

RELATIONSHIP BETWEEN GASTROESOPHAGEAL REFLUX AND RESPIRATORY MANIFESTATIONS, FROM THE PEDIATRIC GASTROENTEROLOGIST'S POINT OF VIEW

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ABSTRACT

Gastroesophageal reflux is a frequent condition in the daily life of infants and older children. When reflux causes symptoms, it is called gastroesophageal reflux disease. Different extraesophageal symptoms have been frequently attributed to gastroesophageal reflux, however, new diagnostic techniques available, such as pH metry with impedance measurement, have allowed us to evaluate and eventually dismiss such relationships. In this article, we review the relationship between gastroesophageal reflux and laryngeal pathology, chronic cough, asthma and aspiration. In general terms, the empirical treatment of a presumed reflux is not recommended in asymptomatic patients, in who's its presence is not demonstrated by techniques such as pH metry with impedance, given that therapeutic response is low and similar to placebo, with potential adverse effects.

Keywords: gastroesophageal reflux, respiratory aspiration, asthma, children.

INTRODUCTION

Gastroesophageal reflux (GER) is defined as the retrograde passage of contents from the stomach into the esophagus. It is a phenomenon that occurs daily even in healthy people, however when it produces annoying symptoms or health consequences, it is called gastroesophageal reflux disease (GERD) (1). A recent meta-analysis shows that GERD can occur in about 19% of children older than 10 years of age (2).

In infants, GER is a common phenomenon, affecting about 25% of those under 6 months and much more if only one episode of daily regurgitation is considered (2). This decreases over time and in most cases does not constitute a disease, defined within the ROME IV criteria as regurgitations of the infant (3).

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GERD can manifest itself at the digestive level due to its classically associated symptoms: heartburn and regurgitation. Occasionally it can produce dysphagia, retrosternal pain and even hematemesis. In young children who do not verbalize, it can manifest as food rejection, crying after episodes of reflux, abnormal postures of cervical hyperextension, among others. It can also cause erosive lesions in the esophagus secondary to excessive exposure to acid, but also to other components such as bile and pepsin, even reaching esophageal stenosis and Barrett's esophagus.

New entities are currently recognized regarding esophageal symptoms, where there is a continuum between the damage caused by reflux, and visceral hypersensitivity phenomena: erosive esophagitis, non-erosive reflux disease, reflux hypersensitivity and functional heartburn, whose characteristics are described in table 1 (4).

Different symptoms and extraesophageal manifestations have been related to reflux. In this article, the respiratory manifestations associated with gastroesophageal reflux, the available evidence on their association and treatment will be reviewed.

Table 1. Characteristics of the different entities associated with gastroesophageal reflux and symptoms. GERD: gastroesophageal reflux disease.

	Erosive esophagitis	Non-erosive GERD	Hypersensitivity to reflux	Functional heartburn
Esophageal exposure to reflux at pathological levels	Yes	Yes	No	No
Symptoms associated with reflux episodes	Yes or No	Yes o No	Yes	No
Esophageal erosions in endoscopy	Yes	No	No	No

PULMONARY MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX

This review will address the symptoms and laryngeal manifestations, chronic cough, asthma and aspiration. We will begin with a description of the diagnostic studies that are usually used in patients with GERD, and that have allowed us to clarify the role of reflux in these manifestations.

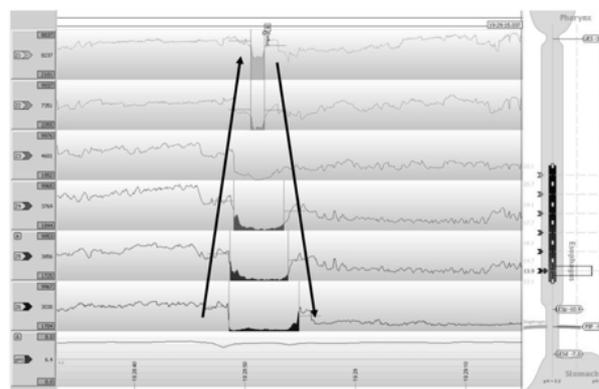
Diagnostic methods of GERD

There is not a single study or gold standard to diagnose GERD, so the diagnostic strategy must adapt to the unique characteristics of each patient.

In the study of GER, an esophageal pH measurement was initially used, in which, through a probe with a pH sensor, inserted through the nose with its distal end in the esophagus (or stomach, according to the measurements of interest), the retrograde passage of acid content was measured. Subsequently, the multichannel intraluminal impedance measurement (IIM) was added, which allows additional evaluation of the passage of liquid, gaseous or mixed content, regardless of its pH (Figure 1). From this, the content of acid and non-acid reflux has been classified (which includes weakly acidic and alkaline reflux). This is important for some age groups such as infants, in whom a large part of the symptoms are caused by non-acid reflux, which could not be detected by a conventional pH metry. The main use of these studies is in the correlation with symptoms, as will be described later. The currently accepted indications of pH-IIM are described in Table 2.

High digestive endoscopy allows direct visualization of the damage caused in the mucous membrane due to reflux, however GERD can exist without mucosal lesions. It also allows for the evaluation of suggestive signs of other pathologies, such as esophageal stenosis and achalasia, and also for obtaining biopsy samples, important for differential diagnosis with eosinophilic esophagitis, a pathology that usually occurs more frequently in patients with a history of atopy and asthma (Table 2). Digestive endoscopy is considered to have a low sensitivity, but high specificity for the diagnosis of reflux (5).

Figure 1. Reflux episode in pH-IIM (pH metry with multichannel intraluminal impedanceometry). Impedance curves fall in all measurement channels. The arrows show the direction of the esophageal content, in this case, from distal to proximal (reflux) and then from proximal to distal (lightening of reflux). In this case, it is an episode of non-acid reflux.



Another study commonly used is contrast radiography, such as esophageal-stomach-duodenal x-rays or esophagogram. These studies allow to detect anatomical alterations that can predispose to gastroesophageal reflux (hiatal hernia, esophageal stricture, intestinal malrotation, pyloric stenosis, duodenal membrane, extrinsic compression, etc.). Although its report usually includes the description of reflux when presented during the test, it should not be used for the diagnosis of GERD (6), given its low sensitivity and specificity (51 and 58%, respectively in a pediatric study) (7). In addition, it exposes the patient to radiation and the detection rate of malformations is low, so it is not recommended routinely in the evaluation of patients with reflux, but is when the suspicion of anatomical alterations is high.

Gastric emptying scan or scintigraphy is used in patients with suspected gastroparesis, for example, patients with delayed postprandial vomiting, who may have a greater

Table 2. Indications to perform pH metry-IIM (multichannel intraluminal impedance measurement) and upper digestive endoscopy. BRUE: brief resolved unexplained event.

Indications to perform pH metry-IIM
<ol style="list-style-type: none"> 1. Differentiate patients with non-erosive esophagitis, esophageal hypersensitivity and functional heartburn. 2. Determine the efficacy of acid suppression therapy. 3. Evaluate the correlation of extra-esophageal symptoms with acid or non-acid reflux. <ul style="list-style-type: none"> • Respiratory symptoms <ul style="list-style-type: none"> - BRUE - Respiratory symptoms that do not respond to therapy • Other extra-esophageal symptoms <ul style="list-style-type: none"> - Sandifer type postures - Unexplained crying - Erosion of tooth enamel associated with neurological diseases - Unexplained laryngeal inflammation
Indications for performing upper digestive endoscopy (related to GER)
<ol style="list-style-type: none"> 1. Presence of alarm symptoms 2. Detect reflux complications: stenosis, Barrett's esophagus 3. Detect conditions that predispose to reflux (eg hiatal hernia) 4. Detect conditions that appear similar to reflux (eg eosinophilic esophagitis, infectious esophagitis)

predisposition to reflux. An adaptation of this test allows evaluating episodes of passage of gastric contents to the airway in patients with suspected aspiration. The test consists in the administration of food (milk or water) with tracers such as ^{99m}Tc detecting activity with gamma cameras during a period of about 120 minutes. However, the technique is not well standardized in different centers, and there are no normal values for children; there are few pediatric studies and the technique has a limited capacity to detect aspiration episodes (8).

Pepsin levels in tracheal or saliva secretion have also been used for the evaluation of patients with respiratory manifestations attributed to reflux or aspiration, however pepsin production is present not only in the stomach, but in other organs, including lungs. A recent study with salivary pepsin showed elevated levels in healthy infants (9). Pepsin isoform A could be useful because of its greater specificity for the stomach, however there is still a need for further development of the technique and studies that evaluate it (10).

The percentage of Lipid laden macrophages in bronchoalveolar lavage has not shown to be useful and is no longer used as a marker for aspiration evaluation (1,11).

GERD and BRUE in infants

The brief resolved unexplained event (BRUE) is often attributed to GERD. In the vast majority of cases the attribution is clinically made and not based on studies or evaluations performed by a gastroenterologist (12). In infants evaluated

by pH-IIM, it has been shown that in up to 85% of cases there is reflux at pathological levels, but only in 11-42% of cases, there is also a temporary and eventually causal relationship between reflux and BRUE / apnea. These episodes are mostly non-acidic, so a pH metry measurement on its own would be insufficient in the study (13).

GERD and laryngeal manifestations

There are a number of findings in laryngeal examinations that have been attributed to reflux (called pharyngolaryngeal reflux); some of them can be found frequently in healthy adults (14). Given the above, a scale of reflux findings denominated Reflux Finding Score, RFS has been developed, based on the evaluation of 8 items related to laryngeal inflammation: subglottic edema, ventricular obliteration, erythema / hyperemia, posterior commissure hypertrophy, granuloma/granulation tissue, and thick endolaryngeal mucus, with different cut-off points to improve sensitivity and specificity regarding the reflux diagnosis (15). However, a pediatric study conducted at a world reference center for aerodigestive pathology showed a poor interobserver correlation of RFS, as well as poor performance as a diagnostic study when comparing with reflux diagnosed by pH-IIM, with 95% sensitivity but 9% specificity when considering a cut-off point > 7 of the score, or an unacceptably low sensitivity of 14% and specificity of 95% with cut-off point > 16 (16). On the other hand, adult patients with nasofibroscope findings suggestive of reflux have a low response to proton pump inhibitor (PPI) treatment, close to 40% and similar to the

placebo response (17). Therefore, it is suggested that the diagnosis of reflux in children should not be based only on the findings of nasofibroscope, thus avoiding the prolonged and unnecessary use of PPI, with the potential side effects that are still being described in the literature (18).

GERD and chronic cough

Chronic cough has long been attributed without an obvious cause to the presence of GERD. From the point of view of biological plausibility, both the airway and the esophagus have a common embryonic origin, and share innervation pathways through the vagus. Given the above, the rise in gastric contents can stimulate nerve terminals proximally, and secondarily induce cough reflex, without necessarily reflux reaching the airway. In adults with chronic cough, it has even been shown that the lack of response to PPI is associated with a low sensitivity threshold to trigger cough reflex. On the other hand, a patient with chronic cough frequently has episodes of positive abdominal pressure, with a rise in secondary gastric contents.

To evaluate the relationship between cough and reflux, the measurement of pH metry-IIM is useful. In this, a temporary relationship between the reflux episodes and cough is sought, through statistical methods, however its main problem is the failure to report each cough episode (up to 90%) (19), both by the patient, in the case of older children, or caregivers. This is why other methods have been added to detect coughing episodes, such as gastric pressure measurement (manometry) or sound recording, which are scarcely available in daily clinical practice. Through studies that include the latter methods, it has been found that among children with chronic unexplained cough, about 40% have GERD, both acidic and non-acidic (13).

A recently published evidence-based clinical guide suggests NOT empirically treating GERD in pediatric patients with chronic cough if they have no symptoms, manifestations or study compatible with this pathology (high digestive endoscopy, pH-IIM) (20), given the low effectiveness of the treatment and the potentiality of associated adverse effects. In patients who do have symptoms, manifestations or study compatible with GERD, treatment is suggested according to current GERD guidelines (1) and reassess the response to therapy after 4-8 weeks.

GERD and asthma

Reflux and asthma are two phenomena that can occur frequently, and therefore can coexist in the same patient. High frequency (up to 80%, but generally around 40-50%) of reflux has been described in asthmatic patients, through pH metry studies (21). There are two theories that would explain this higher frequency: The reflux theory, in which the refluxed material would reach the airway in the form of micro-aspiration, and the reflection theory, similar to what is already described in the previous paragraph, given the common embryonic origin, proximal reflux would stimulate receptors of vagal routes, with effectors at a bronchial level, causing bronchoconstriction (5). On the other hand, obesity

is a common, important and frequently present risk factor in patients with asthma and reflux. Physical factors, such as the greater negative pressure exerted on the esophagus during inspiration in patients with poorly controlled asthma, and positive pressure on the abdomen during expiration and cough, promote the passage of gastric contents in retrograde form. In addition, the use of medications for the treatment of asthma affects the anti-reflux effect of the gastroesophageal junction.

Despite what has been described, treatment with PPI has not been useful in improving asthma control in children without evidence of reflux, so its empirical use in this latter group of patients is not recommended (1).

GERD and aspiration

In a patient with impaired airway defense mechanisms (for example, patients with neurological pathology, vocal cord paralysis, etc.), reflux may be a factor that aggravates respiratory episodes. However, in these patients GER may not be the only condition, but also esophageal motility disorders that prevent the downward passage of swallowed content, including esophageal achalasia or cricopharyngeal dysfunction, evaluable through an esophageal manometry, in which pharyngeal retention occurs and subsequent airway passage of the swallowed material. Other alterations of esophageal motility, such as esophageal achalasia or esophageal atresia, can make it difficult for the bolus to reach the stomach, or promote the permanence of food at the esophageal and pharyngeal level (22). In some of these cases, reflux treatment through the use of PPIs does not reduce the risk of aspiration pneumonia, since the risk of aspiration of oral content persists, and it has been associated more frequently to respiratory infections but this remains to be non-conclusive evidence

TREATMENT

Treatment of GERD depends on each patient and the characteristics of the reflux. Acid reflux could benefit from PPI use. However, its use has shown that mainly the pH of the refluxed acid content changes to non-acidic, without necessarily reducing its volume or frequency (23). This consideration is particularly important in the case of GERD in infants and newborns, where the use of PPI has not shown to be useful in reducing reflux episodes. Its main use is in the improvement of reflux esophagitis. Current existing guidelines of the North American and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (1), recommend the use of PPIs (omeprazole, esomeprazole, lansoprazole) or type 2 histaminergic receptor antagonists (such as ranitidine and famotidine) in patients with typical reflux symptoms or tests that support the diagnosis (such as pH metry-IIM). As already mentioned above, the use of PPI has a very limited utility in extraesophageal manifestations such as chronic cough and poorly controlled asthma, with a response very similar to that of a placebo.

CONCLUSIONS

Gastroesophageal reflux disease is a common pathology in the pediatric population, which may occasionally have extra digestive manifestations. Frequently, respiratory symptoms and particularly larynx are over-attributed to GERD, and results of current PPI treatment are not optimal.

Empirical reflux treatment is not recommended in patients with extraesophageal symptoms attributed to this condition, without clinical evidence or GERD tests.

Conflicts of interest

I declare no conflicts of interest.

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