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GASTROESOPHAGEAL REFLUX DISEASE'S IMPACT ON CHILDREN'S HEALTH

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ABSTRACT

Gastroesophageal reflux becomes pathologic when the reflux episodes determine bothering symptoms and or complications. It is a pathology seen both in adults and children; in pediatric patients is a frequent reason for medical visits because of its symptoms that are bothersome both for children and caregivers, especially in infants. Usually, symptoms frequency declines by the age of one year old but when it persists practitioners must intervene with both general measures and medical treatment. The diagnostic is mainly clinical, but when other pathologies that can determine gastroesophageal reflux must pe excluded, imaging methods and esophageal pH measurement can be used.

Key words: Gastroesophageal reflux; children; gastroesophageal reflux disease; pediatrics

INTRODUCTION

In human subjects of all ages, the physiological phenomenon of retrograde movement of gastric contents into the esophageal lumen that occurs on a daily basis, with or without regurgitation or vomiting, is called gastroesophageal reflux (1). This gastric activity is maintained in physiological parameters by three mechanisms: the anti-reflux barrier (composed of the lower esophageal sphincter, the crural diaphragm, the angle of His and the phrenoesophageal ligament), mechanical esophageal clearance (which through peristaltic moves and alkaline pH of saliva shortens the contact time between the gastric contents and the esophageal cellular tissue) and esophageal mucosal resistance (2,3). When these mechanisms are overcome, the physiological process turns into a pathological one, gastroesophageal reflux becomes gastroesophageal reflux disease (GERD), which is defined by the presence of symptoms that disrupt daily activities and/or the presence of complications (1).

PATHOGENESIS OF GERD

In children, especially those under the age of 6 months, GERD appears as the result of a number of factors, determined by the body's continuous development at these young ages. Therefore, the physiological immaturity of LES, the exclusively liquid diet from the first months of life, the predominantly horizontal position (4), a smaller esophageal capacity, shorter intraabdominal portion of the esophagus and last but not least, the greater volume of food ingested relative to the individual body weight compared to an adult (5) are all elements that contribute to the

pathogenesis of this disease in different proportions.

At older ages, a number of other factors intervene to facilitate the occurrence of GERD, such as medication for other existing pathologies. It is known that calcium channel blockers, nitroglycerin, anticholinergics, beta-adrenergic agonists, aminophyllines and benzodiazepines have a relaxing effect on smooth muscle, thus lowering the pressure in the lower esophageal sphincter (LES). (6). While most of these drugs are more frequently seen in the chronic treatment of the adult (7), there are certain substances that are commonly used in the pediatric population's treatment too, this being the case for asthmatic children. This pathology can be exacerbated by esophageal reflux or reflux can lead to cases refractory to specific asthma treatment. (8,9). At the same time, the decrease in LES's tonus produced by the antiasthmatic treatment can cause episodes of reflux that over time, cumulatively increase the risk of esophageal adenocarcinoma, thus creating o vicious circle in which two pathologies from two anatomical sites influence each other. (6,10).

Another element that contributes to the occurrence of reflux episodes is the digestive microbiome. Physiologically, the specific microbiome for the esophagus is predominantly represented by gram-positive bacteria, most of which belong to the *Streptoccocus* species; when there is a disruption of the microbiota, with the development of gram-negative bacteria in greater proportion at the esophageal level, the lipopolysaccharides in the bacterial wall can cause a decrease in the LES's tonus through the subsequent production of nitric oxide at the cellular level in this portion of the esophagus, facilitating gastric reflux (11,12). This can be the case of children born through cesarean section, in which the microbiota they inherit and develop is similar to their mother's skin, this modification leading to an increased risk of developing certain pathologies modulated by the microbiome (13).

Regarding the relationship with other digestive pathologies, the results of studies on the role of *H. pylori* infection in the pathogenesis of GERD are contradictory. On one hand, it is considered that the alkalizing effect that the bacteria produce in the stomach through the development of chronic atrophic gastritis would protect against acid reflux episodes in the esophagus (12,14). On the other hand, a series of studies did not identify changes from a statistical point of view in the case of patients infected with *H. pylori* simultaneously with the presence of GERD versus patients with GERD tested negative for *H. pylori* (15). Researchers also tried to identify a relationship between location of gastritis in patients with concomitant *H. pylori* infection and GERD, their studies showing that there is a pattern in gastritis in conjunction with GERD (16). Since *H. pylori* infection is a pathology acquired predominantly in the first 5 years of life, studies show a high rate of infection among pediatric patients (17,18), with multiple unwanted effects in the case of symptomatic patients, not only in the digestive tract, where it determines manifestations with potential of chronicity and induction of other pathological entities in the adult life (19), but can also be associated with liver cytolysis (20), headache (21) and at the hematological level, being a possible cause in the occurrence of immune thrombocytopenia (22) or iron deficiency anemia (23,24). Data on the relationship between GERD and *H. pylori* leave room for new studies, especially among pediatric patients.

MANIFESTATIONS OF GERD

GERD has repercussions in almost the

entire human body; the disorders that the acid reflux produces can be grouped into esophageal and extraesophageal manifestations. In the first category, in addition to the typical reflux syndrome, there are reflux strictures, reflux esophagitis, Barrett's esophagus and last but not least esophageal carcinoma (25). If the last two entities are less common in children, as a prolonged exposure of the esophageal mucosa to the action of acidic gastric juice is necessary, reflux esophagitis is a frequently diagnosed pathology among pediatric patients presenting with symptoms of esophageal reflux, having different degrees of mucosal damage, usually A or B, most likely due to the short period of evolution of GERD until the time of investigation by upper digestive endoscopy (26).

In addition to the esophageal manifestations of reflux, we also encounter a series of entities grouped in extraesophageal syndromes, in turn divided into established associations and proposed associations. In the first subcategory were brought together reflux dental erosion syndrome, reflux asthma syndrome, reflux laryngitis syndrome and reflux cough syndrome (25).

As mentioned previously, asthma has been shown to be related to GERD through the prism of two mechanisms for producing asthma-specific changes. The direct mechanism would be that of the action of gastric content on the bronchial structures, and the indirect one when, by stimulating the endings of the vagus nerve located at the level of the lower part of the esophagus, a response is also produced at respiratory tissue level, causing bronchoconstriction (27). Unlike adults, in the case of pediatric patients, we must mention that the occurrence of recurrent wheezing is modulated in the same way, an independent pathology specific for the pediatric age, more often found in preschool children that often precedes asthma (28).

Through similar mechanisms, reflux laryngitis and reflux cough are produced, being often treated as respiratory or allergic pathology but for which, when treatment with proton pump inhibitors is initiated, an improvement is noted until the disappearance of symptoms, thus being a method of diagnosing GERD as a triggering agent of these respiratory manifestations (29).

Another entity in the category of extraesophageal manifestations is represented by the disorders produced in the oral cavity. Exposure to acidic gastric content determines an erosion of the dental surfaces with demineralization, thus exposing the tooth to all the processes that occur in the oral cavity, all the bacterial flora and exogenous substances that enter the oral cavity. Also, bruxism, which can be triggered by GERD, especially nocturnal episodes, can additionally contribute to the destruction of the teeth (30,31).

One must not neglect the fact that GERD can also lead to iron deficiency anemia in some cases, through impaired absorption of iron due to reflux episodes or chronic treatment with proton pump inhibitor but also because of the small bleedings that occur when GERD determines esophagitis lesions (32).

Last but not least, some of the presenting symptoms of GERD, like dysphagia, may be so bothersome that can lead to impairment of eating habits determining avoidance of certain types of food groups which can further lead to nutritional deficiencies if the gastroesophageal reflux disease evolves for too long (33). This whole process can lead to various ailments, from diseases of the oral cavity, to neurological disorders, of the immune system, of the osteoarticular system and so on, depending on the most deficient nutrient. Certain groups of patients may be at higher risk for nutritional deficiencies, for example children with cerebral palsy that associate GERD, in which their food intake pattern can affected by GERD induced

symptoms. (34) Then, when looking forward into adulthood, a case of GERD left untreated or poorly treated or on chronic treatment with proton pump inhibitors can severely impact the health at older ages (35).

DIAGNOSIS OF GERD

In pediatric patients, the symptoms vary and are sometimes similar to those present in other age-specific pathologies, this fact complicating the diagnostic process. However, depending on age, there are small differences regarding the pattern of symptoms. For children under 5 years of age, GERD is usually manifested by repeated vomiting, weight stagnation or weight loss, refusal to eat, intermittent abdominal pain, repeated respiratory infections, odynophagia, sleep disorders or psychomotor agitation (5), recurrent wheezing and asthmatic manifestations, dentition damage, iron deficiency anemia refractory to treatment. After the age of 6-8 years old, when the child cand verbalize and has a better developed sense of his own person, can describe the symptoms more precisely, these being similar to those of adults with GERD, of which we list: heartburn, pain in the upper abdominal floor or retrosternal pain during the day or at night, dysphagia, cough especially at night, hoarseness, halitosis. Of course, repeated respiratory infections, dentition damage, sleep disorders, irritability may also occur, as in younger children (36).

Usually, the diagnosis of GERD is based on a detailed medical history and a detailed physical examination. Paraclinical investigations are usually used to exclude the pathologies that enter the differential diagnosis of this disease. At the same time, the lack of a gold standard regarding the diagnosis of this pathology makes it difficult to identify the true value of its prevalence.

In 2019, Singendonk et al published the first literature review that also covered the 0-18 years age group regarding the prevalence of GERD. The authors identified the presence of GERD symptoms in over a quarter of the pediatric patients included in the selected studied, with the progressive decrease in the number of cases towards the age of 1 year. More precisely, the results of the review showed that the prevalence of symptoms varies widely, from 0% to 38% within the studies included, and regarding the percentage depending on the weekly or monthly presence of manifestations, it was found that they were reported in over 10% or 25% of cases (37).

The diagnosis of this pathology in pediatric patients is difficult to establish, especially in small children, usually under the age of 8, who cannot identify and communicate very clearly the disturbing symptoms. The diagnosis is currently based on the 2018 joint recommendations of ESPGHAN and NASPGHAN.

In particular, we must remember the fact that physiological reflux appears between the ages of 1 week to 6 months, therefore any manifestations occurring outside this age interval can only exceptionally be considered normal. Classically, an infant with frequent episodes of vomiting or regurgitation can be diagnosed with GERD only after taking a medical history and making a thorough physical examination, more difficult being the cases of infants with a satisfactory weight curve, in which vomiting is absent, the only manifestation being the common and nonspecific signs and symptoms such as irritability, arching of the back, inconsolable crying (1).

For children older than 1 year, with frequent vomiting and regurgitation, the use of paraclinical investigations helps to quantify and classify GERD, but are also a support for the practitioner when it is necessary to exclude other pathologies that can mimic GERD such as food allergies, hiatal hernia, hepatitis, renal

tubular acidosis, urinary tract infection, irritable bowel syndrome (36).

One of the imaging studies, considered the method of choice in the beginning, is barium contrast imaging. Although studies have shown that it does not help in diagnosing more cases of GERD compared to the ones diagnosed through clinical examination and medical history, it remains a method used mostly to identify potential anatomical anomalies that may have similar manifestations to GERD or may ultimately cause GERD that does not respond to treatment (i.e. tracheoesophageal fistula, hiatal hernia, pyloric stenosis, esophageal stenosis, Schatzki's ring, achalasia, extrinsic masses that determine compression on the esophagus). However, it is not a very reliable method in terms of capturing anatomical details, so it is used less and less in daily clinical practice, being gradually replaced by dynamic imaging of swallowing using magnetic resonance imaging, which is gaining ground in practice, both for the diagnosis of GERD and for monitoring the effectiveness of the treatment (1,38).

Esophageal pH-metry was used for the first time for the diagnosis of GERD in 1969 and then considered the gold standard for diagnosis in the '80s. Even it is still the most accessible method used it does have some limitations, mainly due to the fact that it cannot sense reflux episodes with a pH greater than 4, a feature frequently seen in children. In this age category it also poorly corelates reflux episodes with the presence of symptoms due to the inability of small children to report them, thus making it inappropriate in diagnosing extraesophageal syndromes (1). Despite these limitations, pH-metry is still useful in the GERD diagnosis scheme; for example, when used in combination with upper digestive endoscopy, it has been shown that it helps to evaluate the lesions produced by the acid content on the mucosal damage. When we refer to the scores used in pH-metry, in the case of pediatric patients, the most suitable is the Boix-Ochoa score, having high specificity and sensitivity (39).

A more specific diagnostic method based on pH measurement is pH-impedance monitoring. It can precisely detect reflux episodes with pH lower and greater than 4, that contain both liquid or gas and it can also differentiate between drops in pH due to reflux versus swallow-related pH drops. These features give pH impedance monitoring a greater sensitivity compared to that of pH-metry, making it useful especially in children and infants in whom non-acid reflux episodes are more frequent, due to pattern of feedings. Despite all this, the technique is not frequently used due to the fact that is not available everywhere, making pH-metry the most used diagnostic method (40).

TREATMENT FOR GERD

The treatment of this pathology first aims the lifestyle and dietary changes, at all pediatric ages. The general measures involve: avoiding large volume meals in favor for smaller and more frequent ones, maintaining a vertical position for at least 30 minutes after a meal, keeping an interval of approximately 2 hours between dinner and bedtime, avoiding wearing tight clothing, especially in the abdomen area, maintaining an adequate body weight (36). Caregivers must be educated that certain types of foods, like spices, carbonated drinks, vegetables with high acidity can trigger acid reflux episodes therefore must be avoided or kept to a minimum. They must be reassured that it is not necessary to develop a phobia for certain food groups, as children need a balanced diet to ensure both the age-appropriate energy intake and all the nutrients for a harmonious development (41).

After general measures have been implemented, depending on the targeted age

category, the guidelines recommend different treatment schemes. In general, like the treatment of GERD in adults, the pharmaceutical class used is represented by proton pump inhibitors (PPI). First of all, in patients aged between 1 month and 1 year, before starting the administration of PPIs, other nonpharmacological therapeutic measures are recommended; here we have the use of thickened milk formulas or the thickening of meals in infants who already eat solids, avoiding bulky meals, eliminating cow's milk from the diet for 2 to 4 weeks and performing allergy test to detect a possible allergy to cow's milk proteins, as this pathology frequently associates GER (42,43). Also, since these children have long periods of time in which they sit in a horizontal position due to their motor immaturity, it is recommended to keep them in the left lateral position, both during sleep and when awake. If these measures do not work, treatment with PPI will be started, esomeprazole being the molecule approved for use in children under 12 months of age, and omeprazole for children over 1 year of age, in short courses of 4 to 8 weeks, in age-appropriate doses (1,44).

It should be taken into account that there are numerous adverse effects reported in the use of PPIs, especially for long periods of time, such as hypochlorhydria, headache, diarrhea or constipation, vomiting, manifestations that may occur in approximately 14% of pediatric patients. The hypochlorhydria induced by these drugs further disrupts the intestinal microbiota, with the induction of intestinal bacterial proliferations in approximately 25% of children (44,45). There are also more marked adverse effects, such as respiratory or digestive tract infections, which involve increased risks especially for patients with other associated pathologies, such as those with cystic fibrosis (46). For those cases that require chronic treatment with PPIs, laparoscopic surgery cand be a therapeutic measure, in order to avoid the unwanted adverse effects of the medication (47).

CONCLUSIONS

Frequent regurgitation is one of the main causes of concern in parents of infants and one of the main reasons they seek for medical help. Most children will become asymptomatic when they pass the infant stage, but for those that still present with vomiting or regurgitation, poor weight gain, respiratory symptoms that do not resolve under specific treatment, the diagnosis of GERD must be taken into account, as this pathology can further impact their wellbeing and development, leading to chronical medical conditions into adult life.

AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript. AAR, ALC, TIL, GS, MAM, LSG, RAB, DCG contributed equally with AMLB to this article.

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