

Upper aerodigestive tract disorders and gastro-oesophageal reflux disease

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Author contributions: Ciorba A, Bianchini C and Zuolo M provided the literature search and drafted the manuscript; Feo CV wrote and revised the manuscript.

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Received: July 26, 2014

Peer-review started: July 27, 2014

First decision: August 28, 2014

Revised: September 20, 2014

Accepted: October 28, 2014

Article in press: October 29, 2014

Published online: February 16, 2015

unproven and controversial, and its treatment is then still empiric. Aim of this paper is to review the current literature on upper aerodigestive tract disorders in relation to pathologic gastro-oesophageal reflux, focusing in particular on the pathophysiology base and results of the surgical treatment of GORD.

Key words: Clinical management; Gastro-oesophageal reflux; Extraoesophageal disease; Upper aerodigestive tract disorders; Etiopathogenesis; Therapy

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Core tip: Despite a growing number of clinical evidences, the association between gastro-oesophageal reflux disease (GORD) and extraoesophageal manifestations still derives from uncontrolled studies on small groups of patients. The evidences in the literature to support the proton pump inhibitor treatment of respiratory symptoms associated with GORD, in the absence of typical symptoms of reflux (heartburn and regurgitation), are scanty. A specific diagnostic tool, of respiratory symptoms associated with GORD, is missing even if oesophageal 24-h pH monitoring has been recommended. Large and prospective studies to assess the successful outcome of antireflux therapy, as well as surgical therapy, are still missing.

Abstract

A wide variety of symptoms and diseases of the upper aerodigestive tract are associated to gastro-oesophageal reflux disease (GORD). These disorders comprise a large variety of conditions such as asthma, chronic otitis media and sinusitis, chronic cough, and laryngeal disorders including paroxysmal laryngospasm. Laryngopharyngeal reflux disease is an extraoesophageal variant of GORD that can affect the larynx and pharynx. Despite numerous research efforts, the diagnosis of laryngopharyngeal reflux often remains elusive,

Ciorba A, Bianchini C, Zuolo M, Feo CV. Upper aerodigestive tract disorders and gastro-oesophageal reflux disease. *World J Clin Cases* 2015; 3(2): 102-111 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v3/i2/102.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v3.i2.102>

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a

recognized cause of oesophageal symptoms (*i.e.*, heartburn, regurgitation, chest pain, and dysphagia) and inflammatory damages such as erosive esophagitis and intestinal metaplasia (*i.e.*, Barrett's oesophagus). The association between upper airways disease and pathologic gastro-oesophageal reflux was firstly made in 1968, when laryngeal contact ulcers and granulomas were noted to occur in patients suffering from GORD^[1,2], although the concept that GORD could have an impact on laryngeal and pharyngeal disorders has been fully developed in the last 30 years. The reported extraoesophageal manifestations of GORD include asthma, chronic cough, laryngeal disorders, chronic sinusitis, otitis media, and postnasal drip^[1]. Laryngo-pharyngeal reflux disease (LPRD) is the term suggested by some authors to define GORD beyond the oesophagus up to the laryngeal and pharyngeal level, thus causing extraoesophageal damages^[2,3]. Despite a growing number of clinical evidences to support the association between GORD and extraoesophageal disorders^[1], presently the majority of reports still derive from uncontrolled studies of small groups of patients^[1]. Nonetheless, in most of the published series, it is difficult to establish a firm connection between GORD and upper aerodigestive disorders (even within the laryngopharyngeal areas), since the presence of gastric content in supraoesophageal structures has been always difficult to document^[1,2,4].

This article reviews the current available evidence on extra-oesophageal manifestation of GORD, devoting special attention on the pathophysiology base and results of the surgical treatment of GORD, particularly in relation to aerodigestive tract disorders.

RESEARCH

The PubMed database was searched up to June 2014, for meta-analysis, systematic reviews, randomized controlled trials, and controlled trials. Full text articles were obtained when the title, abstract or keywords suggested that the study could be eligible for this review. The search was carried out independently. The search was restricted to adults, while no language restriction was applied.

The medical subject heading used included "gastroesophageal reflux", "laryngopharyngeal reflux", "gastroesophageal reflux etiopathogenesis", "extraoesophageal gastroesophageal reflux disease symptoms", "reflux laryngitis", "posterior laryngitis".

EPIDEMIOLOGY

GORD is the most common disease of the oesophagus, possibly the most frequently faced by the gastroenterologist. Surveys in the United States have shown that it affects about 20% of the population, while about half experiences heartburn as a minimum

once in a month, and 5% to 7% of the population have symptoms related to GORD every day^[2,5,6].

Also because of the many clinical variables, the true prevalence of GORD among patients with suspected upper aerodigestive disorders secondary to pathologic gastro-oesophageal reflux is difficult to determine accurately, and it varies depending on the population analysed. For instance, in a study by Koufman *et al*^[7], it has been estimated that about 10% of patients presenting to ears, nose and throat (ENT) clinician may have symptoms and/or findings related to GORD. In another study, it has also been reported that about two-thirds of laryngeal and voice disorders had either pathologic gastro-oesophageal reflux as primary cause or as a significant etiological co-factor^[8], and that the prevalence of GORD among patients with laryngeal stenosis is 78%, reflux laryngitis 60%, globus sensation 58%, and chronic cough 52%^[9,10]. In another survey, symptomatic reflux was diagnosed by pH monitoring in 30% to 60% of adults affected by asthma and chronic cough and nearly 40% of patients had endoscopic signs of esophagitis^[2,11]. More recently, a systematic review has demonstrated typical symptoms of GORD in 59% of 10491 patients with asthma^[12]. The proportion of asthma patients with GORD remained as high as 51% when more stringent criteria to prove GORD were adopted (*i.e.*, ambulatory 24-h pH monitoring). The average prevalence of asthma in patients with GORD was 4.6% as compared to 3.9% in controls. The overall odds ratio was 5.5 (95%CI: 1.9-15.8) for studies reporting the prevalence of GORD symptoms in patients with asthma and 2.3 (95%CI: 1.8-2.8) for those studies measuring the prevalence of asthma in patients with GORD. Interestingly, two studies that assessed whether GORD precedes asthma gave inconsistent results. The authors concluded that the analysis indicated a significant association between GORD and asthma, but the direction of causality remained undetermined^[12].

PATHOPHYSIOLOGY

Upper aerodigestive tract disorders from pathologic gastro-oesophageal reflux appear to be sustained either directly or secondarily. Direct injury can be due to the result of a direct contact of gastric contents with the mucosa of the extra-oesophageal structures. Alternatively, a neurally mediated vagal reflex can be stimulated by the refluxate in the oesophageal body affecting indirectly the bronchopulmonary system, thus triggering cough, bronchial constriction or laryngospasm^[6,13]. However, the evidence confirming the mechanisms of injury in LPRD is still inadequate, and in the literature very few laboratory investigations with animal models have substantiated the noxious effects of the refluxate on these anatomic sites by

both direct and indirect mechanisms^[14,15].

Certainly, microaspiration of gastric contents can occur during gastro-oesophageal reflux episodes^[16]. Direct contact of the refluxate with the mucosa of the pharynx and larynx could therefore represent the main mechanism of injury in LPRD. Unlike the distal oesophagus, the airways are not protected by anti-reflux clearance mechanisms or intrinsic mucosal properties. Moreover, it has been shown that a low lower oesophageal sphincter pressure as well as ineffective oesophageal motility may frequently be present in patients affected by GORD with associated respiratory disease (chronic cough, asthma, laryngitis)^[17,18]. It is possible that just a single reflux episode above the oesophagus can be responsible of pharyngeal, laryngeal, and respiratory disorders.

The triggering of a vagal reflex has also been proposed as a consequence of the direct aspiration of refluxed acid into the pharynx or upper airways, besides the stimulation of the distal oesophageal mucosal receptors by the refluxed gastric content^[17]. When stimulated, airway nociceptors activate protective responses such as cough and bronchospasm. It is also interesting to evidence that the pathways of some oesophageal and airway sensory nerve fibres terminate within the same regions of the central nervous system; thus, connections among oesophageal nociceptors and airway sensory nerves can exacerbate cough and the asthma-like disorders associated with GORD^[19]. So, given the common vagal innervations of lungs and oesophagus, it is not surprising that many patients with asthma and chronic cough also have GORD, and that reflux often precipitates respiratory symptoms that are clinically indistinguishable from asthma^[2,19].

Also the specific reflux agent or agents responsible for producing otolaryngology symptoms and pharyngo-laryngeal injury are currently debated^[20]. Potential candidates include gastric contents (*i.e.*, acid and pepsin) as well as duodenal contents, including both bile acids and the pancreatic enzyme trypsin. Several animal studies suggested an injurious potential for both acid gastric contents and pepsin^[2,20,21].

CLINICAL AND DIAGNOSTIC FEATURES OF AERODIGESTIVE TRACT DISORDERS RELATED TO GORD

The Montreal evidence-based global consensus, defining GORD and its constituent syndromes, recognized oesophageal syndromes and established an association between GORD and asthma, chronic cough, and laryngitis, while proposed an association with pharyngitis, sinusitis, and otitis media^[22]. The Montreal consensus also acknowledged that such extra-oesophageal disorders have a multi-factorial

aetiology and pathologic gastro-oesophageal reflux may well be a co-factor rather than a cause. Thus, patients with asthma, chronic cough or laryngitis should firstly be evaluated for causes not related to GORD, considering that extra-oesophageal syndromes rarely occur without concomitant typical symptoms of GORD^[22]. However, the diagnosis of GORD as the cause of extra-oesophageal symptoms is very challenging and relies on the following investigations.

PPI TRIAL

Traditionally, otolaryngologists have commonly used an empiric course of double dose of proton pump inhibitors (PPIs) (*i.e.*, PPI trial) to initially diagnose and treat patients with upper aerodigestive tract disorders suspected to be related to GORD, deeming the resolution of symptoms with such a treatment as diagnostic of LPRD^[3,5,6,23]. PPIs have been shown to improve asthma outcomes in terms of a significant reduction in the proportion of subjects experiencing respiratory symptoms including dyspnoea, cough, wheeze in randomized controlled trials^[24,25], although a recent meta-analysis of 11 randomized trials found only small improvements of the respiratory function in adult patients with asthma, unlikely to provide a real clinical benefit^[26]. Another meta-analysis of randomized trials by the Cochrane Collaboration regarding cough control with PPIs in GORD reported that PPIs were not better than placebo to resolve cough in such a patient, although they improved cough scores^[27]. Finally, also for suspected GORD-related chronic laryngitis a meta-analysis of randomized trials has demonstrated no advantage of PPIs vs placebo^[28]. Therefore, the evidence to support the treatment with PPIs in the absence of typical symptoms (*i.e.*, heartburn and regurgitation) or objective pathologic gastro-oesophageal reflux (*i.e.*, esophagitis on upper endoscopy or positive ambulatory pH monitoring) is scant^[29].

ENDOSCOPY

The most frequent laryngoscopic findings that have been related to reflux are oedema and erythema: (1) of the arytenoid cartilages mucosa; (2) of the interarytenoid region; and/or (3) of the posterior third of the true vocal folds (*i.e.*, posterior laryngitis). A reflux finding score based on the presence and the severity of at least eight different grades of lesions at laryngoscopy has been proposed by Belafsky *et al.*^[30] to improve the diagnostic accuracy. However, laryngoscopy has revealed laryngeal irritation in more than 80% of healthy controls prospectively evaluated^[31] and the concordance among ENT physicians for signs of reflux laryngitis is low when blindly evaluated^[32]. Thus, a causal relationship between GORD and laryngitis should not be posed

relying on laryngoscopy findings alone.

Indeed, upper endoscopy has excellent specificity for the diagnosis of GORD in the presence of erosive esophagitis^[33]; however, only one third of patients with symptoms of GORD, and even less following treatment with PPIs, have erosive esophagitis which does not establish *per se* a causal relationship between GORD and aerodigestive tract disorders^[34,35].

AMBULATORY PH MONITORING

This is the only test that can objectively demonstrate the presence of abnormal oesophageal acid exposure, characterize the reflux episodes and determine their association with symptoms. The pH monitoring has high sensitivity and specificity in the presence of erosive esophagitis (both up to 100%); but its sensitivity lowers (about 70%) in patients without erosive esophagitis, although may be increased adopting impedance pH monitoring (up to 90%)^[36,37].

The use of dual pH monitoring (with a probe at the level of the upper oesophageal sphincter) has been proposed by some authors to investigate for respiratory symptoms associated with GORD^[23,38]. However, this procedure is not universally performed due to the significant practical problems performing pH monitoring in the pharynx^[23,38].

Certainly, there is a great variability in the prevalence of abnormal pH monitoring reported in patients with asthma, chronic cough, and laryngitis^[12,39-41]. However, a negative pH monitoring may address the diagnostic investigations toward aerodigestive disorders non-related to GORD, while a positive pH monitoring establishes a diagnosis of GORD, although it does not imply that the latter is the cause of the respiratory symptoms. The temporal association between reflux episodes and respiratory symptoms may be evaluated by the symptom index (SI, *i.e.*, percentage of symptoms preceded by a drop in oesophageal pH below 4.0 within a 5-min time window divided by the total number of symptoms)^[42] and the symptom association probability (SAP, *i.e.*, statistical probability with which symptoms and reflux episodes are associated)^[43]. The patient must promptly record the symptoms, while the machine should accurately detect the reflux episodes (*i.e.*, drop in oesophageal pH below 4.0) in order to evaluate precisely the temporal association between symptoms (*i.e.*, asthma attacks or cough events) and acid reflux episodes. A positive symptom association is declared if the SI is greater than or equal to 50% (*i.e.*, at least half of the reported symptoms are preceded within a 5-min time window by an intra-oesophageal pH below 4.0) or if the SAP is greater than 95% (*i.e.*, the probability of this association having occurred by chance is less than 5%). Unfortunately, both sensitivity and specificity of symptom association analysis tools is

limited and there are no outcome studies to support treatment of extra-oesophageal GORD based on this parameter alone^[29]. Recently, Smith *et al.*^[39] by using a microphone to record cough concurrently with the pH-impedance recording, to overcome patients not always recording timely their symptoms during pH monitoring, reported 6 to 18 times more coughing than with patient reported cough, and 2 to 3 times more than relying on manometry to suppose when cough possibly occurred. If these data will be confirmed by further studies, the evaluation of the temporal association between reflux episodes and respiratory symptoms will be improved.

ASTHMA

Some authors have reported about the possible relationship between asthma and GORD, since a percentage between 30% to 80% of asthmatic patients, have been found to have GORD and/or esophagitis^[43-45]. Nonetheless, a cause effect association between GORD and asthma has not been found yet^[43-45]. Most of the reports show that GORD medical therapies such as histamine H2 antagonists or PPIs can be effective on asthma outcome^[45,46], even if such medications have not been reported to improve asthma symptoms or pulmonary function^[43-45].

Finally, on the contrary, few reports have claimed that inhaled b2 agonists and oral corticosteroids, currently used for asthma therapy, may increase oesophageal acid refluxate^[2,45-50].

CHRONIC COUGH

Chronic cough is also believed to be possibly related to GORD as proposed by several studies^[51-54]. In fact Harding^[44] and Pacheco-Galván *et al.*^[49] have reported that both, medical and surgical therapy of pathologic reflux, can improve or even resolve chronic cough in up to 51% to 100% of adult patients. Unfortunately, most of the data available in the literature come from uncontrolled studies with small sample sizes of patients, and evidences about the efficacy of therapy are still lacking. Long term follow-up studies with a large number of patients are missing.

LARYNGEAL DISORDERS

GORD is also considered to be a possible cause of laryngeal disease: it has been suggested that the aetiopathogenetic mechanism underlying laryngeal disorders, such as chronic laryngitis, could be caused by the contact of the acid refluxate with the laryngeal mucosa. Therefore, patients affected by chronic laryngitis who lack anomalies at the laryngoscopic evaluation should be addressed to a pH monitoring and gastroesophageal endoscopy in order to reveal signs of reflux^[55-57]. Some authors have already

reported that they have successfully treated with PPIs some laryngeal diseases such as chronic laryngitis as well as contact granuloma and acquired subglottic stenosis^[58-60]. In the study by El-Serag *et al.*^[61], patients treated with PPIs showed efficacious resolution of laryngeal symptoms when compared to a placebo group. Nonetheless, the small amount of patients involved, as well as the limited follow-up, represent the main drawbacks of this and of similar studies^[2,49,56,61,62].

CHRONIC SINUSITIS

Some reports have advocated GORD to have a possible role in the aetiopathogenesis of chronic sinusitis and that medical anti-reflux therapy may be useful for these patients^[63]. It has been speculated that GORD may cause sinonasal congestion and alteration of sinus drainage with consequent inflammation^[2,49,64].

PAROXYSMAL LARYNGOSPASM

Also paroxysmal laryngospasm episodes have been associated by some authors to GORD, and medical anti-reflux therapy with PPIs has been reported to be of benefit for these patients. According to the aetiopathogenic mechanism indicated by these authors, paroxysmal laryngospasm could be considered as a vagally mediated reflex response of the larynx to acid refluxate, a potentially injurious stimulus^[2,49,63,65-67].

OTITIS MEDIA

To date, there are only few reports indicating GORD as a possible cause of persistent middle ear problems (*i.e.*, otitis media with effusion). Unfortunately studies considering this specific issue, in adults and children, still are scant^[68-70].

POSSIBLE DIAGNOSTIC ALGORITHM

The diagnosis of LPRD is still very controversial, both in clinical practice and research. Most guidelines and reviews recommend starting the diagnostic work-up and treatment of patients with upper aerodigestive symptoms of GORD with an empiric trial of PPI therapy at a double dose given for at least three months^[3,5,6,23]. Traditionally, in clinical practice, otolaryngologists have considered diagnostic of LPRD the resolution of symptoms following such a PPI trial. Failure to respond, on the other hand, would indicate incorrect diagnosis of GORD or inadequate dosing or resistance to the treatment. Nonetheless, in patients who do not respond to the empirical trial, further investigations (*e.g.*, ambulatory 24-h oesophageal pH monitoring) have been recommended^[2,3,5,23].

MEDICAL TREATMENT

As stated above, PPIs are the main proposed treatment for LPRD. Caution must be used, however, interpreting the available literature, as it is hampered by studies lacking strict inclusion and diagnostic criteria investigating large populations and, consequently, inconclusive meta-analyses. Nonetheless, partial improvement of both symptoms and laryngoscopic signs of laryngitis has been reported with PPI treatment and behavioural changes. Lifestyle modifications comprise the avoidance of heavy and late meals, alcohol consumption, and smoking. Also, to elevate the head of the bed and to reduce the body weight may be beneficial^[6]. Most handbooks and reviews suggest a three-month treatment with PPIs at a double dose as the first step in the diagnosis and treatment of patients with upper aerodigestive symptoms attributed to GORD^[3,5,6,23]. Patients who do not respond, however, are indeed particularly challenging. Several factors have been suggested to explain refractory cases, such as inadequate dosing or resistance to PPIs, sensitivity to non-acid refluxate, and incorrect diagnosis of GORD. Thus, the dosages of PPIs as well as the frequency of their administration can be increased and pro-motility agents and histamine receptor antagonists may be added. Finally, in patients with signs and symptoms of LPRD despite PPIs treatment, 24-h ambulatory pH monitoring while the patient is on medication may demonstrate persistent acid refluxate due to the lack of acid control^[6].

SURGICAL TREATMENT OF AERODIGESTIVE TRACT DISORDERS RELATED TO GORD

Historical background

In 1956, Rudolph Nissen, a German surgeon, opened the era of modern anti-reflux surgery describing a complete plication of the gastric fundus around the abdominal portion of the esophagus that restored an anti-reflux barrier^[71]. The Nissen operation has been modified throughout the years, new valves around the abdominal oesophagus, either complete (360°) or partial (240°-270°) have been described, but the basic principle of the operation remained unchanged: to restore a high pressure zone (HPZ) at the gastro-oesophageal junction^[72-80]. In 1991, Dallemagne *et al.*^[81] reported the first laparoscopic anti-reflux operation. In the following decade the technique has been adopted worldwide becoming the gold standard for surgical management of GORD.

Indications and technical details

The surgical treatment of GORD is focused on restoring a HPZ at the lower oesophageal sphincter (LOS), while medication aim to modify the pH of

the refluxate. Nowadays, this purpose is achieved by a fundoplication performed laparoscopically, which offers excellent results combined with the postoperative advantage of a short hospital stay, minimal discomfort, and fast recovery time as compared to the open (*i.e.*, laparotomic) traditional operation^[82-85]. According to the 2010 guidelines of the Society of American Gastrointestinal Endoscopic Surgeons, the surgical operation should be considered in the following situations: (1) failure of medical treatment because of inadequate symptom control, persistent severe regurgitation or disturbing side effects; (2) preference of the surgical treatment despite symptom control on PPIs due to quality of life, refusal of lifelong need for medication or costs of medications; (3) presence of Barrett's oesophagus or peptic stricture; and (4) extra-oesophageal symptoms such as asthma, hoarseness, cough, and chest pain or aspiration^[86].

The surgical literature is full of eponyms of anti-reflux operations that quite often do not even correspond to the operation originally described by the authors^[87]. Therefore, it seems very reasonable to go beyond such eponyms, and stress the surgical elements, common to most of these operations, that have been shown to guarantee long term control of reflux for the patient, namely: (1) to reduce the hiatal hernia in the abdomen; (2) to mobilize extensively the oesophagus and gastro-oesophageal junction; (3) to reduce the hiatus; (4) to interrupt the gastro-splenic ligament; (5) to construct a partial or complete fundoplication of adequate length and tightness; and (6) to fix with posterior and coronal stitches the wrap^[87].

Results of anti-reflux surgery

Anti-reflux surgery (*i.e.*, fundoplication) has been shown in clinical studies to control GORD symptoms in 93% and 89% of patients after 5 years and 10 years, respectively^[82]. Surgical fundoplication restores the LOS competence and improves the oesophageal peristalsis^[88]. Of note, due to the restoration of a HPZ, the reflux control is equally effective when the patient is supine or upright^[83]. Anti-reflux surgery has been shown to be safe and effective also in elderly patients affected by GORD^[84]. In a randomized trial at a Veteran Affairs Cooperative comparing medication to anti-reflux surgery for GORD, patients on medication at 10-year follow-up in the medical therapy group as opposed to the surgical group were 92% and 62%, respectively^[89]. The surgical treatment of GORD may, however, expose patients to some morbidity and increased risk of mortality. The most common complication related to anti-reflux surgery is the so called gas-bloating syndrome, affecting 15% to 20% of patients. Recently, a meta-analysis concluded that a partial (240°) fundoplication as compared to a complete (360°) wrap was associated to less postoperative dysphagia and inability to

belch in patients undergoing surgical treatment of GORD^[90]. A Cochrane review including more than 1200 patients from four randomized trials comparing medical to surgical therapy has demonstrated higher improvements in GORD specific quality of life after surgery, although a meta-analysis of such data was not performed^[91]. Symptoms of heartburn, regurgitation, and bloating improved more after surgical fundoplication than with medication, even if small proportion of patients had persistent dysphagia after surgery. Nonetheless, the surgical operation is associated with some risk of complications and the decision to perform a surgical fundoplication needs to be thoroughly discussed with the patient.

Results on respiratory symptoms

The control of respiratory symptoms in patients with GORD undergoing anti-reflux surgery is less predictable. In the era of the open (*i.e.*, laparotomic) surgical operation, objective data regarding the ability of a fundoplication to control respiratory symptoms in patients with GORD were scarce^[92,93]. For instance, Pellegrini *et al.*^[93] reported the successful results of a complete fundoplication performed in a small group of patients in whom GORD-induced aspiration had been diagnosed. In the past two decades, due to the advent of laparoscopic anti-reflux surgery, the number of patients undergoing fundoplication for GORD has greatly increased^[87,94]. Hunter *et al.*^[94] reported resolution or improvement of respiratory symptoms in 76 out of 87 patients (87%) undergoing laparoscopic fundoplication. However, outcomes of patients with extra-oesophageal symptoms undergoing anti-reflux surgery are not always predictable. A Veteran Affairs Cooperative study, reported no significant improvement in pulmonary function tests one year after fundoplication, even in those patients presenting abnormal preoperative tests^[95]. Analogously, a randomized trial showed that both medical and surgical therapy did not increase significantly the forced expiratory volume in 1 s after 6 mo^[96]. Anti-reflux surgery can control extra-oesophageal symptoms in carefully selected patients with GORD, although these patient should be informed that the success rate is lower than in patients with typical symptoms^[97]. It is particularly important to carefully evaluate the response of such patients to PPIs, as in patients who do not respond to medications, even in the presence of oesophageal acid exposure demonstrated by pH-monitoring, the results of fundoplication are not effective^[98].

CONCLUSION

Upper aerodigestive tract disorders related to pathologic reflux appear to be a common but controversial disease, with conflicting data on pathophysiology, diagnosis, and treatment. Whereas trends are observed and many clinical practices are accepted widely on the basis

of experience, definitive, prospective, and controlled studies are strongly needed^[2,6].

Also considering the possible implication of GORD in the development of supra-oesophageal neoplasms, as advocated by several investigators, more efforts are necessary to support the relation between extra-oesophageal disorders and GORD, in terms of prospective randomized trials^[2].

A better comprehension of the physiopathological mechanisms of these conditions can help clinicians in the management of such patients. In particular, further large randomized-controlled trials in order to clarify LPRD pathophysiology, as well as to evaluate diagnostic algorithms and treatment approaches could be then particularly useful for the diagnosis and the management these disorders.

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DOI: 10.1016/j.cgh.2006.01.011]

P- Reviewer: Dumitrascu DL, Figura N, Nishio K
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