Abstract

Objective: to discuss clinical, diagnostic and therapeutic aspects of gastroesophageal reflux.

Method: we accomplished a literature review of the last 30 years, by means of Lilacs and Medline databases.

Results: the gastroesophageal reflux is one of the most frequent causes of medical appointments with pediatric gastroenterologists. It represents a benign condition, characterized by regurgitations that can be resolved with general measures. Medical management with prokinetics and antacid agents controls clinical manifestations and prevents complications. Fundoplication is reserved to a minority of cases.

Comments: some aspects of the clinical treatment have to be emphasized. Thickened/Solid diet and erect posture must be always recommended. Cisapride, the most commonly employed prokinetic agent, may prolong ventricular repolarization. Other prokinetic agents should be used in children. Bronchospasm or clinical manifestations of esophagitis indicate the use of antacid drugs.

Gastroesophageal reflux

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Introduction

Gastroesophageal reflux (GER) can be defined as the retrograde and repetitive flux of gastric content for the esophagus. It is frequent in children, and usually presents a benign evolution. It is characterized by the presence of regurgitations. Besides abdominal pain and intestinal constipation, it constitutes one of the main reasons of appointments with pediatric gastroenterologists.

Most part of the cases corresponds to physiological reflux, resulting from the immaturity of the antireflux barrier mechanisms. Although it is likely to evolve with life-threatening conditions, such as apnea crises, the physiological reflux usually presents a satisfactory evolution, not compromising the child’s growth and development. On the other hand, the pathological reflux presents clinical repercussions, such as growth deficit, abdominal pain, irritability, digestive hemorrhages, bronchospasm, repeated pneumonia, ototorhinolaryngological complications, which require capacity on the diagnosis and attention on the choice of the most adequate treatment to each case.

Epidemiology

GER is surely one of the main gastroenterological conditions among children. Although predominant in males, the difference between the sexes is not statistically significant.¹ It is estimated that among children that present regurgitation at a frequency that worries the parents, only 2% will require investigation, and 0.4% will require surgery.¹

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GER classification

GER may be physiological or pathological, primary or secondary, and, still, occult.

Physiological GER is more common in the first months of life. Among older children and adults, it may occur in the postprandial period, due to the transient lower esophageal sphincter relaxation. Regurgitations arise between the birth and 4 months of age, usually presenting spontaneous resolution up to 1 or 2 years of age. In these cases, the child’s growth is normal, and there are no other symptoms or associated complications. The frequency of regurgitations decreases after 6 months of age, coinciding with the introduction of a solid diet and with the adoption of a more erect posture by the child.

Pathological GER may be suspected when the vomits and regurgitations do not improve after 6 months of age, when they do not respond to postural and dietetic measures, and when clinical repercussions are present, such as growth stoppage or symptoms and signs that suggest esophagitis. The reflux is denominated occult when respiratory, otorrinolaryngological, or esophagitis-indicating manifestations (irritability, constant cry) occur at the absence of vomits and regurgitations.

Primary GER results from dysfunction of the esophagogastric junction. Secondary GER is associated with specific conditions, such as esophageal congenital stenosis, tracheoesophageal fistula, esophageal atresia, deglutition disorders, hypertrophic pyloric stenosis, gastric or duodenal ulcer, annular pancreas, intestinal pseudoobstruction, cow’s milk allergy, urinary infection, intestinal parasitoses, genetic-metabolic diseases, asthma, cystic fibrosis, and alterations in the central nervous system.

Pathophysiology

The esophagogastric region presents several structures that contribute to the antireflux barrier: lower esophageal sphincter (LES), angle of His, phrenoesophageal ligament, crural diaphragm and gastric rosette.

LES is a circular smooth muscle segment at the terminal esophagus, adapted to generate a high-pressure zone, which may range from 15 to 40 mmHg. LES maturation starts at the first weeks of intra-uterine life, and continues during the whole first year of life. Its extension measures around 2.5 to 3.5 cm in the adult, with equal supra and infradiaphragmatic portions. In the newborn, it measures 0.5 to 1.0 cm, and is predominantly located in the thorax. The characteristics change after 3 months of age, with the development process.

The phrenoesophageal ligament is constituted by the subdiaphragmatic fascia, and its function is to impede that the LES is submitted to negative intrathoracic pressure.

The diaphragmatic hiatus is formed by fibers of the right crus of the diaphragm, the place through which the esophagus penetrates the abdomen. During inspiration, the diaphragmatic hiatus is contracted, increasing the intraluminal pressure of the esophagogastric junction and impeding the reflux.

The angle of His is formed by the abdominal esophagus and the gastric fundus. In normal conditions, this angle is acute. So, the volume of gastric content increases the pressure at the abdominal esophagus by extrinsic compression, resulting from the stomach fund distension. In the newborn, this angle is obtuse.

The gastric rosette, formed by concentric plicae of the gastric mucosa in the transition between the esophagus and the stomach, helps in the continence of the gastric content, avoiding its passage to the esophagus.

In young children, because of immaturity of some components of the antireflux barrier, vomits and regurgitations are common, but they tend to improve with aging. Adults also present reflux episodes in the postprandial period, without any clinical repercussions. The reduction of regurgitations and vomits is expected to happen at the age of 4 to 6 months, with the introduction of solid food and the adoption of a more erect posture, resulting from the advance in the neuropsychomotor development.

The reflux disease, or pathological disease, is multifactorial and affects the LES function, the esophageal peristalsis, and the gastric emptying.

The LES pressure is considered an important element of the antireflux barrier, although its hypotonia is not a frequent cause of reflux. In a study involving children presenting reflux, a reduction of the LES tonus at 8% in cases of esophagitis was shown.

Transient lower esophageal sphincter relaxation consists of short episodes of abrupt reduction in the LES pressure. They are probably mediated by the action of inhibitory vasoactive peptides and/or of the nitric acid. Transient lower esophageal sphincter relaxation lasting more than 35 seconds and independent of normal peristaltic waves is observed in 60 to 83% of reflux episodes.

Increase in the stomach volume, abnormal motor function of the gastric fundus and retardation of its emptying may be involved in the reflux etiopathogenesis. The gaseous gastric distension is an important cause of transient lower esophageal sphincter relaxation, probably after vagal stimulus.

The retardation of esophagus emptying, possibly associated with the inefficacy of salivation and peristalsis, seems to be important for the development of reflux esophagitis. Studies with animals showed that the lesion of the esophageal mucosa occurs when the pH remains below 4. The presence of gastric acid alters the esophageal defenses, and, consequently, causes mucosal lesion. Pepsin and bile salts increase the gravity of damages.

Hiatal hernias seem to have a relation with the gravity and refractivity to the clinical treatment of reflux esophagitis. Permanent increase of the intra-abdominal pressure (obesity) or its transitory increase (deep inspiration, coughing, physical exercises, Valsalva manoeuvre, constipation and others),
besides posture predominantly in decubitus, are factors that predispose to reflux.

GER may cause chronic respiratory disease through three mechanisms: aspiration of significant quantities of gastric content into the superior airways and lungs, causing aspiration pneumonia; aspiration of small quantities of gastric content, causing secondary inflammatory reaction; and intratracheal acidification, which, by the stimulus of nervous endings, may cause bronchospasm.

Clinical status

Depending on the patient’s age during the first symptoms, GER may have several meanings and clinical courses. There are two forms of presentation: in children and in adults. In the first case, the symptoms appear during the first months of life and improve up to 12-24 months in 80% of the cases. The second type may be a continuation of the first one, or appear later; it has persistent symptoms and usually requires treatment.

The clinical manifestations may be: specific, such as ruminations, vomits, regurgitations, eructation, related to esophagitis, such as pain, anemia, and bleeding; respiratory, such as bronchospasm and repeated pneumonia; otorhinolaryngological, such as laryngitis, sinusitis, otitis, and others.

Vomits and regurgitations are present in most children with GER, mainly in the postprandial period. Regurgitation may be defined as the involuntary return of a small quantity of gastric or esophageal content to the pharynx and the mouth. It may be distinguished from vomit for the absence of gastric or esophageal content to the pharynx and the mouth. It may be defined as the involuntary return of a small quantity of gastric or esophageal content to the pharynx and the mouth. It may be distinguished from vomit for the absence of gastric or esophageal content to the pharynx and the mouth.

The presence of esophagitis may be suspected through the transient lower esophageal sphincter relaxations, which occur after deglutition, during gastric distention, or during the performance of the examination. It is possible to establish a zone of high pressure at the LES does not assure the absence of reflux.

Diagnosis

The diagnosis of GER should start with the elaboration of the complete clinical history. Clinical history of regurgitations in young children, without other complaints and without alterations on the physical examination, suggests the diagnosis of physiological GER. In these cases, there is no need for any complementary examination, and clinical follow-up is recommended. Symptoms and signs such as insufficient gain of weight, irritability, constant crying, evident or occult digestive bleeding, persistent bronchospasm, repeated pneumonia, and recurrent otorhinolaryngological symptoms may be manifestations of pathological GER. For the confirmation, there are several complementary examinations available, and each of them presents its specificity.

Esophagus, stomach and duodenum radiograph

This is the most used examination for the assessment of GER, for there are not more specific and sensitive procedures available. It presents a sensitivity of 50 to 65%. It may be false positive due to the transient lower esophageal sphincter relaxations, which occurs after deglutition, during gastric distention, or during the performance of the examination. The short period of observation is responsible for 10 to 15% of false negative results. It is useful for the detection of anatomic abnormalities, deglutition disorders, intestinal malrotation, intestinal obstruction, tracheoesophageal fistula, hiatal hernia, and motility disorders. The dynamic study may show motility alterations and the presence of stomach spasms, which may be related to GER.

Manometry

Esophageal manometry is difficult to be performed in children, since it requires the patient’s collaboration. It does not diagnose the presence of GER, for a zone of high pressure at the LES does not assure the absence of reflux.
The LES pressure is normally higher than 15 mmHg; so, values below 6 mmHg may indicate the presence of GER.

**Scintigraphy**

Scintigraphy is performed after the oral administration of technetium, obtaining images through a gamma counter. It is not invasive, causes low exposition to radiation, and is adequate to evaluate gastric emptying and the presence of pulmonary aspiration in late imaging.

**Esophagus ultrasonography**

This noninvasive examination has been recommended for the diagnosis of occult GER, neutral refluxes, and for the determination of gastric emptying time. It also allows the study of stomach motility. Its only inconvenience is the short period of observation used by the technique.

**Upper digestive endoscopy and esophageal biopsy**

In children, this invasive examination requires sedation or anesthesia in order to be performed. It does not diagnose reflux, but the associated esophagitis. It may also identify stenosis zones, Barrett esophagus and hiatal hernia. There are over 30 classifications for endoscopic alterations found in the esophagus, but none is universally accepted. The presence of erosions or ulcerations at the terminal esophagus confirms the endoscopic diagnosis of esophagitis.

The esophagus biopsy should be performed in all the patients with suspicion of esophagitis, although some authors consider it unnecessary in cases without endoscopic esophagitis. In 1970, Ismail-Beigi described histological alterations resulting from gastroesophageal reflux: papillae growing longer than 60% of the epithelium thickness, small number of intraepithelial neutrophils and eosinophils (<5/field). A number of eosinophils superior to 15 per field of great enhancement suggests eosinophilic esophagitis. Barrett esophagus, which is characterized by the presence of intestinal metaplasia at the esophagus, is a premalignant condition, little frequent in the pediatric group.

**Esophagus pH monitoring (pH-metry)**

Normal esophageal pH ranges from 5 to 7; when it goes below 4, it suggests acid reflux. The esophageal pH monitoring documents the esophagus acidification during prolonged periods, with the patient carrying out his/her usual activities. The examination sensitivity ranges from 87 to 93%, and its specificity, from 92.9 to 97%. It is indicated in unusual presentations of GER, characterized by difficult-to-control chronic respiratory disease, rumination, Sandifer syndrome, apnea, risk of sudden death, growth deficit, difficult-to-control iron deficiency anemia, pharyngeal itching, thoracic pain of noncardiologic origin, and less common symptoms. It is also indicated to evaluate the patient’s response to clinical and surgical treatment. The performance of pH-metry is necessary in patients with endoscopically proved esophagitis.

The main indicators vary according to the predominant symptomatology, but the rate of reflux (total % of the time during which pH was below 4) is considered highly important in almost all cases, being related to esophagitis and to cases of apnea. The area under the curve of pH<4 has been related to the presence of esophagitis. The values considered normal, according to Johnson & DeMeester, are presented in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Data obtained through pH-metry</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of episodes with pH&lt;4 in 24 h</td>
<td>50</td>
</tr>
<tr>
<td>% of time with pH&lt;4</td>
<td>&lt; 4.2%</td>
</tr>
<tr>
<td>% of time with pH&lt;4 in the erect position</td>
<td>&lt; 6.3%</td>
</tr>
<tr>
<td>% of time with pH&lt;4 in the supine position</td>
<td>&lt; 1.22%</td>
</tr>
<tr>
<td>No. of episodes of reflux lasting for &gt;5 minutes in 24 h</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Duration of the longest episode of reflux (pH&lt;4)</td>
<td>&lt; 9.2 min</td>
</tr>
</tbody>
</table>

Alkaline GER prevalence is not known yet. Alkaline GER is suspected in children that present pH values over 7 on pH-metry. In these patients, an investigation directed to the alkaline GER should be performed.

**Modiffed Bernstein Test**

Bernstein’s test was originally used for the diagnosis of esophagitis. The esophagitis symptoms were provoked in the patient through the instillation of acid and saline solution in the distal esophagus. The modified Bernstein test is useful to determine the relationship between GER and respiratory symptoms through the instillation of acid and saline solution in the esophagus.

**Intraluminal impendacementry**

This examination permits the determination of episodes of physiological pH reflux. Together with pH-metry, it is worthwhile in the assessment of respiratory manifestations in gastroesophageal reflux.

**Differential diagnosis**

The clinical manifestations of GER are variable and related not only to the digestive tract. This way, the differential diagnosis is extensive, and includes mechanical obstructions of the upper digestive tract, alimentary allergies,
especially to the cow’s milk protein, infectious and neurological diseases, bronchial hyperreactivity, peptic ulcer, colic, and other causes of irritability in the infant.

**Treatment**

The reflux, depending on the predominant form of presentation, may require general measures, drug treatment, or surgery. The objectives of the treatment are relief of symptoms, healing of the established esophageal lesions, as well as prevention of complications. General measures should be recommended in all cases. Drugs are indicated for patients with the reflux disease (pathological reflux), or as a testing treatment in some specific situations, for short periods. Surgery should be left for cases that are refractory to the clinical treatment, or for situations that involve risk of death.1

**General measures**

**Orientation to parents**

Regurgitations, when not accompanied by complications, constitute a transitory process, related to the immaturity of the gastrointestinal tract. Families sometimes may consider it a serious problem. This way, the first step consists of listening to the parents, without underestimating their complaints. They should receive simple explanations about the nature, natural evolution, prognosis, and treatment of the disease. Sometimes, after an adequate orientation, the regurgitation frequency decreases.

**Dietary recommendations**

The dietary modifications proposed to reduce the episodes of GER should respect the child’s nutritional needs. Among the recommended measures, milk thickening is greatly efficacious.1 Solid diet is known to reduce the number of episodes of reflux. However, the duration of the longer episode may increase, making the efficacy of the esophageal emptying more difficult. In some patients with esophagitis or respiratory manifestations, this may intensify the symptomatology.15 Anyway, the buffer effect of the food over the gastric acidity would avoid the intensification of the esophageal lesion.

Foods and drugs that decrease the LES tonus or that increase the gastric acidity, such as fat foods, citric fruit, tomatoes, coffee, alcohol, smoking, as well as anticholinergic and adrenergic drugs, xanthine, prostaglandin and calcium channel blockers, for example, should be avoided whenever possible.

**Posture**

In general, the head is recommended to be elevated at 30 degrees, and the child should be kept erect in the postprandial period. No study has shown efficacy of lower elevations.15

**Drug treatment**

The use of drugs is reserved for the cases of pathological reflux. In some situations, they may be used empirically and for short periods.1

**Prokinetics**

Combined with dietetic and postural measures, the prokinetics are important therapeutic tools in the treatment of GER. They determine an increase in the LES pressure, and stimulate esophageal peristalsis and gastric emptying.

Cisapride acts as a serotonin postganglionic agonist. It is derived from benzamide, and its action seems to result in the liberation of acetylcholine into the myenteric plexus. The use of cisapride was allowed in 1988, and it is available in more than 90 countries since then.30 It has a half-life of 7 to 19 hours, and it is metabolized by the hepatic enzymatic system (cytochrome P450 CYP3A4). Cisapride improves motility in all the gastrointestinal tract, facilitates antroduodenal coordination, accelerates gastric emptying and increases LES pressure.15 Side effects are in general transitory, and include colic, diarrhea, and cephalae.15 There are reports of more serious reactions:15 alterations in the central nervous system (extrapiramidal reactions and seizures), cholestasis in preterms (preterms present decreased action of the cytochromes), cardiac alterations (QT interval prolongation, characterizing prolonged ventricular repolarization). Although cisapride is the most used prokinetic in GER,15,31 recently, because of the adverse cardiovascular effects, the European Society of Pediatric Gastroenterology and Nutrition published recommendations for its utilization: cisapride dosages should not be higher than 0.8 mg/kg/day (maximum of 40 mg/day), and should be divided into three of four daily administrations. It is contraindicated in the following situations: use of macrolide antibiotics (clarithromycin, erythromycin, azithromycin), benzimidazoles (fluconazole, ketoconazole,itraconazole), protease inhibitors (antiretroviral), phenotiazine (promethazine), antiarhythmics, antidepressives, antipsychotics, and other agents, even orange juice.33 So, preference should be given to the use of prokinetic drugs, which cause less adverse effects.

Domperidone is a peripheral dopaminergic antagonist, without cholinergic effects. It does not cause hematoencephalic reactions. Maximum concentrations of the drug occur 10 minutes after oral administration. It presents hepatic and intestinal metabolism, as well as renal and intestinal excretion, with a half-life of approximately 7 hours. It increases esophageal peristalsis and improves the antroduodenal motility. It rarely causes side effects, such as dry mouth, cutaneous eruption, diarrhea, and transitory itching. It may cause potent prolactin secretion, causing an enlargement of the mammas, galactorrhea, and amenorrhea. It is as efficacious
as metoclopramide, and has less side effects. The recommended dosage is 0.2 to 0.6 mg/kg/dosage, three to four times a day, before meals and when going to bed. Its highest efficacy may be reached after the 4th week of usage.

Metoclopramide acts peripherally, increasing the action of acetylcholine in muscarinic synapses, and antagonizing dopamine in the central nervous system. It increases LES pressure, facilitates gastric emptying, improves esophageal motility through the action of gastrin. They increase the gastric content, and, consequently, increase gastric motility through the action of gastrin. They increase the pressure at the lower portion of the esophagus and the esophageal depuration by an independent mechanism of gastrin. They are recommended for the symptomatic relief in patients with light and moderate esophagitis.

Histamine H2-receptor antagonists compete with the histamine for H2-receptors, inhibiting the gastric secretion of acid induced by histamine or other H2 agonists (muscarinic agonists and gastrin). The H2-receptor antagonists available to use are cimetidine, ranitidine, famotidine, and nizatidine. These drugs are almost totally absorbed orally. The recommended dosages are 5 to 10 mg/kg of cimetidine, four times a day before meals and before going to bed, and 5 mg/kg of ranitidine, twice a day. There has not been enough experience with the prolonged use of famotidine yet.

H+ channel blockers represent a class of drugs as safe as the H2-receptor antagonists. They are the most potent inhibitors of acid secretion.

Omeprazole is a benzimidazole that inhibits the enzyme responsible for the transportation of hydrogen ions to the stomach light. They have a prolonged action, even when blood levels are not detectable anymore. One only dosage may eliminate over 90% of the acid secretion in 24 hours. Dosages of 0.7 to 3.3 mg/kg/day, with an average dosage of 1.9 mg/kg/day, have been recommended. It is a labile drug, composed by granules of enteric absorption, with 1-2 mm diameter, which dissolve at pH>6, allowing duodenal absorption. The maximum plasmatic concentrations occur 1 to 3 hours after oral medication, so that the administration is recommended to happen before the first meal in the morning. In case of pediatric administration, the granules are separated and administrated with acid fruit juice.

Surgical treatment

The antireflux surgery (gastric fundoplication) is one of the three most performed surgeries in children in the United States. The Nissen technique is the most used in the world, and, more recently, videolaparoscopy has been gaining adhesions, especially because of the lower risk for complications and the shorter time of recovery. The antireflux surgery should be reserved to patients that do not respond to clinical treatment and/or present life-threatening conditions. After the appearance of more potent prokinetic agents and acid secretion inhibitors, the role of surgery as a definite therapeutic resource for the complicated reflux has been questioned. The best option for the long-term treatment of children with esophagitis, be it either surgery or clinical treatment, still has to be defined. Besides the high cost, surgery presents high recidivism rates. On the other hand, the clinical treatment demands adhesion and comprehension on the family’s part, and it also has associated side effects. Aiming to prevent complications, the therapeutic option may be always individualized, and the clinical follow-up should be prolonged.

References


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