP, et al. Review article: reflux and its consequences--the laryngeal, pulmonary and oesophageal manifestations. Conference held in conjunction with

the 9th International Symposium on Human Pepsin (ISHP) Kingston-upon-Hull, UK, 21-23 April 2010. *Aliment Pharmacol Ther*. **2011**; 33 Suppl 1:1-71. doi: 10.1111/j.1365-2036.2011.04581.x.
9. Lechien JR, Bobin F, Muls V, Saussez S, Remacle M, Hans S. Reflux clinic: proof-of-concept of a Multidisciplinary European Clinic. *Eur Arch Otorhinolaryngol*. **2021**. doi: 10.1007/s00405-021-06705-9.
10. Lechien JR, Bobin F, Muls V, Mouawad F, Dequanter D, Horoi M, Thill MP, Rodriguez Ruiz A, Saussez S. The efficacy of a personalised treatment depending on the characteristics of reflux at multichannel intraluminal impedance-pH monitoring in patients with acid, non-acid and mixed laryngopharyngeal reflux. *Clin Otolaryngol*. **2021**; 46(3):602-613. doi: 10.1111/coa.13722.
11. Lechien JR, Rodriguez Ruiz A, Dequanter D, Bobin F, Mouawad F, Muls V, Huet K, Harmegnies B, Remacle S, Finck C, Saussez S. Validity and Reliability of the Reflux Sign Assessment. *Ann Otol Rhinol Laryngol*. **2020**; 129(4):313-325. doi: 10.1177/0003489419888947.
12. Lechien JR, Rodriguez Ruiz A, Dequanter D, Bobin F, Mouawad F, Muls V, Huet K, Harmegnies B, Remacle S, Finck C, Saussez S. Validity and Reliability of the Reflux Sign Assessment. *Ann Otol Rhinol Laryngol*. **2020**; 129(4):313-325. doi: 10.1177/0003489419888947.
13. Lechien JR, Saussez S, Schindler A, Karkos PD, Hamdan AL, Harmegnies B, De Marrez LG, Finck C, Journe F, Paesmans M, Vaezi MF. Clinical outcomes of laryngopharyngeal reflux treatment: A systematic review and meta-analysis. *Laryngoscope*. **2019**; 129(5):1174-1187. doi: 10.1002/lary.27591.
14. Hoppo T, Sanz AF, Nason KS, et al. How much pharyngeal exposure is "normal"? Normative data for laryngopharyngeal reflux events using hypopharyngeal multichannel intraluminal impedance (HMII). *J Gastrointest Surg*. **2012**. 16:16–24.
15. Lechien JR, Bobin F, Muls V, Horoi M, Thill MP, Dequanter D, Rodriguez A, Saussez S. Patients with acid, high-fat and low-protein diet have higher laryngopharyngeal reflux episodes at the impedance-pH monitoring. *Eur Arch Otorhinolaryngol*. **2020**; 277(2):511-520. doi: 10.1007/s00405-019-05711-2.
16. Lechien JR, Allen JE, Barillari MR, Karkos PD, Jia H, Ceccon FP, Imamura R, Metwaly O, Chiesa-Estomba CM, Bock JM, Carroll TL, Saussez S, Akst LM. Management of Laryngopharyngeal Reflux Around the World: An International Study. *Laryngoscope*. **2020**. doi: 10.1002/lary.29270.
17. Howden GF. Erosion as the presenting symptom in hiatus hernia. A case report. *Br Dent J*. **1971**; 131(10):455-6. doi: 10.1038/sj.bdj.4802772.
18. Lechien JR, Chiesa-Estomba CM, Calvo Henriquez C, Mouawad F, Ristagno C, Barillari MR, Schindler A, Nacci A, Bouland C, Laino L, Saussez S. Laryngopharyngeal reflux, gastroesophageal reflux and dental disorders: A systematic review. *PLoS One*. **2020**; 15(8):e0237581. doi: 10.1371/journal.pone.0237581.
19. Preetha A, Sujatha D, Patil BA, Hegde S. Oral manifestations in gastroesophageal reflux disease. *Gen Dent*. **2015**; 63(3):e27-31.
20. Hakeem A, Fitzpatrick SG, Bhattacharyya I, Islam MN, Cohen DM. Clinical characterization and treatment outcome of patients with burning mouth syndrome. *Gen Dent*. **2018**; 66(3):41-47.
21. Cheung D, Trudgill N. Managing a patient with burning mouth syndrome. *Frontline Gastroenterol*. **2015**; 6(3):218-222. doi: 10.1136/flgastro-2014-100431.
22. Lechien JR, Hans S, De Marrez LG, et al. Prevalence and Features of Laryngopharyngeal Reflux in Patients with Primary Burning Mouth Syndrome. Submitted *Laryngoscope*, **2021**.
23. Brunworth JD, Mahboubi H, Garg R, Johnson B, Brandon B, Djalilian HR. Nasopharyngeal acid reflux and Eustachian tube dysfunction in adults. *Ann Otol Rhinol Laryngol*. **2014**; 123(6):415-9. doi: 10.1177/0003489414526689.
24. Brunworth JD, Garg R, Mahboubi H, Johnson B, Djalilian HR. Detecting nasopharyngeal reflux: a novel pH probe technique. *Ann Otol Rhinol Laryngol*. **2012**; 121(7):427-30. doi: 10.1177/000348941212100701.
25. Lechien JR, Bobin F, Dapri G, Eisendrath P, Salem C, Mouawad F, Horoi M, Thill MP, Dequanter D, Rodriguez A, Muls V, Saussez S. Hypopharyngeal-Esophageal Impedance-pH Monitoring Profiles of Laryngopharyngeal Reflux Patients. *Laryngoscope*. **2021**; 131(2):268-276. doi: 10.1002/lary.28736.
26. Lei L, Yu Z, Yu R, Yang H, Zou J, Ren J, Zhang J, Zhong D. Correlation of pathogenic effects of laryngopharyngeal reflux and bacterial infection in COME of children. *Acta Otolaryngol*. **2021**: 1-5. doi: 10.1080/00016489.2021.1883732.
27. O'Reilly RC, Soundar S, Tonb D, Bolling L, Yoo E, Nadal T, Grindle C, Field E, He Z. The role of gastric pepsin in the inflammatory cascade of pediatric otitis media. *JAMA Otolaryngol Head Neck Surg*. **2015**; 141(4):350-7. doi: 10.1001/jamaoto.2014.3581.
28. Hamizan AW, Choo YY, Loh PV, Abd Talib NF, Mohd Ramli MF, Zahedi FD, Husain S. The association between the reflux symptoms index and nasal symptoms among patients with non-allergic rhinitis. *J Laryngol Otol*. **2021**; 135(2):142-146. doi: 10.1017/S0022215120002492.
29. Ceylan SM, Kanmaz MA, Disikirik I, Karadeniz PG. Peak nasal inspiratory airflow measurements for assessing laryngopharyngeal reflux treatment. *Clin Otolaryngol*. **2021**. doi: 10.1111/coa.13737.

30. Magliulo G, Pace A, Plateroti R, Plateroti AM, Cascella R, Solito C, Rossetti V, Iannella G. Laryngopharyngeal reflux disease in adult patients: tears and pepsin. *J Biol Regul Homeost Agents*. **2020**; 34(2):715-720. doi: 10.23812/19-437-L-26.
31. Samuels TL, Johnston N. Pepsin in gastroesophageal and extraesophageal reflux: molecular pathophysiology and diagnostic utility. *Curr Opin Otolaryngol Head Neck Surg*. **2020**; 28(6):401-409. doi: 10.1097/MOO.0000000000000664.
32. Lechien JR, Saussez S, Harmegnies B, Finck C, Burns JA. Laryngopharyngeal Reflux and Voice Disorders: A Multifactorial Model of Etiology and Pathophysiology. *J Voice*. **2017**; 31(6):733-752. doi: 10.1016/j.jvoice.2017.03.015.
33. Blumin JH, Johnston N. Evidence of extraesophageal reflux in idiopathic subglottic stenosis. *Laryngoscope*. **2011**; 121(6):1266-73. doi: 10.1002/lary.21776.
34. Lechien JR, De Vos N, Everard A, Saussez S. Laryngopharyngeal reflux: The microbiota theory. *Med Hypotheses*. **2021**; 146:110460. doi: 10.1016/j.mehy.2020.110460.
35. Biagi E, Candela M, Turroni S, Garagnani P, Franceschi C, Brigidi P. Ageing and gut microbes: perspectives for health maintenance and longevity. *Pharmacol Res*. **2013**; 69(1):11-20. doi: 10.1016/j.phrs.2012.10.005.
36. Motta JP, Wallace JL, Buret AG, Deraison C, Vergnolle N. Gastrointestinal biofilms in health and disease. *Nat Rev Gastroenterol Hepatol*. **2021**. doi: 10.1038/s41575-020-00397-y.
37. Hillel AT, Tang SS, Carlos C, Skarlupka JH, Gowda M, Yin LX, Motz K, Currie CR, Suen G, Thibeault SL. Laryngotracheal Microbiota in Adult Laryngotracheal Stenosis. *mSphere*. **2019**; 4(3):e00211-19. doi: 10.1128/mSphereDirect.00211-19.
38. Tang HHF, Teo SM, Sly PD, Holt PG, Inouye M. The intersect of genetics, environment, and microbiota in asthma-perspectives and challenges. *J Allergy Clin Immunol*. **2021**; 147(3):781-793. doi: 10.1016/j.jaci.2020.08.026.