ГОСТУВАЩ АВТОР

RESPIRATORY SYMPTOMS IN CHILDREN WITH GASTROESOPHAGEAL REFLUX DISEASE

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РЕСПИРАТОРНИ СИМПТОМИ ПРИ ДЕЦА С ГАСТРОИНТЕСТИНАЛЕН РЕФЛУКС

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Summary: The Gastroesophageal Reflux Disease (GERD) is a frequent entity in pediatrics, which is still under-diagnosed ("the disease of the third millennium"). The polymorphic clinical symptoms are dominated not only by post-feeding vomiting, but in many cases also by respiratory symptoms (from night cough to apnea episodes, recurrent wheezing, aspiration pneumonia and even sudden death syndrome). The GERD therapy consists in: general measures, pharmacological and/or surgical therapy. The original drugs (prokinetic agents) have been replaced lately by the proton-pump inhibitors (PPIs), as these are considered medication able to generate the disappearance of the reflux symptoms in most cases. When GERD is associated with respiratory manifestations, the PPIs therapy is controversial. Therefore, the specialized literature is to be reviewed in order to highlight such cases of this complex disease.

Key words: gastroesophageal reflux, respiratory manifestations, child

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INTRODUCTION

The gastroesophageal reflux (GER) is the intermittent or permanent passage of the gastric content to the esophagus, determining a series of symptoms: digestive, respiratory and/or neuro-behavioural, or the absence of complaints. Most episodes of reflux are short and asymptomatic, as they appear postprandially in the distal oesophagus [1].

The main role of the esophageal tract is of leading the bolus by means of the common action of the buccal, pharyngeal and esophageal muscle formations and indirectly of the laryngeal ones. Another important role of it is its secretory function: the esophagus secretion has a mucous consistency and plays a major role in lubricating the surface of the oesophageal mucous membrane, favouring the progression of the bolus; it is vagally mediated; the mucus is produced by numerous acinar glands located in the submucous membrane.

Reflux is physiological during the first 3 months of life, manifested very early, usually during the first 6 weeks of life [2]. For the majority of cases, regurgitations disappear by the age of 12-24 months, and their persistence after this age raises the problem of the reflux consequences – reflux esophagitis, and the inclusion of cases in the gastro-oesophageal reflux disease group [3].

The population with a risk of GERD includes: 1) premature and dysmature babies; 2) newborns who suffered from hypoxia or perinatal asphyxia; 3) babies who benefited from a gastric tube "a demeure"; 4) babies with a delayed gastric emptying (primary or secondary); 5) newborns operated for oesophageal atresia with or without fistula; 6) Cystic fibrosis, 7) encephalopathic children [4].

ETHIOPATHOGENESIS

Three pathogenic links participate in variable proportions in the appearance of the pathological gastro-oesophageal reflux [5]: dysfunction of the lower esophageal sphincter (LES), esophageal dysfunction, and gastric dysfunction.

Dysfunction of the Lower Esophageal Sphincter

*Transitory relaxation i*s the major mechanism producing GER, while basal (underlying) relaxation of the lower esophageal sphincter (LES) is the minor mechanism producing gastroesophageal reflux [5, 6].

The transitory relaxation of the LES can be spontaneous and usually emerges after the normal peristaltic movements. Literature studies attempted to individualize factors responsible for the transitory relaxations of the LES, but the data obtained are insufficient. More studies assert the involvement of a vagal reflex – a type of neural mechanism with a starting point at the level of mechanoreceptors of the gastric wall stimulated by the gastric distension [7].

The production of abnormal pressure at the LES level or changes in the LES length or position creates the premises of the emergence of the gastro-esophageal reflex:

● *Mechanic dysfunctions of the LES* – the shortening of the intraabdominal segment of the esophagus [8] – determines the change in the LES normal pressure, therefore it can no longer maintain its tonus in certain conditions: changes of the body position, situations in which the intraabdominal pressure increases, favouring reflux;

● *Dystonias of the LES* – appear in case of: 1) changes in the anatomic relations of the structures ensuring the eso-cardiac-tuberosity fixation (phrenic oesophageal ligament and gastrophrenic ligament) [9]; 2) conditions of the sphincter and esophageal muscles in systemic diseases that change the LES peristalsis and pressure: scleroderma, Sjogren syndrome, diabetes mellitus, myxoedema, SLE, polymyositis; 3) different incoordinations, vagotomy, sclerotherapy [10].

● *Hormones, peptides, pharmacological agents* [11] – acting by: 1) increasing the pressure of the lower esophageal sphincter – acetylcholine, histamine, encephalin, bombesin, motilin, α-adrenergic agonists; 2) decreasing the LES pressure – α-adrenergic agonists, serotonin, progesterone, glucagon, dopamine, VIP, AMPc.

Esophageal Dysfunction

It is represented by the insufficiency of the esophageal clearance leading to esophagus lesion. The clearance defines the capacity of the esophagus of removing the reflowed material and, thus, of shortening its contact with the oesophagus mucous membrane.

Four mechanisms ensure the efficiency of the oesophageal clearance:

– *the motor activity of the esophagus (peristaltic waves)* – the gastric reflowed material that reaches the stomach during transitory relaxation of the LES is resent to the stomach by means of the peristaltic waves [12]. Perturbations of the esophageal motility determine GER.

– *the force of gravity* – in orthostatism, contributes to resending the gastric reflowed material back to the stomach; in supine position or during sleep, in the absence of gravity, esophageal clearance is delayed, favouring the stagnation of the reflowed material in the esophagus and the irritation of its mucous membrane.

– *the salivary secretion* – due to its salivary bicarbonate content, buffers the acid reflowed from the stomach, eliminating its irritating effect on the esophagus mucous membrane.

– *the secretion of the esophageal glands (mucous or non-mucous)* – plays a protective role on the esophageal mucous membrane.

Gastric dysfunction

It is another pathogenic link [10] contributing to the production of GER through:

● *The increase in the gastric volume* – in overfeeding or poor functioning of the gastric emptying (delayed emptying), it determines repeated transitory relaxations of the LES, favouring reflux;

● *Gastric distension* – through aerophagia or prolonged overfeeding, leading to the shortening of the LES length in the intraabdominal segment;

● *The increase in the intraabdominal pressure* – in values exceeding the basal pressure of the lower esophageal sphincter, determining its relaxation;

● *Delayed gastric evacuation* – in over 40% of the GER patients, gastric evacuation is prolonged; patients with gastric stasis have more abundant GER and more severe esophageal lesions.

● *The duodenal-gastric reflux* – seems to be the basis of more severe lesions in case of mixed acid and alkaline gastroesophageal reflux, through the combined action of HCl, pepsin, pancreatic enzymes and biliary acids.

● *Gastric hypersecretion* – the increase in the acid concentration aggresses the esophageal mucous membrane during the transitory relaxations of the LES; likewise, acidity determines perturbations of the normal esophageal peristalsis (study of the endoesophageal perfusion with 0.1N diluted hydrochloric acid done by Triadafilopoulos in 1991) [13].

H. pylori favours the appearance of several severe gastric diseases (including Barret esophagus and esophageal adenocarcinoma), and, on the other hand, exercises a protective role against the gastroesophageal reflux disease [14].

CLINICAL MANIFESTATIONS

The digestive manifestations are represented by symptoms that suggest esophageal pain [15]:

● Regurgitations

The physiologic regurgitation – may be noticed from the first weeks of life. Frequency decreases with age; therefore regurgitations tend to disappear towards 12-18 months.

The pathologic regurgitation is the expression of the pathologic GER, but it may also appear in other etiologic circumstances, therefore requiring a differential diagnosis with: 1) congenital esophageal obstructions:

esophageal stenosis, esophageal atresia with or without fistula, hiatal hernia; 2) acquired esophageal lesions: esophagitis, strictures, pseudo-diverticula, esophageal foreign bodies, retroesophageal abscess [4].

Regurgitations of the pathologic reflux are abnormal as regards duration, number/24 hours and are favoured by posture or by the situations that increase the intra-abdominal pressure.

According to the taste of the regurgitated material perceived in the mouth the acid character (sour taste) or the alkaline character (bitter taste) of the reflux may be appreciated [10].

● **Vomiting** – is accentuated by crying, by prone position, by situations in which the intra-abdominal pressure increases and in most cases it is followed by regurgitations [4].

● **Rumination (mericism)** – is a rare but severe form of chronic regurgitation and consists in the return of the food into the mouth, chewing the food and re-swallowing it.

The respiratory manifestations are determined by the aspiration of the gastric content in the respiratory ducts and are better represented in children in comparison with adults.

The following may occur [2, 11, 14, 16]: chronic cough; obstructive apnea crisis; wheezing; chronic or recurrent pneumonia; a simple chronic hoarseness; spasms of cyanosis at which are added stridor, hiccup, dysphonia; aspiration pneumonia; crises of bronchial asthma; recurrent obstructive bronchitis; recurrent otitis media; rhynopharyngitis and repeated pharyngitis.

The prevalence of the respiratory manifestations associated with GER is variable. Therefore, in a personal study, Navarro [17] establishes a quantification of the respiratory symptoms associated with GER: chronic or recurrent respiratory manifestations – 31%; paroxysmal respiratory manifestations – 10%, including cyanosis spasms – 5%, apnoea – 3%, and sudden death – 2%, and he concludes with the fact that there is not always the case of a causal relationship between the respiratory manifestations and the reflux.

The GER prevalence, that was obtained in a study developed on 39 patients diagnosed through a 24-hour monitoring of the pH, was 60% in cases of gastrointestinal affections, 48.6% in cases of respiratory affections, and 75% in a mixed group; the conclusion of the study was that the coexistence of gastrointestinal and respiratory symptoms in patients with GER may be related with severe reflux [18].

The GER diagnosis may be confirmed by an upper endoscopy with oesophageal biopsy, oesophageal manometry, by monitoring the intraluminal impedance, with a 24-hour monitoring of the oesophageal pH or by monitoring the intraluminal impedance combined with a 24-hour monitoring of the oesophageal pH [1, 19, 20]. None of these methods has all the characteristics necessary to be considered a “golden standard”.

In order to explain the GER association with respiratory manifestations various hypotheses were issued:

● the microaspiration of acid repressing particles in the respiratory tree, suggested by the anatomic relation between the digestive and respiratory paths [21];

● common embryonary origin of the oesophageal and pulmonary nervous fibers – bronchospasm through vagal relation;

● the pulmonary manifestations may be a reflux cause – reverse relation.

The association of GER with bronchial asthma is well proven both in the case of a child, as well as in the case of an adult. Two recent systematic assessments indicated the fact that the prevalence of the GER symptoms is considerable higher in adults and children with asthma than in those without asthma [22].

The elimination of a possible reflux in a child with repeated pneumopathies, chronic cough, recurrent wheezing, repeated crises of bronchial asthma, became a frequent practice [3].

The amelioration of the respiratory symptomatology through medical therapy or anti-reflux surgery is an extra argument that certifies the GER interrelation – respiratory manifestations, mainly asthmatiform ones [23].

The assessment of the respiratory answer to proton-pump inhibitors (PPIs) in a batch of 37 children with obstructive sleep apnoea syndrome and GER lead to the conclusion that in these children, the reduction of the obstructive respiratory events following the short term treatment with PPIs may suggest, in some children, a causal relation between apnoea and reflux [24].

Neurobehavioral manifestations have been associated with “visceral hyperalgesia” [2] or with pain perception and can be characterized by: sleep disorders; crises of agitation and crying; arching and rigidity, hyperextension of the neck; generalized irritability; convulsions or pseudo-psychiatric behavior, occasionally.

In older children, they are particularly associated with Sandifer syndrome, which comprises a complex of signs, such as the extension of the head, torticollis, twisted neck, opisthotonic posturing, occasionally with facial asymmetry, which occurs as a specific response of the head to reflux. Furthermore, they can be associated with hiatal hernia, and in 50% of the cases, lesions of esophagitis are encountered [25].

Nutritional consequences

They are the consequence of a prolonged and severe gastroesophageal reflux disease.

Therefore, the following may occur:

– weight and height growth disorders, when vomiting and nourishment refusal (due to the esophagitis lesions) are long-termed, “the failure to grow” [2];

– signs of chronic dehydration, even states of non-acid chronic ketosis, in persistent, untreated forms;

– microcytic hypochromic anemia, due to chronic vomiting or digestive hemorrhages [9].

TREATMENT

The objectives of the treatment are related to the treatment of the digestive and extra-digestive manifestations, healing of the lesions, if they are present, prevention of reoccurrence of the disease and its complications. These objectives are reached by applying general measures and pharmacologic and surgical therapy.

General measures are mandatory for all patients and consist in educating parents (the physiological and benign nature of the GER during lactation must be explained). They must distinguish between physiological and pathological GER. The recommended posture is the 30-40o proclive one. Dietetic measures are required both for little children and older children.

The pharmacological therapy consists in the association of prokinetic (Domperidone, Cisapride), anti-acid and anti-secretory medication (proton-pump inhibitors: Omeprazole, Pantoprazole, Lansoprazole, Esomeprazole). At present, the PPI therapy is the most widely accepted medical therapy for children and adults. Nevertheless, PPI did not succeed to prove benefits in terms of control of the bronchial asthma in children with GER in most of the well-conceived studies [26]. A study has reported two cases of children with asthmatic symptoms that were difficult to treat and which, eventually, proved to be related to the GER. The two children were treated with anti-reflux procedures and became asymptomatic. Moreover, literature was also reviewed to reveal this complex disease [27]. On the other hand, another recent study disagrees with the repeated use of anti-reflux medication in the treatment of bronchial asthma weakly controlled in childhood, reporting that the PPI treatment was not only inefficient, but the side effects were frequent, including an increased prevalence of symptomatic respiratory infections [28].

The preferred ***surgical procedure*** is represented by Nissen's fundoplication. Surgical measures can be followed by both immediate and distant complications.

CONCLUSIONS

1. GERD is a frequent entity in pediatrics, which is still under-diagnosed ("the disease of the third millennium").

2. Clinical, rather polymorphic symptoms are dominated not only by post-feeding vomiting, but also by respiratory symptoms, in many other cases (from night cough to episodes of apnea, recurrent wheezing, aspiration pneumonia and even the sudden death syndrome).

3. GERD therapy is triple: general measures, pharmacological and/or surgical therapy.

4. The initial drugs (prokinetic agents) were lately replaced by proton-pump inhibitors, as these are considered medicines which can determine the disappearance of reflux symptoms in most of the cases.

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