World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i32.4363

World J Gastroenterol 2012 August 28; 18(32): 4363-4370
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related?

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Received: July 6, 2012 Revised: August 15, 2012
Accepted: August 18, 2012
Published online: August 28, 2012

Abstract

AIM: To investigate the prevalence of gastroesophageal reflux disease (GERD) in patients with a laryngoscopic diagnosis of laryngopharyngeal reflux (LPR).

METHODS: Between May 2011 and October 2011, 41 consecutive patients with laryngopharyngeal symptoms (LPS) and laryngoscopic diagnosis of LPR were empirically treated with proton pump inhibitors (PPIs) for at least 8 wk, and the therapeutic outcome was assessed through validated questionnaires (GERD impact scale, GIS; visual analogue scale, VAS). LPR diagnosis was performed by ear, nose and throat specialists using the reflux finding score (RFS) and reflux symptom index (RSI). After a 16-d wash-out from PPIs, all patients underwent an upper endoscopy, stationary esophageal manometry, 24-h multichannel intraluminal impedance and pH (MII-pH) esophageal monitoring. A positive correlation between LPR diagnosis and GERD was supposed based on the presence of esophagitis (ERD), pathological acid exposure time (AET) in the absence of esophageal erosions (NERD), and a positive correlation between symptoms and refluxes (hypersensitive esophagus, HE).

RESULTS: The male/female ratio was 0.52 (14/27), the mean age ± SD was 51.5 ± 12.7 years, and the mean body mass index was 25.7 ± 3.4 kg/m^2. All subjects reported one or more LPS. Twenty-five out of 41 patients also had typical GERD symptoms (heartburn and/or regurgitation). The most frequent laryngoscopic findings were posterior laryngeal hyperemia (38/41), linear indentation in the medial edge of the vocal fold (31/41), vocal fold nodules (6/41) and diffuse infraglottic oedema (25/41). The GIS analysis showed that 10/41 patients reported symptom relief with PPI therapy ($P < 0.05$); conversely, 23/41 did not report any clinical improvement. At the same time, the VAS analysis showed a significant reduction in typical GERD symptoms after PPI therapy ($P < 0.001$). A significant reduction in LPS symptoms. On the other hand, such result was not recorded for LPS. Esophagitis was detected in 2/41 patients, and ineffective esophageal motility was found in 3/41 patients. The MII-pH analysis showed an abnormal AET in 5/41 patients (2 ERD and 3 NERD); 11/41 patients had a normal AET and a positive association between symptoms and refluxes (HE), and 25/41 patients had a normal AET and a negative association between symptoms and refluxes (no GERD patients). It is noteworthy that HE patients had a posi-

tive association with typical GERD-related symptoms. Gas refluxes were found more frequently in patients with globus (29.7 ± 3.6) and hoarseness (21.5 ± 7.4) than in patients with heartburn or regurgitation (7.8 ± 6.2). Gas refluxes were positively associated with extra-esophageal symptoms ($P < 0.05$). Overall, no differences were found among the three groups of patients in terms of the frequency of laryngeal signs. The proximal reflux was abnormal in patients with ERD/NERD only. The differences observed by means of MII-pH analysis among the three subgroups of patients (ERD/NERD, HE, no GERD) were not demonstrated with the RSI and RFS. Moreover, only the number of gas refluxes was found to have a significant association with the RFS ($P = 0.028$ and $P = 0.026$, nominal and numerical correlation, respectively).

CONCLUSION: MII-pH analysis confirmed GERD diagnosis in less than 40% of patients with previous diagnosis of LPR, most likely because of the low specificity of the laryngoscopic findings.

Key words: Laryngopharyngeal reflux; Gastroesophageal reflux; Multichannel impedance and pH monitoring; Extra-esophageal reflux syndromes; Chronic laryngitis

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de Bortoli N, Nacci A, Savarino E, Martinucci I, Bellini M, Fattori B, Ceccarelli L, Costa F, Mumolo MG, Ricchiuti A, Savarino V, Berrettini S, Marchi S. How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related? *World J Gastroenterol* 2012; 18(32): 4363-4370 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i32/4363.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i32.4363

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in Western countries[1]. The manifestations of GERD have been recently classified into either esophageal or extra-esophageal syndromes (EES)[1]. Among the latter, Vakil *et al*[1] have included the atypical manifestations of GERD such as chronic cough and laryngopharyngeal symptoms (LPS) (i.e., laryngitis, globus, throat discomfort), which are increasingly recognised by general physicians, lung specialists and ear, nose and throat (ENT) surgeons[2,3]. In particular, there is a large number of data on the growing prevalence of LPS in GERD patients[4-6].

Despite the recognition that GERD can provoke laryngeal symptoms, the diagnosis of laryngopharyngeal reflux (LPR) remains a very difficult task. Initially, patients with laryngeal symptoms undergo a laryngoscopy and a chest X-ray to rule out malignancies. Once cancer is excluded, a diagnosis of LPR is suspected. The diagnosis of LPR is usually performed by ENT surgeons in case of detection of the following laryngoscopic findings: erythema, oedema, ventricular obliteration, post-cricoid hyperplasia and pseudosulcus[7]. However, these laryngoscopic findings are also common in healthy volunteers, and this largely limits their diagnostic value[7]. Moreover, there are several controversies regarding how to confirm LPR diagnosis and, more generally, EES diagnosis. Upper gastrointestinal endoscopy has been demonstrated to have low sensitivity[8,9], the proton pump inhibitor test has been shown to have low specificity[10], and radiologic studies have limited sensitivity and specificity[8]. Moreover, the sensitivity and specificity of ambulatory pH monitoring as a means for diagnosing reflux in patients with extra-esophageal GERD symptoms have been challenged[1]. Recently, the availability of multichannel intraluminal impedance and pH monitoring (MII-pH) has modified the diagnostic approach towards atypical manifestations of GERD[11-14]. MII-pH is able to detect not only acid but also non-acid reflux and proximal migration of the refluxate and can correlate symptoms with both types of reflux[15-17]; additionally, there is a rising consensus that this technique should be considered as the gold standard for GERD diagnosis[18]. At present, few data are available on the prevalence of LPR in patients with or without GERD symptoms and on the characteristics of overall reflux episodes in those patients.

The aim of this study was to evaluate the prevalence of GERD in patients with a recent laryngoscopic diagnosis of LPR by means of MII-pH. The second endpoint was to assess the effectiveness of an empirical treatment with proton pump inhibitors (PPIs) in patients with both GERD-related and non-GERD-related LPR.

MATERIALS AND METHODS

Study subjects

Between May 2011 and October 2011, 41 consecutive patients with LPS and an ENT diagnosis of LPR were prospectively enrolled in the study. During the first visit, a distinct investigator completed a structured interview on the patients, recording a careful medical history (with recording of height and weight), current medications, tobacco use and alcohol consumption. All patients signed a written informed consent form before entering into the study. The study was designed and carried out in accordance with the Helsinki Declaration (Sixth revision, Seul 2008).

Inclusion criteria were as follows: LPS for at least three consecutive months during the last year, previous history of dysphonia, cough, hoarseness, throat globe and/or dysphagia and an ENT diagnosis of LPR. In particular, such a diagnosis was performed after an accurate phoniatric and otorhinolaryngoiatric anamnesis and a general ENT examination with a flexible rhino-pharyn-

go-laryngoscope with an optical fibre. The reflux findings score (RFS) was completed by the otolaryngologist (RFS > 7), suggestive value for LPR), and all patients were asked to complete the reflux symptom index (RSI) (RSI > 13, suggestive value for LPR)[19]. Patients with a RSF > 7 and a RSI > 13 were considered affected by LPR.

Exclusion criteria were as follows: Previous surgery in the upper digestive tract, pregnancy and/or breastfeeding, eating disorders with vomiting, underlying psychiatric illness, use of non-steroidal anti-inflammatory drugs and aspirin, and peptic ulcer at a previous endoscopy.

All the enrolled patients were allowed an empirical treatment with PPIs for at least 8 wk, and the therapeutic outcome was recorded through a validated questionnaire (GERD impact scale, GIS), which was completed before and after therapy[20]. The GIS comprises eight questions about the frequency, over the previous 2 wk, of the following items: acid-related symptoms; chest pain; extra-esophageal symptoms; impact of symptoms on sleep, work, meals and social occasions; and the use of additional non-prescription medications. A 4-point rating Likert scale was used to describe the frequency of the symptoms over the previous 2 wk: 0 = none (absence of symptoms), 1 = mild (symptoms present for a little of the time), 2 = moderate (symptoms present for some of the time), and 3 = severe (symptoms present all of the time). Patients who responded with a score of 2 or 3 were considered as non-responders to PPI therapy.

The patients were also asked to rate their satisfaction with the symptom control on a global visual analogue scale (VAS) from 0 (no relief at all) to 10 (complete symptom relief). The VAS score has been used as a self-assessment tool for symptom measurement, which has been used in many other trials for evaluation of ENT symptoms and typical and atypical GERD symptoms[21,22].

After 8 wk of PPI therapy, all patients underwent upper endoscopy, stationary esophageal manometry and 24-h MII-pH esophageal monitoring. All patients discontinued PPI therapy at least 16 d before undergoing the planned esophageal investigations. The patients were only allowed to take alginates, on an as-needed basis, as rescue therapy. During upper gastrointestinal endoscopy, biopsies were taken from the gastric antrum and corpus to assess the presence of *Helicobacter pylori* and atrophic gastritis. Stationary manometry and MII-pH were performed after an overnight fast.

Stationary esophageal manometry

All subjects underwent stationary esophageal manometry to determine the distance of the proximal border of the lower esophageal sphincter (LES) from the nostrils and to evaluate the esophageal peristaltic wave. This study was performed by means of an eight-channel water-perfused manometric catheter with an external diameter of 4.5 mm (Dyno 2000® Menfis, BioMedica, Bologna Italy), equipped with computer-based data recording and storage. Esophageal body motility and LES relaxation were tested by at least 10 wet swallows of 5 mL of water. Wave amplitude and duration were measured by means of four openings located at 5, 10, 15 and 20 cm above the LES. A stationary pull-through technique was then used to accurately locate the position of the LES.

Esophageal MII-pH

MII-pH was performed using a polyvinyl catheter (diameter: 2.3 mm), equipped with an antimony pH electrode and several cylindrical electrodes, with a length of 4 mm, placed at intervals of approximately 2 cm (Sandhill Scientific Inc., Highland Ranch, CO). Each pair of adjacent electrodes represented an impedance-measuring segment corresponding to one recording channel. The single-use MII-pH catheter was positioned with the pH electrode 5 cm above the LES and the six impedance recording channels positioned at 3, 5, 7, 9, 15 and 17 cm above the LES.

The methodology of probe calibration, catheter placement, patient instruction and performance has been previously described[23].

MII-pH data analysis

At the end of the recording period, MII-pH tracings were reviewed manually to ensure accurate detection and classification of reflux episodes. Meal periods were excluded from the analysis. Impedance and pH data were used to determine the number and type of reflux episodes as well as the acid exposure time (AET) (reflux percent time) in each patient. In particular, the distal esophageal AET was defined as the total time with a pH measurement below 4 divided by the total time of monitoring. A percent time lower than 4.2% with pH < 4, over 24-h, was considered normal[23,24]. Reflux events were characterised according to previously reported criteria[25]. Total reflux number, esophageal AET and correlation between symptoms and reflux using the symptom index (SI) and symptom association probability (SAP) were evaluated for each patient as previously described[26]. The symptoms were considered to be related to reflux if they occurred within a 2-min time window after the onset of the reflux episode[27]. For symptom analysis, weakly acidic and weakly alkaline refluxes were pooled as non-acid reflux episodes (nadir pH > 4).

Statistical analysis

MII-pH data were matched with the ENT diagnosis. Statistical analysis was performed with the Chi-squared test and the Fisher exact test to evaluate nominal values, and Pearson's correlation was performed to explore numerical values. The results were considered statistically significant for P values < 0.05.

RESULTS

Demographic and clinical characteristics

The study evaluated 14 males and 27 females (M/F ratio 0.52), with a mean age ± SD of 51.5 ± 12.7 years and a

Table 1 Results of the gastroesophageal reflux disease impact scale questionnaire before and after proton pump inhibitor therapy

How often have you had the following symptoms: (GIS questionnaire)	Before PPI therapy				After PPI therapy				*P* value
	Always	Often	Sometimes	Never	Always	Often	Sometimes	Never	
Pain in your chest or behind the breastbone?	1	0	0	0	0	0	1	0	NS
Burning sensation in your chest or behind the breastbone?	10	4	1	0	3	1	1	10	< 0.05
Regurgitation or acid taste in your mouth?	2	5	2	0	1	1	3	4	< 0.05
Pain or burning in your upper stomach?	1	2	2	0	0	1	1	3	< 0.05
Sore throat or hoarseness that is related to your heartburn or acid reflux?	27	5	9	0	23	8	6	4	NS

NS: Not statistically significant; GIS: Gastroesophageal reflux disease impact scale; PPI: Proton pump inhibitor.

Table 2 Results of the visual analytic scale

Symptoms	Pre-PPI	Post-PPI	*P* value
Chest pain	7.1 ± 2.4	3.3 ± 0.9	0.0001[1]
Heartburn	8.5 ± 3.2	2.3 ± 1.1	0.0001[1]
Regurgitation	6.8 ± 1.5	4.1 ± 1.9	0.0001[1]
Epigastric pain	5.9 ± 3.6	3.7 ± 2.4	0.0021
Hoarseness	7.4 ± 2.2	6.8 ± 2.7	0.273
Globus	9.3 ± 3.8	7.9 ± 3.5	0.087
Cough	7.9 ± 2.6	6.8 ± 2.8	0.069
Throat discomfort	8.1 ± 3.4	6.9 ± 2.1	0.058
Dysphonia	6.5 ± 2.1	5.5 ± 3.5	0.121

[1]Statistically significant differences. PPI: Proton pump inhibitor.

mean body mass index of 25.7 ± 3.4 kg/m^2. Eight patients out of 41 (19.5%) were current smokers (5-10 cigarettes/d); 11/41 (28.8%) reported 2 to 3 units of alcohol consumption per day, and 33/41 (73.3%) drank two cups of coffee daily.

Symptoms

All subjects reported one or more LPS, and 25/41 patients also had typical GERD symptoms (heartburn and/or regurgitation). In particular, they described the predominant symptom (the most troublesome/frequent symptom during the day) and the overall most frequent symptoms in the last 6 mo. The predominant symptoms were globus 13 (31.7%), heartburn 10 (24.4%), hoarseness 9 (22%), sore throat 6 (14.6%), regurgitation 2 (4.9%) and epigastric pain 1 (2.4%). The overall most frequent symptoms were globus 21 (51.2%), heartburn 15 (36.6%), hoarseness 14 (34.1%), sore throat 13 (31.7%), regurgitation 9 (22%), dysphonia 9 (22%), belch 7 (17.1%), epigastric pain 5 (12.2%), and chronic cough 3 (7.3%).

The prevalence of symptom relief after PPI therapy, evaluated with the GIS questionnaire, showed that 10/41 (24.4%) patients reported at least one typical GERD symptom with "well controlled symptoms" (0) and that 23/41 (56.1%) patients reported only LPS without any symptom relief. All the details regarding the prevalence of symptom relief are described in Table 1.

The VAS analysis showed a significant reduction in typical GERD symptoms after PPI therapy. This reduction was not recorded for LPS. All details are presented in Table 2.

Upper gastrointestinal endoscopy

Upper endoscopy showed esophagitis (ERD) in 2/41 (4.9%) patients. None of the patients were diagnosed with complications of GERD (i.e., Barrett's esophagus, stenosis, adenocarcinoma). No other lesion or mucosal abnormality was detected during the examination.

Endoscopic hiatal hernia was found in 17/41 (41.5%) patients. With regard to the histological findings of the corpus and antrum biopsies, 4 out of 41 (9.75%) patients had *Helicobacter pylori* infection, and no one had atrophic gastritis or intestinal metaplasia.

Pathophysiological esophageal investigations

Two out of 41 (4.9%) patients presented with ineffective esophageal motility at the stationary manometry. Thirty-nine out of 41 (95.1%) patients did not present with abnormal esophageal motility.

The MII-pH analysis showed an abnormal AET in 5/41 (12.2%) patients [2 ERD and 3 non erosive esophagitis (NERD)]; 11/41 (26.8%) patients had a normal AET and a positive SAP (hypersensitive esophagus, HE), and; 25/41 patients had a normal AET and a negative association between symptoms and refluxes (no GERD patients). HE patients presented with a positive SAP for typical GERD-related symptoms (7 heartburn and 4 regurgitation).

The percentage of proximal reflux was abnormal (up more than 33%) in 4 cases with ERD/NERD (9.8%).

Gas refluxes were found more frequently in patients with globus (29.7 ± 3.6) and hoarseness (21.5 ± 7.4) than in patients with heartburn or regurgitation (7.8 ± 6.2). The SAP analysis for gas refluxes was positive for extra-esophageal symptoms.

Laryngoscopic examination

The most frequent laryngoscopic findings in our selected patients, classified by our MII-pH results, are shown in Table 3. Overall, no differences were found among the three groups of patients in terms of the frequency of the laryngeal signs. In particular, both ERD and NERD patients did not show severe findings of laryngeal disease.

The differences observed among the three subgroups of patients (ERD/NERD, HE, no GERD) with esophageal pathophysiological analysis (MII-pH) were not demonstrated with the ENT symptom questionnaire (RSI) or with the laryngoscopic findings (RFS), as shown in Table 4.

Table 3 Laryngoscopic findings with the reflux finding score in 41 patients with suspected laryngopharyngeal reflux, classified using multichannel intraluminal impedance and pH monitoring

Laryngoscopic findings	Ordinal scale	ERD/NERD (5)	HE (11)	No GERD[1] (25)	*P* value
Infraglottic oedema (pseudosulcus)	0 = Absent	4	10	23	0.592
	2 = Present	1	1	2	
Ventricular obliteration	0 = None	4	8	21	0.553
	2 = Partial	1	3	4	
	4 = Complete	0	0	0	
Erythema/hyperemia	0 = None	0	0	1	0.474
	2 = Arytenoids only	2	6	15	
	4 = Diffuse	3	5	9	
Vocal fold oedema	0 = None	3	7	19	0.375
	1 = Mild	2	1	4	
	2 = Moderate	0	3	2	
	3 = Severe	0	0	0	
	4 = Polypoid	0	0	0	
Diffuse laryngeal oedema	0 = None	0	4	10	0.271
	1 = Mild	1	4	7	
	2 = Moderate	2	3	5	
	3 = Severe	2	0	3	
	4 = Obstructing	0	0	0	
Posterior commissure hypertrophy	0 = None	0	0	0	0.763
	1 = Mild	2	5	12	
	2 = Moderate	1	5	10	
	3 = Severe	2	1	3	
	4 = Obstructing	0	0	0	
Granuloma/granulation	0 = Absent	5	10	24	0.876
	2 = Present	0	1	1	
Thick endolaryngeal mucus	0 = Absent	2	7	12	0.909
	2 = Present	3	4	10	

[1]Patients with normal acid exposure time and without correlation between symptoms and refluxes. ERD: Erosive esophagitis; NERD: Non erosive esophagitis; HE: Hypersensitive esophagus.

Table 4 Correlation between multichannel intraluminal impedance and pH analysis and the reflux finding score/ reflux symptom index analysis

	ERD/NERD	HE	No GERD[1]	*P* value
AET (%)	7.4 ± 3.2	3.5 ± 1.7	1.9 ± 0.8	< 0.05
Reflux number (*n*)	103.2 ± 12.1	44.7 ± 6.2	35.1 ± 7.4	< 0.05
Proximal refluxes (mean %)	31	29	18	< 0.05
Acid refluxes (*n*)	62.5 ± 15.4	32.9 ± 5.1	19.7 ± 6.2	< 0.05
Non-acid refluxes (*n*)	40.1 ± 7.6	13.1 ± 4.4	15.8 ± 4.9	< 0.05
Gas refluxes (*n*)	11.6 ± 9.7	13.1 ± 8.1	21.7 ± 15.3	< 0.05
SAP/SI	Positive	Positive	Negative	-
RFS	10.9 ± 3.3	9.1 ± 2.7	7.6 ± 3.1	NS
RSI	14.3 ± 5.2	16.3 ± 4.7	15.8 ± 4.9	NS

[1]Patients with normal acid exposure time and without correlation between symptoms and refluxes. AET: Acid exposure time; ERD: Erosive esophagitis; NERD: Non erosive esophagitis; HE: Hypersensitive esophagus. SAP/SI: Symptom association probability/symptom index; RFS: Reflux finding score; RSI: Reflux symptom index; NS: Not statistically significant.

Table 5 Results of nominal and numerical correlation

	Nominal correlation			Numerical correlation	
	RFS	RSI	RGE	RFS	RSI
AET (%)	NS	NS	$P < 0.001$	NS	NS
Total reflux number	NS	NS	$P < 0.001$	NS	NS
Acid reflux number	NS	NS	$P < 0.05$	NS	NS
Non-acid reflux number	NS	NS	$P < 0.05$	NS	NS
Proximal reflux number	NS	NS	$P < 0.04$	NS	NS
SAP	NS	NS	$P < 0.009$	NS	NS
Gas refluxes	$P = 0.028$	NS	NS	$P = 0.026$	NS
Upper endoscopy	NS	$P < 0.001$	$P = 0.009$	NS	NS
MII-pH (diagnosis)	NS	NS	$P < 0.001$	NS	NS

RFS: Reflux finding score; RSI: Reflux symptom index; RGE: Gastroesophageal reflux diagnosis; AET: Acid exposure time; NS: Not statistically significant; MII-pH: Multichannel intraluminal impedance and pH; SAP: Symptom association probability.

A nominal (categorical) correlation (pathological *vs* non pathological) was performed considering endoscopic and esophageal pathophysiological examinations (results of endoscopy, MII-pH, AET value, total number of reflux events, number of proximal refluxes, gas refluxes, SAP). No match results were statistically significant. Only the number of gas refluxes was associated with the RFS ($P = 0.028$). The numerical correlation showed the same results: the correlation between the RFS and gas refluxes was confirmed ($P = 0.026$). All detailed results are shown in Table 5.

DISCUSSION

GERD is considered an important cause of laryngeal inflammation[28]. The most common symptoms of this condition, termed LPS by ENT physicians, include hoarseness, throat pain, sensation of a lump in the throat, cough and repetitive throat clearing. However, these symptoms

are nonspecific and can also be seen in other diseases such as post-nasal drip syndrome or environmental exposure to allergens and other irritants[29]. Lundell *et al*[30] showed that acid is an uncommon cause of LPS in the absence of typical reflux symptoms or endoscopic features of reflux esophagitis. A similar finding was demonstrated in a more recent study by Ang *et al*[31] where 14% of patients investigated for suspected EES showed an abnormal AET, suggesting that acid and non-acid refluxes do not play different roles in the genesis of extra-esophageal symptoms. Likewise, signs of laryngeal inflammation (i.e., hyperemia, oedema) are not specific to GERD. In 2007, Vavricka *et al*[32] evaluated the prevalence of specific laryngopharyngeal changes thought to be GERD-related in patients with known reflux disease (n = 132) *vs* normal subjects (n = 132). Ten specific hypopharyngeal and laryngeal sites were evaluated: the posterior pharyngeal wall, the interarytenoid bar, the posterior commissure, the posterior cricoid wall, the arytenoids complex, the true vocal folds, the false vocal folds, the anterior commissure, the epiglottis and the aryepiglottic fold. Investigators found that the prevalence of laryngeal lesions was the same in both groups. Moreover, most signs identified in patients suspected of having LPR were also present in healthy subjects without any symptoms[33]. Milstein *et al*[34] performed a laryngoscopic evaluation of 52 non-smoking volunteers without any history of ENT disease or GERD-related symptoms and observed the presence of one or more signs of tissue irritation in 93% of the subjects. Laryngoscopic or laryngostroboscopic examinations are determinant for excluding laryngeal nodules or neoplastic lesions but are not specific for diagnosing LPR[35]. Thus, in keeping with these considerations, the utility of laryngoscopy in detecting GERD-associated laryngitis remains uncertain[33,34]. The use of MII-pH technology has provided new insights into the complex pathogenesis underlying atypical GERD symptoms. Based on our findings, LPS are not always due to GERD and RFS. Although RFS is a useful score for ENT, it is not able to accurately identify patients with LPR due to GERD. Nevertheless, in clinical practice, GERD is often considered as the underlying cause of laryngeal symptoms even in those patients who have a negative MII-pH or in those undergoing twice daily PPI therapy without any efficacy. At present, different causes that might be involved in the genesis of GERD-unrelated LPS are not known, highlighting the need for future studies in this field. We should focus our efforts on searching for these other causes; reflux might be the easy answer, but we must look for difficult answers when logic suggests that direction. Chronic laryngitis is a heterogeneous disease, and GERD may be just one of the causes or an aggravating factor. Patients with and without troublesome reflux symptoms may have different pathophysiological mechanisms and may therefore require different therapies.

Notably, one study demonstrated that gas refluxes with weak acidity were more common in patients with reflux-attributed laryngitis compared to GERD patients and controls[36]. In keeping with this finding, our results showed that the only characteristic of refluxes associated with LPR was the presence of gas refluxes. The mechanisms by which gas refluxes may develop into LPS are far from being clarified. It has been hypothesised that gas refluxes carry aerosolised droplets containing hydrogen and pepsin that are able to generate troublesome symptoms into the proximal esophagus and pharyngeal/laryngeal mucosa. Indeed, microaspiration of acid aerosolised droplets is considered one of the most important mechanisms for laryngeal inflammation. Hydrochloric acid vaporises easily and can result in a concentrated cloud of acidic vapour entering the airways[37].

An increasing number of studies are using the presence of pepsin in clinical samples as a marker for gastroesophageal reflux because it is produced exclusively by the stomach. Indeed, reflux has been documented by detection of pepsin in the trachea, lung, sinus, middle ear, combined sputum and saliva, and breath condensate. Of note, pepsin is stable up to pH 7 and regains activity after reacidification[38]. In this regard, two recent review articles have highlighted that an immunologic pepsin assay is a rapid, sensitive, and specific tool for correlation of reflux with airway disease and is a reliable diagnostic marker of EES[39,40]. In particular, extra-esophageal reflux can now be detected by recognising pharyngeal acidification using a miniaturised pH probe and by the non-invasive identification of pepsin in saliva and in exhaled breath condensate using the pepsin immunoassay[40].

Recently, a new technology able to detect aerosols of acid and gaseous clouds of acid has been described: the Dx-pH measurement system (Dx-pH) (Respiratory Technology Corp., San Diego, CA). Dx-pH is a highly sensitive and minimally invasive device for the detection of acid reflux in the posterior oropharynx. It uses a nasopharyngeal catheter with a sensor that is able to measure pH in either liquid or aerosolised droplets[41]. A number of preliminary studies have suggested that this technique may have a role in identifying patients with extra-esophageal symptoms caused by reflux disease[40].

PPI therapy is considered to be the standard of care in patients with LPS when GERD is the underlying suspected aetiology. In clinical practice, it is believed that patients with reflux-related laryngitis require more aggressive and prolonged PPI treatments to achieve an improvement of laryngeal symptoms than those with typical GERD symptoms[42]. Conversely, several placebo-controlled trials and meta-analyses have failed to demonstrate any therapeutic benefit of PPIs[43-47]. Some studies have shown that the proportion of patients with marked improvement in laryngeal symptoms after PPI therapy is higher in GERD patients than in those without GERD[48,49]. On the other hand, the most recent multicenter study, with 145 patients suspected of having LPR, did not show any benefit in patients treated with esomeprazole 40 mg *bid* for 4 mo *vs* placebo[43].

In the present study, patients with typical GERD symptoms and an abnormal AET had increased symptom relief after PPI therapy. Atypical/extra-esophageal

GERD-suspected symptoms are less responsive to antisecretive therapy.

In conclusion, current knowledge on LPR diagnosis and management needs to be expanded with new diagnostic techniques to better understand the underlying pathophysiological mechanisms. In this respect, the present study underscores the importance of MII-pH monitoring to assess the presence of an established association between GERD and suspected LPR.

COMMENTS

Background

Laryngopharyngeal reflux is defined as the reflux of gastric contents into the larynx and pharynx, and it is the most extensively investigated extra-esophageal syndrome with an established association with gastroesophageal reflux disease (GERD). It may be manifested as laryngeal symptoms as well as laryngoscopic findings. However, laryngoscopic findings are not specific, and this largely limits their diagnostic value. Moreover, there are currently several controversies regarding accurate confirmation of such a diagnosis.

Research frontiers

In the area of chronic laryngitis, the research hotspot is how to diagnose and manage laryngopharyngeal reflux (LPR). In particular, new diagnostic techniques to better understand the underlying pathophysiological mechanisms are necessary. Indeed, GERD may represent just one of the causes or an aggravating factor of laryngopharyngeal symptoms (LPS).

Innovations and breakthroughs

The use of esophageal multichannel impedance and pH technology has provided new insights into the complex pathogenesis underlying atypical reflux symptoms. In clinical practice, GERD is often considered to be the underlying cause of laryngeal symptoms, even in those patients who have a negative impedance and pH study or in those undergoing twice daily proton pump inhibitor therapy without any efficacy. In the present study, LPS were not always due to GERD, and laryngoscopic findings were not able to accurately identify patients with LPR due to GERD. Based on the findings, the only characteristic of refluxes associated with LPR was the presence of gas refluxes, although the mechanisms by which gas refluxes may contribute to LPR are far from being clarified. Overall, patients with typical reflux symptoms and abnormal acid exposure time had increased symptom relief after proton pump inhibitor therapy. Conversely, extra-esophageal reflux-suspected symptoms were less responsive to antisecretive therapy.

Applications

The present study underscores the importance of impedance and pH monitoring to assess the presence of an established association between GERD and suspected LPR.

Terminology

Extra-esophageal syndromes: The manifestations of GERD have been recently classified into either esophageal or extra-esophageal syndromes. Among the latter, the atypical manifestations of GERD such as chronic cough and LPS (i.e., laryngitis, globus, throat discomfort) have been included; Laryngopharyngeal reflux: Laryngopharyngeal reflux is a condition with an established association with GERD and is defined as the reflux of gastric contents into the larynx and pharynx; Multichannel intraluminal impedance and pH monitoring: This is a technique that is able to detect both acid and non-acid reflux and proximal migration of the refluxate, to physically characterise the refluxate (i.e., liquid, gas, mixed), and to correlate symptoms with each type of reflux.

Peer review

This is an interesting and well-structured study aimed to evaluate the diagnostic capacity of laryngoscopic findings suspected to be related to GERD, as performed by ear, nose and throat physicians. The LPR definition is based on the symptoms, although the criteria for LPR symptoms have not been established by many papers. The entry number is relatively small. The authors use multichannel intraluminal impedance and pH monitoring and many questionnaires as the diagnostic gold standard. Of note, they found that laryngoscopic findings had a poor sensitivity and were not related to the multichannel intraluminal impedance and pH results. From their data, the authors suggested that another reason for LPR besides acid reflux was gas reflux.

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