

MODERN VIEWS OF GERD IN CHILDREN: PROBLEMS AND PERSPECTIVES (review)

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Abstract: Much attention has recently been paid to the upper digestive tract diseases in children, particularly GERD, as it has an impact on quality of life even in children of school age and thereafter in young adults. Scientists came to a consensus that all kinds of examination used in pediatric practice must be maximally available, simple and non-invasive to the extent practical for the child's condition. The question about practicability of performing esophagogastroduodenoscopy for all patients with heartburn and other symptoms of GERD, the question relative to performing ultrasonography of the esophagus for children as an additional method of examination, usage of questionnaire in pediatric practice, formation of disease course prediction algorithm, and identification of preventive measures specific to every patient remains disputable. Therefore, the goal of this research is to provide an overview of modern literature with reference to problematic issues of clinical evidence, risk factors, diagnostics, prediction of gastroesophageal reflux disease course in children of different age (regarding main causative and pathogenic factors, clinical evidence (esophageal and extra-esophageal), diagnostic methods and modern approaches to gastroesophageal reflux disease treatment).

KeyWords: gastroesophageal reflux disease, non-invasive diagnostics, risk factors, prognosis of the course.



Gastroesophageal reflux disease (GERD) is a chronic recurrent disease associated with disorders of motor-evacuation function of gastroesophageal tract which is characterized by established esophageal and extra-esophageal clinical evidence as a result of spontaneous and/or regular backflow of stomach or duodenal content into the esophagus that results in physicochemical damage of the distal segment of the esophagus [1, 2].

GERD is a current problem in modern gastroenterology specified by high disease incidence, a great number and variety of complaints raised by patients, development of severe complications (Barrett esophagus and adenocarcinoma of the esophagus) as well as necessity for long-term therapy [3].

GERD is one of the most widespread diseases of the digestive system in the Western world with typical symptoms such as heartburn, belching or retrosternal pain and constitute 15% - 20% from overall population. In Asia this number is significantly less and constitutes approximately 5% [4], though over the last years the tendency for morbidity increase is also observed.

GERD incidence in children is uncertain since application of invasive methods of examination (pH measurement and endoscopy) particularly in young children is significantly limited. In the structure of gastroenterological morbidity according to different authors it constitutes 8 to 25% [5, 6].

The significant point is that the risk of digestive system diseases in children is higher than in adults, disease progresses in less time with increasingly frequent and long-lasting recurrence.

The incidence rate of gastroesophageal reflux disease (GERD) has been noted around the world; however, there are significant differences in terms of its frequency in children from 8.7 to 49%. In Ukraine the prevalence rate of GERD (0.83%) and the incidence rate of GERD (0.29%; 2014)

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are significantly less than in other countries that may indicate poor education of professionals in the matter [7].

High prevalence of heartburn as a principal symptom of GERD in the world and Ukraine in combination with invasiveness of research, high cost of diagnosis and treatment is a significant social and economic problem of the state health care system. Particularly well-timed screening diagnosis and identification of disease course prediction algorithms and creating specific prophylactic events can prevent development of complications and severe forms of GERD that will significantly reduce costs for long-term treatment and improve the life quality of patients.

Pathologic gastroesophageal reflux onset can be associated with incompetence of cardia, esophagus clearance disorder, and stomach and duodenum motility disorders. Esophagus clearance disorder and gastroduodenal motility disorder are often associated with autonomic nervous system function disorder of different origin. Important favorable factors of GERD development are obesity, non-differential dysplasia of connective tissue, and sliding esophageal hiatal hernia. Contamination and ablation of *Helicobacter pylori* (Hp) do not play a critical role in GERD genesis [8].

Several meta-analyses showed statistically significant low prevalence of Hp related to GERD [9], as well as Barrett esophagus [8, 10] or esophageal adenocarcinoma [11]. However, ablation of Hp does not affect the course of already present GERD and does not influence the effectiveness of treatment with proton pump inhibitors (PPI) [12].

Gastroesophageal reflux disease is characterized by a complex of clinical symptoms that occur in response to backflow (reflux) of stomach content into the esophagus and proceeds with occasional recurrences and assumes progressive nature [2, 13, 14].

The symptoms of GERD are quite various and numerous, and can be esophageal and extra-esophageal. Clinical implications significantly depend on the child's age and presence of comorbidity and risk factors.

Esophageal symptoms include the following: heartburn, regurgitation, belching, dysphagia, odynophagia (pain when swallowing) that occurs more frequently in the pres-

ence of erosive ulcerated lesions. Nonspecific symptoms for reflux disease that occur more rarely and can be associated with other diseases are as follows: hiccup, vomiting, sensation of a lump in a throat, sensation of excessive amount of liquid in the mouth, throat irritation, burning tongue, etc. Duodenogastroesophageal reflux onset is frequently followed by bitter taste in the mouth, yellow coated tongue [15, 16, 17].

The character of clinical manifestations is influenced by changes in other organs of the digestive system, first of all gastroduodenal pathology which is followed by GERD in a great number of cases. Modern studies showed high frequency of GERD association with functional pathology of organs of the digestive tract particularly with irritable bowel syndrome and functional dyspepsia. Frequent association of GERD with functional disorders of gastrointestinal tract is not accidental and based on their common pathophysiological mechanisms [18].

In addition to significant progression of its incidence and severity, GERD importance is also based on extra-esophageal clinical manifestations and its diagnosis requires extended cycle of laboratory, instrumental methods of examination and collaboration of doctors of different specialties, and in establishing diagnosis they influence the duration and the structure of treatment (Bardhan K.D. et al., 2007, Mayev I.V. and other., 2014).

Children with GERD also complain of belching that is spontaneous backflow of small amounts of food and air or only air into oral cavity. Such belching is a less specific symptom of GERD because firstly it demonstrates an increase in gastric pressure and to a lesser extent depends on presence and activity of GERD [19, 20].

When it comes to heartburn, regurgitation, and belching, attention should be paid to absence of one definition of these terms. It is also necessary to admit that there is no conclusive focus on a regular pattern and frequency of heartburn as a symptom of GERD. Thus, according to Genval Congress recommendations diagnosis of reflux disease can be performed in cases where heartburn occurs twice or more times per week. At Montreal Congress of gastroenterologists international panel 44 specialists from 18 countries

all over the world came to a decision to consider heartburn as a symptom of GERD even if it occurs once a week [17, 20].

More than 60% of children complain of dull pain in epigastric and substernal cavities which appears immediately after meal, increases with trunk bending and reduces after some 1.5-2 hours.

Researchers have recently started paying attention to extraesophageal (atypical) manifestations of gastroesophageal reflux disease because such clinical pattern simulates different diseases. Atypical manifestations of GERD include bronchopulmonary, otolaryngeal, cardiac and dental symptoms. At an early age, the most common are extraesophageal symptoms on the part of the bronchopulmonary system and ENT organs. This association is due to similarity of anatomical relations between the respiratory and digestive systems, and also the same embryological origin [20].

Pathogenesis of GERD is multi-factorial. Comprehension of these factors has recently been sufficiently improved due to understanding of acid pocket and hernia of diaphragm esophageal opening, as well as the interaction between these factors. In spite of recently increased understanding, more investigations should be performed for better comprehension of GERD symptoms, particularly in patients resistant to symptomatic therapy. [17, 21, 22, 23].

By general consent, scientists define GERD as an acid-dependent polysystemic disease because hydrochloric acid is considered to be the main pathogenic factor. The determining risk factors of GERD development in children include disorder of motor-evacuation function of the upper digestive tract, a decrease in resistance of esophageal mucous membrane to hydrochloric acid action, an increase in gastric content aggressiveness, insufficient cardia (absolute or relative), an increase in intragastric and intra-abdominal pressure, a dysfunction of autonomic nervous system, fast growth, heredity, compromised perinatal history, non-differential dysplasia of connective tissues structures and also factors of environment and lifestyle such as: overweight, harmful eating habits, absence of regular physical activity, disproportion of the growth of body and esophagus, consumption of alcohol drinks, smoking in ado-

lescence [15, 16, 24-27].

Duodenogastric reflux is considered to be a complicated factor. In alkaline (biliary) and mixed reflux inflammatory destructive changes of mucous membrane are manifested more than in isolated acid aggression. Presence of both refluxates in esophageal cavity causes risk of columnar epithelium lined lower esophagus (Barrett metaplasia) and esophageal malignancy. In particular, biliary acids increase the activity of COX-2, thereby intensifying proliferation processes [17, 28, 29].

As for probable pathogenic connection between GERD and *Helicobacter pylori* there are still discussions often expressing polar opinions concerning this issue. HP is considered to be determined mostly in patients in mild diseases while in severe diseases (esophagitis of III-IV stages) it is found only in 16% of patients. R. Heading, a famous gastroenterologist from Great Britain, performed a comparative analysis of conservative treatment results in a great number of patients suffering from GERD depending on their "helicobacter status" which showed that the frequency of clinical and endoscopic remission depends not on the presence or absence of *H.pylori* but on the evidence of changes in esophageal mucous membrane [10]. There are no precise conclusions concerning *H. pylori* as a protective factor in respect of GERD occurrence.

GERD diagnosis is based on combination of diagnostic criteria such as: clinical, endoscopic, histologic, roentgenologic, manometric, etc. According to the world experience early diagnosis of GERD dramatically reduces the risk of complications [18, 24, 30-33].

According to international consensus, GERD is a clinical diagnosis; thus, thorough history taking gives a possibility to determine the symptoms associated with gastroesophageal reflux. Basing on national guidelines and clinical recommendations of many countries in Europe and the USA concerning primary diagnosis, this method is the main to identify complications and the onset of treatment at screening stage - qualitative evaluation of clinical symptoms may be more resultant than instrumental methods of diagnosis, which relevance should be estimated by the invasiveness and difficulty of performance in children.

Instrumental methods of investigation are additional or diagnosis confirming [32].

The use of different methods for studying of GERD prevalence has a number of difficulties such as the high cost of large-scale investigations and lack of agreement from great part of people for invasive tests. Therefore, nowadays investigators are studying the opportunity of creation of unified questionnaire which will help to conduct a survey of patients regardless of the country where epidemiology of GERD is studied [34, 35]. Besides, special questionnaire is used to determine specific clinical manifestations associated with GERD in children of early age [2, 6, 7, 16, 32, 36].

Both in Ukraine and in the whole world the main method for clinical diagnosis of GERD is intraesophageal pH-metry which is performed by introducing pH-probe into the distal segments of esophagus and its fixation there for a long time (pH daily monitoring). This method is characterized by high sensitivity in GERD diagnosis and helps to choose individual tactics for the case management. GERD confirmation by pH monitoring is not recommended in the following cases: uncomplicated GERD if test results are not necessary in treatment or prognosis, dysphagia, pain in epigastrium, positive results of other methods of investigation.

Contrast X-ray study is a sufficiently informative method of diagnosis of diaphragm esophageal opening hernia, determination of gastrointestinal tract abnormalities which destroy its motor activity (phrenospasm, diverticula, coarctation, etc.), but this method of diagnosis is rarely used in pediatrics.

Additional methods for determination of GERD risk factors can include the following: diagnosis of reflux-esophagitis in children by echographic investigation of abdominal part of esophagus and cardial section of the stomach which is performed to investigate thickening of esophageal wall, edge roughness of esophageal wall, increase in esophagus diameter after liquid contrasting (not during swallowing), widening of esophageal lumen (not during swallowing); manometry of esophagus - this method helps to register pressure in different parts of esophagus,

its ability to relax while swallowing, contracting function of esophagus and also to evaluate the character of peristaltic waves; impedansometry is based on measurement of electric parameters of intraesophageal environment while introducing gastric contents into the esophagus; investigation is performed with the help of intragastric impedance probe and reogastrograph.

Invasiveness of this method in children as in pH-metry limits its application. Due to specialists' interest regarding GERD co-morbidity with other diseases of the digestive, ENT and respiratory organs and also with great attention to the increased atypical and extraesophageal symptoms it is necessary to develop algorithms of additional individualized investigation according to the identified extraesophageal symptoms.

Taking into consideration significant prevalence of GERD, variability of clinical manifestations, severe extraesophageal symptoms, presence (sometimes combination) of risk factors which lead to GERD development or complicate its course in children and teenagers, probability of serious complications and continuous worsening of life quality determine medical and social character of gastroesophageal disease. Its relevance proves the necessity of further search in the study of pathogenesis and clinical manifestations of GERD to improve diagnosis, individualize case management and predict the course of gastroesophageal reflux disease.

Conflict of interests

There is no conflict of interests.

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