Clinical Relevance and Therapeutic Findings of Chronic Cough Related to Laryngopharyngeal Reflux Disease☆

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Summary: Objective. To investigate clinical significance of chronic cough in patients with laryngopharyngeal reflux disease (LPRD) and evaluate the potential of cough as a predictor for clinical findings and treatment outcomes.

Methods. Data of patients with a positive diagnosis of LPRD at the 24-hour hypopharyngeal-esophageal multi-channel intraluminal impedance-pH monitoring (HEMII-pH) prospectively followed at the European Reflux Clinic and Elsan Hospital from January 2017 to August 2024 were retrieved. Four study groups were established based on chronic cough severity. Between-group analysis included HEMII-pH parameters (number and pH of pharyngeal reflux events), pretreatment and post treatment reflux symptom scores (RSS), reflux sign assessment (RSA), and gastrointestinal endoscopy findings.

Results. The study included 523 patients [303 females (57.9%) and 220 males (42.1%)]. Of the 523 patients with LPRD, 326 (62.3%) had mild-to-severe chronic cough. The mean ages of patients ranged from 50.3 to 52. 7 years. The cough severity score was associated with the severity of otolaryngological, digestive, and non-cough respiratory symptoms, with the mildest presentations in patients without chronic cough. The magnitude of pretreatment to post treatment changes in RSS and RSA decreased as cough severity increased. Patients with chronic cough demonstrated higher post therapeutic otolaryngological and non-cough respiratory symptom scores, while there were no significant differences across groups for digestive symptoms. The therapeutic response rate was 75.1%, without demonstrating significant differences between patients with chronic cough (75. 9%) and those without (73.8%). The cough severity score was a predictor of the post treatment RSS ($r_s = 0.222$; $P = 0.001$).

Conclusion. Chronic cough is a predominant symptom in LPRD with a prevalence of 62.3%. At baseline presentation, chronic cough severity is suggestive of a significant prognostic indicator of LPRD RSS severity.

Key Words: Laryngeal—Laryngopharyngeal—Reflux—Gastroesophageal—Chronic—Cough—Voice—Otolaryngology—Head neck surgery—Laryngology.

INTRODUCTION

Laryngopharyngeal reflux disease (LPRD) is a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract.[1] LPRD is commonly associated with laryngopharyngeal symptoms, including globus sensation, throat clearing, mucus, or chronic cough.[2,3] In otolaryngology and pulmonology settings, LPRD and gastroesophageal reflux disease (GERD) are identified in 10%-52% of outpatients presenting with chronic cough.[4–6] Patients with chronic cough are challenging because this symptom leads to significant impairments of quality of life (QoL), and the medical therapeutic responses can be unpredictable.[7,8] The multifactorial pathogenesis of reflux-related chronic cough, involving reflux theory, reflex theory, weakly acid reflux, and esophageal dysmotility, often results in suboptimal outcomes with standard LPRD treatments.[9] Furthermore, the prevalence and clinical significance of LPRD-associated chronic cough remain understudied, with limited data available from small cohort studies.

The present study investigated the clinical significance of chronic cough in LPRD, evaluating its utility as a predictor of diagnostic parameters and treatment response.

METHODS

Subjects and setting

This study was a retrospective case series with prospective data on LPRD patients who were consecutively recruited from September 2017 to August 2024 in two European Hospitals (Poitiers Elsan Polyclinic and CHU Saint-Pierre of Brussels). Patients were followed by the author of the study (J.R.L.) and a retired otolaryngologist for laryngopharyngeal symptoms and findings lasting for more than 8 weeks according to the same prospective protocol. According to the Dubai consensus,[1] the LPRD diagnosis was considered for patients with more than one acidic, weakly acidic, or alkaline pharyngeal reflux events at the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing (HEMII-pH).

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Gastrointestinal (GI) endoscopy was indicated in patients with GERD symptoms and findings, history of Barrett metaplasia, and for aging patients (> 60 years). Patients were excluded if they had severe neurological or psychiatric disorders, head and neck malignancies, asthma, chronic obstructive pulmonary disease, or a history of neck radiotherapy. Specifically, patients included in this study underwent pulmonary evaluation prior to referral to the reflux clinic. Patients with active and untreated allergies (skin prick test/RAST) were excluded. Patient with a long history of treated and asymptomatic allergies were included.

The prospective protocol was approved by the ethics committee (CHU Saint-Pierre, Brussels, n°BE076201837630). Patients consented to participate. The STROBE Statement was followed for this paper.[10]

Hypopharyngeal-esophageal multi-channel intraluminal impedance-pH monitoring

The placement of the HEMII-pH probe was consistent with the Dubai Consensus Criteria and the European Guidelines for managing and treating LPRS.[1,11] The catheter was composed of eight impedance ring pairs and 2 pH electrodes (Versaflex Z®, LPR ZNID22+8R FGS 9000-17, Medtronic, Hauts-de-France, France). Six impedance segments were placed along the esophagus zones (Z1-Z6) below the upper esophageal sphincter (UES). Two pharyngeal impedance segments were placed 1 and 2 cm above the UES. The LPRD was based on the identification of more than one acidic (pH < 4.0), or nonacidic (pH ≥ 4.0) hypopharyngeal reflux events at the 24-hour HEMII-pH. A hypopharyngeal reflux event was an episode reaching the pharyngeal sensors. GERD diagnosis was based on the Lyon guidelines, which consider the diagnosis for patients with Los Angeles grade C and D esophagitis, long-segment Barrett's mucosa, peptic esophageal stricture, and acid exposure time in the distal esophagus > 6% of 24 hours.[12]

Symptoms, findings, and cough

Reflux Symptom Score (RSS)[13] and Reflux Sign Assessment (RSA)[14] were used to document LPRD and GERD symptoms and findings. The RSS evaluates frequency and severity of otolaryngological, digestive, and respiratory symptoms, and their related impact on QoL (RSS-QoL).[13] From the RSS, the "*troublesome cough*" item was used to assess cough presence (scored as 0 or 1) and severity (rated from 1 to 25). Based on score distribution, cough severity was classified as mild (1-4), moderate (5-9), or severe (> 9). The RSA signs were assessed in a blinded manner by two laryngologists (the author of this paper and the retired laryngologist), demonstrating adequate inter-rater reliability (r_s = 0.663) regarding previous studies.[14]

Therapeutic strategies and responses

The therapeutic regimen was based on the European guidelines for treating LPRD,[11] which consider a 3-month diet and standardized therapy combining proton pump inhibitor (PPI; pantoprazole 40 mg/day) with postmeal antacids (Riopan®, Takeda, Zaventem, Belgium) or alginates (Gaviscon®, Reckitt Benckiser, Slough, UK), both administered three times daily. Therapeutic regimens were prescribed according to diagnosis: GERD and acidic LPRD patients received PPI with alginate, whereas nonacidic LPRD patients were treated with alginate or magaldrate. A standardized anti-reflux dietary and lifestyle protocol was recommended for all patients.[11,15] Treatment response was evaluated using 3-month RSS changes, with the following criteria: no response (RSS increase, no change, or < 20% reduction), mild-to-moderate response (20.1%-60% RSS reduction), and high-to-complete response (60.1%-100% RSS reduction).[16]

Statistical methods

Statistical Package for the Social Sciences for Windows (SPSS version 29.0; IBM Corp, Armonk, NY) was used for statistical analyses. According to variables, the between-group differences in demographic, HEMII-pH, GI endoscopy, clinical, and therapeutic outcomes were investigated with Kruskal-Wallis test and Chi-square. The pretreatment to post treatment symptom and finding changes were assessed with the Wilcoxon Rank test. The influence of cough severity on clinical and therapeutic outcomes was investigated through the Spearman correlation coefficient, which was considered as low (k < 0.40), moderate (k = 0.40-0.60), and strong (k > 0.60), respectively. A level of significance of P < 0.05 was used.

RESULTS

The study included 523 patients [303 females (57.9%) and 220 males (42.1%)]. Of the 523 patients with LPRD, 326 (62.3%) had mild-to-severe chronic cough. In 23.5% of LPRD cases, patients judged their cough as severe using RSS. The mean ages of patients ranged from 50.3 to 52.7 years (Table 1). There were no significant differences between groups for demographics, HEMII-pH, and GI endoscopy findings. The 24-hour HEMII-pH revealed no significant differences in acid exposure time, esophageal, or pharyngeal reflux events between patients with and without chronic cough. The predominant pattern showed acidic reflux events in the distal esophagus and nonacidic reflux events in the pharynx, occurring primarily daytime and in the upright position. The GI endoscopy revealed hiatal hernia and esophagitis in 25.6%-43.3% of patients, without demonstrating significant differences across groups.

Clinical findings

Baseline symptoms and findings of patient groups are reported in Table 2. Symptom severity for otolaryngological, digestive, and non-cough respiratory manifestations demonstrated a progressive increase correlating with chronic cough severity, with the mildest presentations in patients without chronic cough and the most severe in those with severe chronic cough (Table 2). The RSA laryngeal and

TABLE 1.
Demographics and Gastrointestinal Findings

Characteristics	No-chronic cough (*N* = 197)	Chronic cough Mild (*N* = 138)	Moderate (*N* = 65)	Severe (*N* = 123)	*P* value
Mean age (range, years)	50.3 ± 15.1	51.1 ± 16.6	51.9 ± 15.4	52.7 ± 15.5	NS
Body mass index (mean, SD)	24.9 ± 4.3	24.9 ± 5.2	24.8 ± 6.9	25.6 ± 5.4	NS
Gender (*N*, %)					
Female	103 (52.3)	68 (49.3)	47 (72.3)	85 (69.1)	NS
Male	94 (47.7)	70 (50.7)	18 (27.7)	37 (30.8)	
Gastrointestinal endoscopy	*N* = 112	*N* = 90	*N* = 49	*N* = 88	
Normal	28 (25.0)	23 (25.6)	19 (38.8)	21 (23.9)	NS
Esophagitis	38 (33.9)	39 (43.3)	15 (30.6)	26 (29.5)	NS
Hiatal hernia	30 (26.8)	23 (25.6)	15 (30.6)	25 (28.4)	NS
LES insufficiency	45 (40.2)	31 (34.4)	19 (38.8)	37 (42.0)	NS
Gastritis	35 (31.2)	28 (31.1)	13 (26.5)	25 (28.4)	NS
Helicobacter pylori infection	12 (10.7)	5 (5.6)	1 (2.0)	2 (2.3)	NS
HEMII-pH feature (mean, SD)					
Distal esophageal reflux events					
Acid esophageal reflux events	38.7 ± 35.6	53.3 ± 89.1	46.1 ± 33.7	41.6 ± 41.1	NS
Nonacid esophageal reflux events	28.2 ± 25.2	28.9 ± 28.4	38.0 ± 27.0	34.9 ± 35.9	NS
Total number of distal esophageal events	63.5 ± 46.6	89.5 ± 102.8	83.2 ± 35.2	74.9 ± 53.5	NS
Pharyngeal events					
Pharyngeal acid reflux events	9.9 ± 8	10.8 ± 15.8	15.0 ± 19.5	11.6 ± 16.3	NS
Pharyngeal nonacid reflux events	27.1 ± 42.4	21.1 ± 24.9	19.0 ± 14.7	27.6 ± 63.7	NS
Total number of pharyngeal events	36.6 ± 42.0	34.6 ± 41.5	34.0 ± 21.2	38.6 ± 63.9	NS
Position events					
Pharyngeal event upright	34.2 ± 41.4	28.7 ± 29.2	30.8 ± 20.4	32.5 ± 64.2	NS
Pharyngeal event supine	4.4 ± 8.7	4.9 ± 16.0	4.7 ± 5.2	6.4 ± 10.7	NS
Number of patients with GERD (%)					NS
Acid exposure time (%)	13.4 ± 23.9	13.1 ± 19.1	11.9 ± 19.9	11.3 ± 21.9	NS

Abbreviations: GERD, gastroesophageal reflux disease; HEMII-pH, hypopharyngeal-esophageal multi-channel intraluminal impedance-pH monitoring; LES, lower esophageal sphincter; N, number; NS, nonsignificant; SD, standard deviation.

total scores were significantly higher in patients without chronic cough compared with others (Table 2).

The pretreatment to post treatment changes in symptoms and findings are reported in Table 3. The magnitude of treatment response, measured by changes (Z) in RSS and RSA scores (including otolaryngological and digestive parameters), decreased as chronic cough severity increased. Patients with severe chronic cough demonstrated significantly less improvement in their pre-to-post-treatment scores compared with those with milder or no-chronic cough. At the 3-month post treatment, significant intergroup differences persisted in total RSS and their otolaryngological and respiratory subscores, while digestive RSS subscores showed no significant variation between groups. The RSA evaluation revealed comparable scores across groups for all subscores (oral, pharyngeal, laryngeal, and total scores).

Therapeutic responses

The therapeutic response rates of patient groups are reported in Table 4. The overall therapeutic response rate was 75.1%, with group-specific rates ranging from 71.6% to 80.5%. The therapeutic response rates of patients with and without chronic cough were 75.9% and 73.8%, respectively. While the five therapeutic response subcategories showed no significant differences between groups, non-chronic cough patients tended to achieve higher complete response rates than those with chronic cough, though this difference approached but did not reach statistical significance ($P = 0.080$).

Associations

The cough severity score was significantly associated with the baseline otolaryngological RSS ($r_s = 0.335$; $P = 0.001$) and total RSS ($r_s = 0.488$; $P = 0.001$). Moreover, the cough severity score was a predictor of the 3-month otolaryngological RSS ($r_s = 203$; $P = 0.001$), and 3-month RSS ($r_s = 0.222$; $P = 0.001$). A low but significant association was found between the number of nonacid distal esophageal reflux events, and the cough severity score ($r_s = 0.146$; $P = 0.035$).

DISCUSSION

Cough has been found to be the most frequent ambulatory visit complaint across all ages in the United States.[7,17] While cough frequently manifests as acute or subacute, its persistence over 8 weeks defines it as chronic cough.[18] The

TABLE 2.
Clinical Presentation of Patients

Reflux symptom score	No-chronic cough (*N* = 197)	Chronic cough Mild (*N* = 138)	Moderate (*N* = 65)	Severe (*N* = 123)	*P* value
Otolaryngological symptoms					
1. Voice disorder	4.0 ± 6.9	5.3 ± 6.4	6.9 ± 8.0	8.0 ± 8.7	0.001
2. Throat pain	4.7 ± 7.2	6.3 ± 7.6	8.7 ± 8.5	9.3 ± 9.0	0.001
3. Odynophagia	2.5 ± 5.5	4.0 ± 5.9	4.1 ± 6.4	5.0 ± 7.1	0.001
4. Dysphagia	2.0 ± 5.2	3.6 ± 5.1	4.0 ± 5.2	6.1 ± 7.8	0.001
5. Throat clearing	6.5 ± 8.6	9.0 ± 8.2	11.7 ± 9.0	13.6 ± 9.4	0.001
6. Globus sensation	6.3 ± 8.6	7.9 ± 8.3	11.0 ± 9.7	13.5 ± 9.7	0.001
7. Excess throat mucus	8.3 ± 9.6	11.1 ± 15.7	15.1 ± 8.9	13.5 ± 9.6	0.001
8. Ear pressure/pain	2.8 ± 5.2	3.8 ± 5.7	3.9 ± 6.4	5.5 ± 7.4	0.003
9. Tongue burning	1.9 ± 5.2	3.4 ± 7.3	4.1 ± 8.0	3.5 ± 6.7	0.003
Otolaryngological score	39.2 ± 31.6	54.4 ± 37.5	69.4 ± 40.4	77.9 ± 47.8	0.001
Digestive symptoms					
1. Heartburn	6.4 ± 8.2	7.6 ± 8.2	9.7 ± 8.0	10.3 ± 9.3	0.001
2. Regurgitations or burps	3.9 ± 6.8	4.4 ± 6.0	5.6 ± 7.1	8.7 ± 9.1	0.001
3. Abdominal pain	3.7 ± 6.6	3.9 ± 6.4	4.2 ± 6.3	5.6 ± 7.8	NS
4. Diarrheas	2.3 ± 5.5	2.1 ± 4.6	3.9 ± 6.6	3.5 ± 6.5	0.040
5. Constipation	2.4 ± 5.2	2.9 ± 5.9	4.4 ± 6.6	4.0 ± 7.4	0.044
6. Indigestion	2.0 ± 4.8	2.3 ± 4.3	3.8 ± 6.4	3.5 ± 5.9	0.001
7. Abdominal distension	5.2 ± 7.6	5.9 ± 7.2	8.1 ± 7.1	8.1 ± 9.1	0.001
8. Halitosis	4.8 ± 7.9	4.4 ± 7.4	7.1 ± 8.3	5.8 ± 8.1	0.041
9. Nausea	1.6 ± 3.8	2.4 ± 5.0	3.9 ± 5.6	4.4 ± 6.6	0.001
Digestive score	32.2 ± 28.7	35.9 ± 33.0	50.8 ± 35.4	53.8 ± 41.9	0.001
Respiratory symptoms					
1. Cough after eating/lying down	0.4 ± 1.7	1.8 ± 2.1	5.6 ± 5.5	17.0 ± 8.2	0.001
2. Cough	0.0*	1.9 ± 1.4*	7.7 ± 1.9*	15.7 ± 8.1*	0.001
3. Breathing difficulties	1.9 ± 4.5	2.6 ± 5.3	3.7 ± 5.2	5.4 ± 7.5	0.001
4. Chest pain	2.7 ± 5.5	5.2 ± 7.6	6.5 ± 6.7	9.1 ± 9.4	0.001
Respiratory score	4.9 ± 9.0	11.4 ± 11.8	23.6 ± 10.0	47.1 ± 21.2	0.001
RSS total score	76.3 ± 52.6	101.8 ± 66.5	143.8 ± 70.0	178.8 ± 91.7	0.001
RSS—Quality of Life Score	22.6 ± 14.0	31.2 ± 16.4	41.3 ± 18.8	45.7 ± 20.6	0.001
Reflux Sign Assessment					
Oral score	5.4 ± 2.3	5.0 ± 2.4	5.4 ± 2.1	5.4 ± 1.9	NS
Pharyngeal score	9.0 ± 4.3	6.6 ± 4.1	8.1 ± 3.6	9.7 ± 4.3	NS
Laryngeal score	13.2 ± 5.8	8.7 ± 5.1	8.4 ± 4.9	11.5 ± 5.2	0.018
RSA total score	27.4 ± 8.4	20.0 ± 8.1	21.8 ± 6.6	25.7 ± 7.3	0.010

*Cough item was considered as the inclusion criteria. Results consist of mean and standard deviation. *Abbreviations*: NS, nonsignificant; RSA, reflux sign assessment; RSS, reflux symptom score.

prevalence of chronic cough ranges from 5.0% to 12.7% in Western country populations.[19,20]

Considering all consecutive LPRD outpatients visiting our departments over a 7-year period, the prevalence of chronic cough in LPRD patients was established to 62.3% of cases, which is substantially high compared with the findings of the literature. In a recent review, Wu et al reported that chronic cough was found in approximately 10%-59% of patients with GERD,[9] while others indicated that approximately 20% of patients with chronic cough have diagnosed with LPRD.[4,21,22] The variable prevalence rates of chronic cough among reflux populations across studies can be attributed to heterogeneous diagnostic criteria and diverse patient selection protocols. Thus, over the past decade, investigations of chronic cough prevalence in reflux patients have based the reflux diagnosis on GERD-related symptoms, GI endoscopy findings, Montreal criteria, Lyon consensus, or used nonstandardized GERD diagnostic criteria, thereby failing to distinguish between GERD and LPRD as distinct conditions.[9] To date, the pathophysiological and clinical pattern differences across GERD and LPRD are well-known, and it is not surprising to find a higher-than-expected prevalence of chronic cough in LPRD patients who predominantly do not meet GERD diagnostic criteria. The consideration of LPRD and not only GERD in patients with chronic cough makes particularly sense regarding the low rate (26%) of chronic cough patients who are managed successfully without the need for numerous investigations to find the etiology.[23]

The development of chronic cough in patients with reflux disease has long been attributed to several pathophysiological mechanisms, including microaspiration, esophageal

TABLE 3.
Pretreatment to Post Treatment Symptom and Finding Changes

Clinical outcomes	Pretreatment	3 month Post Treatment	*Z*	*P* value	Intergroup
Otolaryngological RSS					
No-chronic cough	39.2 ± 31.6	26.3 ± 29.2	−5.24	0.001	
Mild chronic cough	54.4 ± 37.5	35.5 ± 34.6	−5.18	0.001	
Moderate chronic cough	69.4 ± 40.4	37.1 ± 39.1	−4.63	0.001	0.001
Severe chronic cough	77.9 ± 47.8	48.9 ± 39.3	−4.57	0.001	
Digestive RSS					
No-chronic cough	32.2 ± 28.7	22.7 ± 25.6	−4.70	0.001	
Mild chronic cough	35.9 ± 33.0	25.0 ± 29.7	−4.58	0.001	
Moderate chronic cough	50.8 ± 35.4	22.3 ± 26.2	−4.47	0.001	NS
Severe chronic cough	53.8 ± 41.9	32.9 ± 38.3	−4.00	0.001	
Respiratory RSS					
No-chronic cough	4.9 ± 9.0	3.4 ± 7.0	−1.19	NS	
Mild chronic cough	11.4 ± 11.8	11.7 ± 17.3	−2.04	0.041	
Moderate chronic cough	23.6 ± 10.0	11.3 ± 16.0	−3.97	0.001	0.001
Severe chronic cough	47.1 ± 21.2	26.8 ± 23.5	−5.22	0.001	
RSS total score					
No-chronic cough	76.3 ± 52.6	52.4 ± 49.9	−5.44	0.001	
Mild chronic cough	101.8 ± 66.5	72.9 ± 66.6	−4.85	0.001	
Moderate chronic cough	143.8 ± 70.0	70.7 ± 73.9	−4.65	0.001	0.001
Severe chronic cough	178.8 ± 91.7	108.6 ± 88.8	−5.40	0.001	
Reflux Sign Assessment					
No-chronic cough	27.4 ± 8.5	20.6 ± 8.1	−5.19	0.001	
Mild chronic cough	27.3 ± 8.2	20.1 ± 8.1	−5.17	0.001	
Moderate chronic cough	30.0 ± 7.2	21.8 ± 6.6	−4.50	0.001	NS
Severe chronic cough	25.7 ± 7.3	21.3 ± 8.2	−3.43	0.001	

Results consist of mean and standard deviation. *Abbreviations*: RSS, reflux symptom score; Z, difference.

TABLE 4.
Therapeutic Responses

		Chronic cough			
Therapeutic response	No-chronic cough	Mild	Moderate	Severe	*P* value
No response	26.2	28.4	19.5	21.0	
Mild response	7.1	10.8	12.2	9.9	
Moderate response	13.5	19.6	19.5	22.2	NS
High response	17.5	19.6	24.4	21.0	
Complete response	35.7	21.6	24.4	25.9	

Results consist of percentages of patients among groups. *Abbreviations*: mo, month; NS, nonsignificant.

dysmotility, pepsin-induced upper aerodigestive tract mucosa injuries, and the reflex theory, which consists of stimulation of the subesophageal mucosal receptors by reflux contents, activating the cough center through the esophagus and ultimately causing the bronchial cough reflex.[24] The similarity in HEMII-pH patterns and GI endoscopy findings between LPRD patients with and without chronic cough—including predominant daytime nonacidic pharyngeal reflux events, comparable acid exposure times, and equivalent rates of esophageal abnormalities—challenges the hypothesis of GERD-induced reflex mechanisms as primary drivers of neurogenic cough. The absence of elevated digestive symptom scores in patients with chronic cough and the strong correlation between cough severity and otolaryngological symptoms (excluding cough from RSS otolaryngological subcategories) are additional observations suggesting that GERD and esophageal acid reflux irritation play a minimal role in the development of reflux-induced chronic cough.

Meta-analyses demonstrate limited efficacy of conventional reflux therapies, including PPIs, in managing reflux-induced chronic cough, with significantly lower response rates compared with classical GERD symptoms (odds ratio for clinical failure: 0.24; 95% CI: 0.04-1.27).[25] This therapeutic challenge has led some authors to consider reflux-induced chronic cough as a relatively treatment-refractory condition.[25] In this study, the therapeutic response rates were comparable between patients with chronic cough

(75.9%) and those without chronic cough (73.8%), which may be attributed to the combined use of alginates and antacids that effectively target both acidic and nonacidic reflux events. To the best of our knowledge, there is no study comparing the effectiveness of alginates, antacids versus PPIs in the management of reflux-induced chronic cough, which limits our comparison with the literature. However, in a prospective controlled study, Wilkie *et al* compared the effectiveness of PPIs versus PPIs plus Gaviscon in the management of patients with suspected LPRD.[26] The authors did not demonstrate a benefit of adding PPIs to alginate in the symptom relief of patients, including cough symptom.[26] Then, suboptimal therapeutic outcomes reported in previous studies may be attributed to the exclusive use of PPIs, which fail to address nonacidic reflux events.

The predominance of nonacidic pharyngeal reflux events in chronic cough patients may suggest a potential pathogenic role of gastroduodenal enzymes that remain active at alkaline pH. Recent preliminary data identified elastase as a key biomarker in the saliva of LPRD patients.[27] The alkaline salivary pH of LPRD patients combined to the presence of elastase in the upper aerodigestive tract mucosa may suggest that elastase and other alkaline-activated enzymes (eg, trypsin and bile acids) could contribute to respiratory mucosal injuries and subsequent symptomatology, including chronic cough. Interestingly, Sacco et al demonstrated significantly elevated elastase concentrations in bronchoalveolar lavage specimens from children with GERD compared with controls, which suggested that elastase plays an important role in GERD-associated respiratory symptomatology in pediatric populations.[28]

The large number of patients and the use of 24-hour HEMII-pH are the primary strengths of this study, addressing a critical limitation in existing literature where objective LPRD diagnostic criteria were frequently absent in the evaluation of reflux-associated chronic cough. The careful exclusion of confounding conditions associated with chronic cough, including asthma, chronic obstructive pulmonary disease, and allergy, is an additional strength.

Both RSS and RSA are nonspecific clinical instruments and, therefore, the lack of a specific patient-reported outcome questionnaire dedicated to chronic cough is the primary limitation of the present study. Moreover, some important conditions have not been explored in patients, including diet, lifestyle habits, and autonomic nerve dysfunction, which can significantly influence pharyngeal reflux event pathophysiology,[29] and the potential heterogeneous distribution across patient groups. In the present study, data of patients with asthma, lung disorders, chronic rhinosinusitis, and untreated allergy were excluded. Nevertheless, there was the possibility that some cough-associated conditions may have escaped detection through our inclusion criteria, especially neurogenic cough, inhaled irritants, or apnea. The possibility to have patients with several cough triggers may explain the less likely to respond to reflux treatment.

CONCLUSION

Chronic cough concerns a substantial proportion of LPRD patients (62.3%), with symptom severity correlating with other otolaryngological and digestive symptoms. The consideration of personalized therapy, combining PPIs, alginates, or antacids, yields favorable therapeutic outcomes (75.1%), despite attenuated symptom improvement in patients with chronic cough.

Author Contributions

Jérôme R. Lechien: Patients were recruited from the Reflux Consultation of the author of the paper. Contributions: Design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The author has no financial interest in the subject under discussion. All authors have read and approved the paper. Would you be so kind to consider this paper and send us the reviewer's comments.

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