ORIGINAL ARTICLE

Silent reflux: Ex juvantibus criteria for diagnosis and treatment of laryngeal disorders

SIMONETTA MONINI¹, ARIANNA DI STADIO², ANNARITA VESTRI³ & MAURIZIO BARBARA¹

¹Department of Neurology and Otorhinolaryngology, II Medical School, ²I Medical School and ³Department of Experimental Pathology, I Medical School, University of Rome La Sapienza, Rome, Italy

Abstract

Conclusions. Some primary laryngeal pathologies with specific clinical presentation may be related to silent laryngeal reflux. An ex adjuvantibus proton pump inhibitor (PPI) treatment may be helpful for showing evidence of such a hidden laryngeal disorder. Objective. To assess the validity of PPI as an ex adjuvantibus criterion for diagnosis and treatment of suspected reflux-associated laryngitis. Patients and methods. Sixty patients with clinical suspicion of laryngo-pharyngeal reflux (LPR) were identified on the grounds of laryngeal symptoms (dysphonia, cough, globus sensation, increased throat clearing, bad taste, and laryngeal spasm), laryngeal features (arytenoid edema/erythema, partial or total vocal fold erythema, and posterior glottic edema) with or without gastro-esophageal reflux disorder (GERD). They were consequently subdivided in three groups: type I, with LPR symptoms and features without GERD; type II with LPR symptoms and features with GERD; and type III with LPR features only. Types I and III were randomly treated with omeprazole (group A) or with immunostimulating vaccine (group B) for 3 months. Pre- and post-treatment laryngeal features and symptoms in all groups were evaluated by laryngo-stroboscopy and analyzed for statistical correlation. Results. All omeprazole-treated patients showed improvement of laryngeal features and symptoms. With PPI treatment, a more significant improvement was noticed with respect to nonspecific immunostimulant therapy. Also, patients without LPR symptoms showed improvement of laryngeal features.

Keywords: Reflux, laryngitis, omeprazole, GERD

Introduction

Much attention has recently been focused on laryngeal manifestations of gastro-esophageal reflux disorder (GERD). The relation between GERD and laryngeal signs and symptoms has been demonstrated by the presence of laryngo-pharyngeal reflux (LPR) in most patients showing posterior laryngitis [1].

Reflux-related pharyngo-laryngeal disorders, mostly due to the inflammatory reaction of laryngeal mucosa to pepsin and gastric acid, have also been described [2]. Although the GERD symptomatological profile, with heartburn and acid regurgitation, is usually observed in a minority of these patients [3], approximately 50% of patients with functional voice disorders and laryngeal signs and symptoms suffer from GERD, as shown by the 24-h pH monitoring [2,4]. In this regard, although single and double pH monitoring have been shown to be reliable and sensitive for diagnosing LPR, this sensitivity may be variable and the test itself is often not well tolerated by the patients. Thus, some reports have justified an ex adjuvantibus anti-reflux treatment in cases of suspected reflux-associated laryngitis, i.e. a treatment involving proton pump inhibitors (PPI) [5].

PPI pharmacotherapy is thought to have a site of action on sero-mucinous glands of the human larynx where H⁺/K⁺-ATPase (proton) pump has been localized [6]. A thorough clinical evaluation, with endoscopic laryngeal grading, would be likely to give more accuracy for the diagnosis of laryngeal mani-
festations of GERD and for a better indirect evaluation of the therapeutic effects [3, 7–9].

This study was designed to shed some light on LPR-related primary laryngeal disorders which may not be accompanied by symptoms, i.e. the so-called silent reflux. For this purpose, a careful diagnostic and therapeutic study was carried out for: (a) evidence of laryngeal manifestations due to both symptomatic and asymptomatic reflux; (b) comparison of ex juvantibus PPI versus nonspecific treatment.

Patients and methods

Sixty patients (43 women, 17 men; age range 22–80 years) with clinical suspicion of LPR, mainly based on laryngeal signs and/or reflux symptomatology, were recruited for this study. All of them underwent an interview to ascertain reflux-related laryngeal symptoms and GERD symptoms. Laryngeal symptoms included chronic cough, temporary or persistent dysphonia, laryngeal spasm, globus sensation, and need for repetitive throat clearing. GERD symptoms were mainly represented by heartburn and dysphagia. Patients with a clinically defined GERD, assessed through gastroscopy, videofluoroscopy, and pH monitoring, were also identified.

Laryngeal features were visualized and collected through videolaryngostroboscopic images. All the patients were examined with rigid telescopes and/or flexible nasopharyngoscopes, connected to a light source ATMOS® EndoStroboscope and to video equipment. Video recording allowed evaluation of glottic morphology and vibratory patterns of the vocal folds. Particular attention was paid to observation of the posterior glottic wall, the medial aspect of the arytenoids and the cartilaginous portion of the vocal folds, i.e. the entire posterior glottic area.

Laryngeal features included edema and erythema of the arytenoid, partial or total vocal fold erythema, edema of the membranous part of the vocal folds, edema of the cartilaginous part of the vocal fold, granulomatous reaction and thickening/edema of the posterior laryngeal wall. Each item was rated as absent or present.

Three clinical pictures of patients have been identified, as follows. Type I, with reflux-related laryngeal features and symptoms without GERD (21 patients). Type II, with reflux-related laryngeal features and symptoms with certain GERD (23 patients). Type III, with nonreflux-related laryngeal features and symptoms (16 patients).

Type I and III patients randomly underwent two types of treatment and were subsequently included in two pharmacological groups: group A (26 patients) treated with PPI; and group B (11 patients) treated with immunostimulating vaccine. Type II patients (23) were treated with PPI alone, and were included in subgroup A.

Forty-nine patients (26 from group A and 23 type II) received omeprazole 20 mg twice a day for 12 weeks. Group B received JO7AX lyophilized lisatum bacterium 50 mg sublingually, once daily for 10 days, for 3 consecutive months.

After 12 weeks of treatment, a new clinical evaluation was performed and a comparison between pre- and post-treatment findings was carried out.

Statistical analysis was used to verify the effect of omeprazole therapy versus aspecific antibacterial therapy in suspected reflux-correlated primary laryngitis. Categorical data are presented as absolute values and percentages, whereas continuous data are summarized as mean value ± SD. Kruskall-Wallis and Mann-Whitney tests were used for baseline homogeneity of symptoms between groups. Wilcoxon test was used to evaluate the efficacy of treatments. The three groups were then compared by nonparametric test (Kruskall-Wallis and Mann-Whitney) as appropriate. Differences were considered significant at p < 0.05 (two-tailed). Statistical analysis was performed with SPSS 10.0 for Windows.

Results

Symptom surveys

The most common complaints before treatment are shown in Figure 1. More specifically, they were as follows. In type I: chronic persistent dysphonia (75%), cough (75%), globus (70%) and need of throat clearing (55%), followed by heartburn (45%), dysphagia (35%) and bad taste (30%). In type II: heartburn (75%), chronic persistent dysphonia (70%), globus (58%), cough (50%), need of throat clearing (35%), bad taste (33%) and dysphagia (12%). In type III: chronic persistent disphonia (55%) and globus sensation (30%).

Videolaryngoscopy

Pre-treatment evaluation revealed laryngeal features differently distributed among the three types (Figure 2), as follows. Type I: arytenoid erythema (70%), arytenoid edema (50%) and vocal folds erythema (30%). Type II: arytenoid erythema (50%), vocal fold erythema (50%), arytenoid edema (42%), and posterior glottic edema (17%). Type III: arytenoid edema (44%), vocal fold erythema (44%), arytenoid erythema (37%), edema of membranous part of vocal fold (12.5%).
The three basal types were homogeneous for laryngeal features ($p=1.000$) and not homogeneous for laryngeal and GERD symptoms ($p=0.000$).

Group A and B results were statistically homogeneous before the therapy ($p=1.000$), whilst they were not statistically homogeneous after the treatment ($p=0.000$).

In group A ($n=49$), 100% had reflux-related laryngeal features, 73% had reflux-related laryngeal symptoms and 82% had GERD symptoms (Figure 3). After omeprazole treatment, laryngeal features improved in 93% of patients, laryngeal symptoms in 42% and GERD symptoms in 78%.

In group B ($n=11$), 100% of patients had reflux-related laryngeal features, 45% had reflux-related laryngeal symptoms and 54% had GERD symptoms (Figure 4). After immunostimulating therapy, laryngeal features improved in 54.5% of patients, laryngeal symptoms in 36% and GERD symptoms in 27%.

After therapy, groups A and B were statistically different in reflux-related laryngeal features ($p=0.005$) and GERD symptoms ($p=0.001$), and not statistically different in reflux-related laryngeal symptoms ($p=0.912$).

Pre- and post-treatment symptoms in group A were all statistically different ($p=0.000$). Pre- and post-treatment symptoms in group B were statistically different in reflux-related laryngeal features ($p=0.025$) and symptoms ($p=0.046$), but no statistical difference was found in GERD symptoms ($p=0.157$).

**Discussion**

While the presence of reflux-related pharyngo-laryngeal disorder has been widely reported, the GERD profile as heartburn and acid regurgitation usually occurs in only a minority of these patients [7]. In fact, reflux-related laryngeal manifestations, such as
recurrent dysphonia, cough, increased throat clearing and laryngeal spasm, without specific symptoms of GERD, could all be symptoms attributable to a silent LPR. Laryngeal effects of GERD are basically multifactorial: direct gastric content exposure, vagal-mediated reflex, secondary increase in throat clearing and increased laryngeal muscle tone, which may all contribute to the laryngeal disorder. The specific inflammatory reactions of the posterior laryngeal mucosa may induce a further deterioration of laryngeal symptoms [10]. Often, reflux-related laryngeal signs are the only clinically objective LPR manifestation, which otolaryngologists have the opportunity to recognize when trying to identify the etiology of suspected primary laryngeal pathologies, especially when isolated laryngeal symptoms are resistant to the common therapies.

A suspected LPR diagnosis made on the basis of evaluation of laryngeal symptoms and signs represents the rationale for applying an ex adjuvantibus anti-reflux therapy, especially in those cases without GERD symptomatology, i.e. the so-called physiological reflux [11], or diagnosed as GERD [3,7,8].

According to the recommendations of the Consensus Conference Report on LPR and the position statement of the Committee on Speech, Voice and Swallowing Disorders of the American Academy of Otolaryngology-Head and Neck Surgery [12], the empiric treatment proposed needs to be prolonged for 3–6 months. In fact, following this policy, the resolution of laryngeal features can be achieved in the majority of cases [13]. As far as PPI dosage is concerned, there is evidence of the necessity of using 20 mg twice daily, while an aggressive therapy based on high-dose pantoprazole in combination with prokinetic agents (40 mg twice daily) has also been shown to give significant benefit as regards laryngeal symptoms in LPR patients [5].

From these premises, the present investigation aimed to demonstrate that chronic laryngeal pathologies and symptoms which appear to have a primary (idiopathic) origin may be correlated to LPR,
whenever they benefit from PPI treatment rather than nonspecific anti-inflammatory therapy.

For this purpose, two pharmacological groups of patients, statistically homogeneous in the pre-treatment period, were generated randomly. After therapy, a significant difference within and between the groups was evidenced. The main differences were due to a greater improvement of laryngeal features and symptoms after omeprazole treatment than after immunostimulating/anti-inflammatory therapy. As far as GERD symptoms are concerned, they improved significantly only in group A, where the whole GERD population merged.

In contrast, the improvement of laryngeal symptoms was shown to be therapy-independent, suggesting that they may be induced from the inflammatory state only. Also, patients without laryngeal symptoms showed improvement of laryngeal features. One may thus assume that most of the primary laryngeal manifestations, even in the absence of reflux-related and GERD symptoms, are presumably related to silent LPR.

How a physiological, asymptomatic LPR becomes pathologically evident is still to be clarified. In fact, at present, it remains unknown if and how much acid exposure is required to cause laryngitis in humans. The $H^+K^+\text{-ATPase}$ (proton) pump is present in sero-mucinous glands of the laryngeal mucosa [6]. Moreover, sensory deficits of the posterior larynx have been shown to be associated with posterior laryngeal wall edema [14].

The results of the present study may shed some light which may be helpful in explaining the clinical manifestations during silent LPR. Furthermore, considering that small volumes of acid reflux, such as those observed under physiological conditions could impair the laryngeal pump, breaking down the mucosal barrier (especially when a laryngeal inflammatory process is contemporarily present), it could be hypothesized that, besides the pH of the tissues, other factors should concur for a posterior glottic lesion, such as the individual reaction of the larynx to acids. In fact, coughing and repetitive throat clearing occurring after acid exposure may themselves induce trauma and inflammatory processes in the larynx. Finally, it should not be underestimated that primary or secondary sensory deficits, by reducing the local sensitivity, may increase the chemical trauma and reduce the acid clearance from the laryngeal mucosa.

The positive ex adjuvantibus effect of omeprazole on suspected laryngeal reflux-related pathologies in patients without GERD symptoms would suggest the implication of silent LPR in the pathogenesis of many cases of supposed primary laryngitis. The rationale of the present study was to prove that this pathology is LPR-related when more responsive to PPI treatment than to nonspecific anti-inflammatory therapy. As a matter of fact, PPI therapy induced a greater and more significant improvement of laryngeal features and symptoms in the majority of the patients. Moreover, the improvement in LPR symptoms seemed to be therapy-independent, suggesting that they can be induced by the inflammatory state alone. Also, patients without LPR symptoms had improvement of laryngeal features, confirming the clinical suspicion that some supposed primary laryngeal pathologies, in absence of LPR symptomatology, are related to silent acid reflux.

As regards the therapeutic dosage, there are further considerations. The results of the present study suggest the efficacy of a 3-month therapy at a daily dosage of 20 mg. Secondly, starting from absolute percentages of improvement derived from an absent/present qualitative step for judgment of signs and symptoms, it would seem that the most frequent LPR laryngeal features significantly improve after 30 days of therapy, as was the case for posterior glottic edema, which was completely cured in almost 100% of the affected patients.

References


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