Gastroesophageal reflux disease (GERD) is the most common esophageal disorder and the most frequent reason why infants are referred to the pediatric gastroenterologist, affecting as much as 30% of the pediatric population. Presenting features of GERD in infants and children are quite variable and follow patterns of gastrointestinal and extra-esophageal manifestations that vary between individual patients and may change according to age. Patients may be minimally symptomatic, or may exhibit severe esophagitis, bleeding, nutritional failure, or severe respiratory problems.

GERD is also complex for the diagnostic techniques required to assess its repercussions or explain its origin. Although different abnormalities in motility variables, such as lower esophageal sphincter (LES) function, esophageal peristalsis and gastric motor activity can contribute to the development of GERD, the degree of esophageal acid exposure represents the key factor in its pathogenesis.

Esophageal pH monitoring, based on both the detection of acid reflux episodes and the measurement of their frequency and duration, has been regarded as the most sensitive and specific diagnostic tool for diagnosing reflux disease. The aim of this paper is to give a concise review for the clinicians encountering this specific disease in infants and children.

Key words: GERD, children, pH study

INTRODUCTION

Physiologic gastroesophageal reflux represents a highly prevalent condition in childhood. Gastroesophageal reflux disease (GERD), meaning reflux with a complication present, is less so. The challenges facing the clinician are to distinguish the physiologic from the pathologic, to decide whether to investigate and/or to treat at all, and if so, how to do so.

In infants, gastroesophageal reflux (GER) most commonly manifests as regurgitation, vomiting or "spitting up". These symptoms occur in up to 67% of infants, around age 4 to 5 months, declining rapidly to 21% by age of 6 to 7 months (development of neuromuscular lower esophageal sphincter control), and less than 5% by 12 months. Based on pH probe studies, only 8% of healthy infants younger than 1 year have abnormal reflux. Thus, in the great majority of infants, reflux is "physiologic", and it will be outgrown. Symptoms of GER abate without treatment in 60% of infants by 2 years of age, as these infants begin to assume an upright position and eat solid foods. The remaining may have symptoms until 4 years of age. Nevertheless those infants who had daily or problematic regurgitation were more likely to have feeding problems within the second year of life, even though their regurgitation had seemingly resolved. The prevalence of GERD symptoms in children 3-18 years of age vary from 1.8% to 22%.

However, despite its frequency and, theoretically, its customary mildness, GER has a complex pathology and is therefore not easily manageable. As a matter of fact, GER may give origin to disabling and even severe extraesophageal conditions: recurrent otitis, which may lead to decreased hearing ability, pulmonary pathology, which may result in severe disabling asthma and as consequence, respiratory failure and specific pediatric diseases that may sometimes range from severe to extremely severe. Furthermore, this pathology may also lead to esophageal complications such as reflux esophagitis, peptic stenosis or even Barrett’s esophagus. Needless to say, such relevance requires accurate evaluation.

GER in infants and children is classified as follows: 1) functional, 2) pathogenic (GERD) and 3) secondary. Patients with functional GER have no underlying predisposing factors or conditions. Growth and development in these patients are normal, and treatment is typically not necessary. Patients with pathogenic GER, meaning GERD, frequently experience complications, including esophagitis, bleeding, strictures, malnutrition, respiratory distress,
and changes in the normal epithelial lining of the lower esophagus. Patients require careful evaluation and treatment. Patients with secondary GER refer to a cases in which an underlying conditions, predisposes to GER. Examples include esophageal hiatal hernias and gastric outlet obstruction.

**PATHOGENESIS**

Pathogenesis of GERD is complex, resulting from an imbalance between defensive factors protecting the esophagus (antireflux barriers, esophageal clearance and tissue resistance) and aggressive factors from the stomach content (gastric acidity, volume and duodenogastric reflux). Transient relaxation of the lower esophageal sphincter (TRLES) is currently believed to be the main pathologic mechanism of GER, accounting for up to 94% of reflux episodes in children and adults. Decreased gastric compliance is believed to lead to TRLES at lower intragastric volumes in infants. This aspect in conjunction with abdominal wall muscle contraction (if it occurs during periods of LES relaxation) propels refluxate into the esophagus with subsequent regurgitation.

Anatomic factors that also can predispose to GER include:

1) Obtuse angle of His (made by esophagus and the axis of the stomach). It is especially dominant in newborns, when it is called chalasia, but the angle tends to decrease as infants develop. Angle of His is also severely altered in infants operated for esophageal atresia (up to 80% of patients have GERD);

2) The presence of esophageal hiatal hernia. Hiatal hernia displaces the LES into the thoracic cavity, therefore facilitating GER by the negative intrathoracic pressure. Hiatal hernia by itself does not indicate the presence of GER, because many patients who have hiatal hernia do not have GER;

3) Resistance to gastric outflow. Impaired gastric outflow raises intragastric pressure and leads to reflux and vomiting. Examples include motility disorders (delayed gastric emptying, gastroparesis), especially dominant in premature infants, and gastric outlet obstruction (pyloric spasm, stenosis, antral web). Other factors that predispose to GER include: medications (Theophylline), poor dietary habits (overeating, eating late at night, assuming a supine position shortly after eating), food allergies, certain foods (greasy, highly acidic), etc.

**SYMPTOMS**

Presenting features of gastroesophageal reflux in infants and children are quite variable, and follow the patterns of esophageal and extra-esophageal manifestations that vary between individual patients and may change according to age. Patients may be minimally symptomatic, or may exhibit severe heartburn, bleeding, nutritional failure, or respiratory problems. Complexity of symptoms in patients with GERD may also derive from its multiple clinical presentations, which are in some cases obvious, as in the presence of postprandial regurgitations, although more often they are difficult to interpret, as in the case of painful colicky pain suggestive of esophagitis. The clinical manifestations may be more complex to interpret if the child seems to have no digestive symptoms at all. In addition, the clinical profile may become extremely complicated if upper respiratory or pulmonary symptoms prevail, or if more general symptoms, such as faintness, or allergic manifestations, such as rhinitis or asthma are present.

There are also more subtle forms of GERD, presenting as failure to thrive alone or associated with behavioral and/or feeding problems. In addition to these various clinical pictures, there are those described in patients with diseases classically complicated by reflux disease: mentally and physically handicapped children, those affected by paraplegia, spastic conditions, where an insidious reflux is an important cofactor of morbidity. The already long list

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**TABLE 1**

<table>
<thead>
<tr>
<th>Gastrointestinal features</th>
<th>Respiratory symptoms</th>
<th>General features</th>
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<tbody>
<tr>
<td>Painless regurgitation</td>
<td>Wheezing</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Chronic cough</td>
<td>Insufficient weight gain</td>
</tr>
<tr>
<td>Epigastric or thoracic pain</td>
<td>Esophagosom-stridor</td>
<td>Irritability</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>Bronchospasm</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Reanimation</td>
<td>Apnea</td>
<td>Crying</td>
</tr>
<tr>
<td>Rejection</td>
<td>Asthma</td>
<td>Hypotony</td>
</tr>
<tr>
<td>Sensation of lump in the throat</td>
<td>Laryngitis</td>
<td>Seizures</td>
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<tr>
<td></td>
<td>Choking</td>
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<td></td>
<td>Bronchitis</td>
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of complications due to reflux disease continues to grow, since in addition to the classical ones described above, we should add conjunctivitis, dental, lingual, gingival or vocal involvement, muscular conditions (torticollis) and probably some personality troubles.

The symptoms produced by GER in infancy and in childhood can best be divided into four groups: gastrointestinal, respiratory, systemic and miscellaneous (Table 1).

As many as 65% of patients may present with multiple symptoms. Gastrointestinal clinical presentations vary with age: regurgitation or vomiting is the most common clinical findings in infants and small children, whereas in older children and adults GER presents more frequently with heartburn and retrosternal pain. Most infants and children with GER are referred for evaluation because of acute or chronic respiratory complications. At present a causal relation between GER and respiratory disorders is not completely accepted, although the clinical experience reported by many authors seems to prove that treatment of GER can eliminate the respiratory symptoms in many patients. Recurrent aspiration leads to coughing, choking, and other respiratory complications depending on the volume of refluxed fluid and the frequency of reflux episodes.

Insufficient weight gain or failure to thrive has also been very closely identified with GERD. The first postulated mechanism for failure to thrive is a significant calorie deficit due to persistent vomiting, while the second is the child’s refusal to eat as a consequence of the symptoms of esophagitis. An alternative explanation for the failure to grow may be a protein-losing enteropathy secondary to the inflammatory changes in the esophagus. Such infants tend to be pale, thin, hypoactive, listless, and underweight, and usually improve promptly and dramatically after surgery. Constant irritability (infantile heartburn) or sleep disturbance are commonly related to esophagitis in infancy. These babies present as fussy, irritable, or "colicky". Crying is a very common complaint of parents.

Conditions mimicking GERD, and associated with high incidence of problems, include dietary protein allergy, eosinophilic esophagitis, hypertrophic pyloric stenosis, reflux esophagitis, and gastroparesis. In conclusion regarding the symptomatology of patients with GERD, it is of the utmost importance that the diagnosis of GER must be based on a complete history and structural as well as functional diagnostics, that also can include an evaluation of symptom diary.

**DIAGNOSIS**

The large number of tests are available for evaluation of the children with suspected GERD. For appropriate evaluation of these patients, a special diagnostic algorithm must be performed starting with the structural (barium meal, endoscopy) and followed by the functional (manometry, pH study, scintigraphy and impedance) diagnostic tests. Unfortunately, the diagnosis of GERD in children is often made in the later stages of the disease, when the complications such as aspiration pneumonia, esophagitis, or peptic stenosis develop. Early recognition and interventions by primary care physicians is necessary to prevent such serious complications of untreated GER.

Barium swallow is the first step in performing adequate diagnostics, but it has a very low specificity rate because many infants who have little or no clinical symptoms of reflux, do have some degree of barium reflux into the esophagus. The major radiologic features regarding the use of barium swallow in the diagnostic work-up of GER focus on the demonstration of the anatomo-pathologic substrate, the event of reflux and its complications such as esophagitis or strictures, and on the demonstration of a hiatal hernia. Other important elements that can be seen by barium swallow are presence of atypical anatomic causes of recurrent vomiting (pyloric stenosis, antral or duodenal web).

Foregut endoscopy represents the diagnostic mainstay of complicated forms of GERD. Endoscopy allows direct visualization of the esophageal mucosa for determining the severity of reflux esophagitis as well as the presence of hiatal hernia (that is often missed by barium swallow). Biopsy specimens having eosinophilic infiltrates have been found to be specific indicators of reflux esophagitis in infants.

Esophageal stationary manometry is a diagnostic tool that provides both a qualitative and quantitative assessment of esophageal motor functions, measuring intraluminal pressures and coordination of pressure activity of esophageal body and its two sphincters. Manometric studies in the infants are difficult to perform and have proven of little clinical use. In older children having GERD symptoms stationary manometry must be a part of standard evaluation. It is important to emphasize that symptoms arising from esophageal mucosal disease or abnormal esophageal motility can be very similar to those of GERD. Detected manometric abnormalities in patients with GERD include impaired peristalsis, lower esophageal sphincter (LES) hypotension, and high rate of TRLES. Esophageal pH monitoring is the most sensitive and specific diagnostic tool for diagnosing reflux disease, and today represents a "golden standard" of evaluation in all children having GERD. The use of thin, flexible probes that are able to detect pH in the distal esophagus has created an inexpensive way to accurately detect the amount of acid reflux in the distal esophagus. pH probes are restricted by their ability to detect only episodes that cause a change in the esophageal pH. They are unable to determine the volume of reflux fluid into the esophagus, but they are able to detect the frequency of episodes of reflux, the time it takes for an episode of acid reflux to be cleared, and over a given period of time, the frequency of episodes of acid reflux in the distal esophagus. A 24-hour pH probe study can obtain fairly reproducible information on the amount of reflux that is occurring in an infant. Still, they offer little information about the pathogenesis of GER during infancy.

The ingestion of radionuclide-labeled formula allows the performance of a nuclear medicine scan known as a gastroesophageal scintiscan. It is possible to calculate how much radionuclide empties from a the stomach over a given period of time and for how often reflux occurs in-
to the esophagus. The scintigraphy does allow the detection of duodenogastric reflux (DGR) as well as rates of gastric emptying that may be helpful in the evaluation and future treatment of children who have GERD. Experience indicates that the most common error in PPI prescribing in children is underdosing. In fact, if the diagnosis in a child is GERD, and there is a poor response to PPI, the likely problem is either that an insufficient dose has been used or that the patient is not taking medication. The optional administration mode for PPIs is once per day, just before the first meal of the day. The available literature supports the value of sustained treatment (at least 6 months) with PPIs in managing symptoms of esophagitis in children that is unresponsive to, or recurs following other interventions and in preventing relapse of symptoms and esophagitis in patients with well-documented GERD. Whether such treatment will have very long, sustained effects is not established.

**SURGERY FOR GERD**

Until some years ago, antireflux surgery was justifiably the mainstay of treatment for severe GERD in children, as there was no real medical alternative. However, despite the availability and proven efficacy of PPIs for severe GERD, antireflux surgery remains widely used in children. Benefits of surgery extend beyond the mechanical effect of creating an external valve around the esophagus. The procedure also reduces a hiatal hernia when present, re-establishes anatomical position of the distal esophagus and restores an intra-abdominal component to the lower esophageal high pressure zone. Likely related to some of these effects, a well-performed fundoplication also may decrease the frequency of reflux - associated TRLES.

**A. Indications for surgery**

Indications for antireflux surgery vary somewhat with the age of the patient. In most otherwise healthy children under 1 year of age, gastroesophageal reflux is a temporary condition with spontaneous resolution of symptoms occurring in up to 90% of patients. Because the prognosis for resolution of GERD is better in infants than in older children, the risks of antireflux surgery must be carefully considered against this better prognosis in infants without associated anatomic abnormalities and potentially life-threatening events. In contrast, when GERD occurs in association with congenital malformations (congenital abdovinal wall defects, repaired congenital diaphragmatic hernia or esophageal atresia) and/or life threatening conditions (reflex apnea, subglotic edema, subglotic stenosis etc) early operative correction may be necessary.

In infants, as in older children with GERD, pulmonary aspiration of gastric contents causing pneumonia and reactive airway disease, failure to thrive, and esophagitis remain as reasonable indications in this older patient group, es-
especially if adequate dosages and treatment courses of antisecretory agents have been offered.

B. Antireflux surgical procedures

Antireflux surgical procedures are one of the most common procedures performed by pediatric surgeons today. Historically, early operations for GER were aimed to reconstruct the normal anatomy of esophageal hiatus and gastroesophageal junction (Allison, 1950). Lortat-Jacob advocated a rather similar technique, while Hill focused on the fixation of the cardia by suturing the lesser curvature of the stomach to the median arcuate ligament. Similarly, other investigators developed operations to correct what is thought to be only an anatomical disorder. Soave proposed a pathophysiologic mechanism for a surgical repair of GER, withstanding the importance of maintaining cardial continence. He advised the creation of a positive pressure on the abdominal esophageal segment. He also suggested that an effective operation to prevent reflux should create a valve mechanism and ensure a significant length of intraabdominal esophagus. Both of these goals were achieved by the Nissen technique, originally proposed by Rudolph Nissen in 1956. After initial skepticism this procedure has gained widespread acceptance, becoming the most often used surgical procedure in the pediatric patients today. First modification of Nissen’s procedure was described by Rosseti, who created a fundoplication using only the anterior wall of gastric fundus. Other wrap configurations have been proposed in order to prevent some of the potential disadvantages associated with a 360° fundoplication. They mainly consist of 180° to 270° wraps, either anterior (Thal, Boix-Ochoa, Dor), or posterior (Toupet). A partial 270° posterior Toupet wrap can be used for patients with severe associated motor abnormalities who may be at greater risk for postoperative dysphagia.

The original Nissen operation underwent modifications by himself, as well as by other surgeons. Variables include approach (transthoracic or abdominal), portion of stomach wall used (anterior or posterior), combination with other procedures such as vagotomy and/or pyloroplasty, and looseness, completeness, and length of the wrap. Donahue and DeMeester also worked to improve the Nissen’s operation. They were the first to truly understand the physiologic mechanism of Nissen’s fundoplication and modified it by division of short gastric vessels and the creation of loose floppy wrap. DeMeester also evaluated the optimal length of the wrap and convincingly showed that a loose wrap of just 2 cm was sufficient for reflux suppression and reduced the incidence of troublesome postoperative bloating and dysphagia. Mainstays of this procedure are: 1. complete dissection of the crura, 2. mobilization of the distal esophagus, 3. complete mobilization of the gastric fundus by dividing the short gastric vessels, 4. crurorrhaphy, 5. creation of a short wrap (about 2 cm), and 6. positioning and fixation of the wrap. This technique allowed a drop in the incidence of temporary and persistent dysphagia from 83% to 39% and 21% to 3%, respectively, while in most cases patients preserved the ability to belch. The other point that was stressed in order to prevent wrap tension, was the calibration by bougie and/or by passing an instrument or a finger between esophagus and the wrap after finishing creating the fundoplication. Even on suture technique they described an interesting detail; they advised closing the wrap with a horizontal mattress suture tied on Teflon pledgets to minimize the cutting effect of the stitch on the tissues. The effectiveness of such a detail has also been described in children.

One of the latest advances has been the introduction of laparoscopic fundoplication that has a serious impact on the history of GER treatment. The development of minimally invasive surgical techniques has led to a dramatic increase in the number of antireflux operations being performed. Operations similar to those previously performed by the open approach were not only feasible without opening the abdomen, but had apparently the same result with considerable less suffering and with shorter hospital stays.

C. Personal experience

In the period between November 2003 and November 2007, 24 infants and children aged from 3 months up to 16 years underwent modified floppy Nissen fundoplication at University Children’s Hospital in Belgrade. All patients had intractable reflux symptoms, which were mainly emesis, recurrent respiratory infections, failure to thrive and heartburn. Three patients had distal esophageal peptic stenosis combined with large hiatal hernias that were previously endoscopically dilated. In all patients diagnosis of GERD was confirmed by barium meal, foregut flexible endoscopy and 24-hour esophageal pH monitoring. Due to endoscopically non-erosive reflux disease (NERD) in 5 patients stationary manometry was performed. Each patient underwent a trial of medical therapy, acid suppressants (H2RAs) and/or proton pump inhibitors (PPIs), combined with upright position and small frequent feeds for at least 6 months before being referred to surgery. Main causes for operation were: recurrent respiratory symptoms (9 patients), sliding hiatal hernia (5 patients), emesis and failure to thrive (4 patients), peptic stenosis (3 patients), hiatal hernia combined with Barrett esophagus (2 patients) and neurological impairment (1 patient). Modified Nissen fundoplication was performed in all patients through the upper midline laparotomy. Postoperative recovery in all patients was uneventful. Regular postoperative follow up in all patients was performed after 1, 3, 6, 9 and 12 months. All patients reportedly are symptom free, and had no signs of recurrent reflux disease one year after the operation.

Fundoplication has led and continues to lead to the improvement of the quality and quantity of life in many selected children. Surgery may be preferable to a lifetime medical treatment, when risk factors for relapse are absent (neurologically normal child with no previous esophageal surgery) and necessary in the face of life-threatening events. If we recall and take advantage of what has already been done in open surgery, and if we improve collabo-
ration among surgeons, pediatricians, anesthesiologists and gastroenterologists, long term results of surgery for the treatment of GERD will surely continue to improve in the years to come.

REZIME

GASTROEZOFAGEALNI REFLUKS KOD DECE

Gastroezofagealni refluks (GER) je najčešći poremećaj funkcije jednjaka i jedan od najčešćih razloga dovođenja dece kod pedijatara-gastroenterloga. Javlja se kod oko 30% pedijatrske populacije.

Klinički simptomi GER-a u odojčadi i male dece su vrlo varijabilni i ispoljavaju se kao gastrointestinale i ekstрагastrointestinalne manifestacije koje variraju od bolesnika do bolesnika i mogu se menjati u zavisnosti od uzrasta. Bolesnici mogu imati minimalne simptome ili pak imati simptome teškog ezofagitis, krvarenja, zaostajanja u rastu ili ozbiljne respiratorne probleme. Dijagnoza GER-a i utvrđivanje njegovog porekla potrebuje istraživanje vremenskih epizoda. Iako različiti poremećaji motilnosti kisela želudka i jednjaka i jedan od najčešćih razloga dovodenja dece kod pedijatara-gastroenterloga, jabolčićeva smrtnost u njegovom uređenju može biti različiti od jedne do druge dece. Dijagnoziranje GER-a potreba istraživanja vremenskih epizoda.

Ključne reči: GER, deca, pH monitoring

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