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ASTHMA ASSOCIATED WITH EOSINOPHILIC ESOPHAGITIS IN CHILDREN: CURRENT CONDITION OF THE PROBLEM

Key words: *asthma, eosinophilic esophagitis, children.*

Worldwide, allergic diseases have reached pandemic proportions, with their prevalence currently at 50 % [13,23], and doctors of all specialties are commonly faced with this problem [4].

According to WHO 235-300 million people on the planet suffer from asthma [5, 21, 25, 29, 30, 56]. According to forecasts, this number could reach 400 million by 2025 [9, 19]. In different countries and populations, the incidence of asthma varies from 1 to 18 % [1,2]. Asthma occurs at any age and most often manifests in childhood [22]. In childhood this number varies within 5-10 % [1,8], and reaches 37.6 % [1,16]. It has been found that at an early age boys are more likely to develop a disease than girls (6 and 3.7 % respectively). However, in adolescence, the incidence of asthma reaches the same rates. The highest prevalence of asthma is in children of school age. High incidence of asthma in children is characteristic for industrial regions with air polution. Thus, asthma is more often found in the city than in small towns (7.1 and 5.7 % respectively) [25].

There were 210 000 patients in Ukraine in 2015 and there is a trend for increase in the future [30]. According to the statistics of the Ministry of Health of Ukraine among children in recent years, the prevalence of asthma fluctuates within the range of 0.56-0.60 %, which indicates the problem of under-diagnosis of the disease [25].

According to modern concepts, asthma is a heterogeneous disease characterized by a chronic inflammatory process of the respiratory tract, and it is the inflammatory nature of the disease that determines the approaches to diagnosis and treatment. In children, this disease is one of the most common pathologies of the respiratory system and, unfortunately, often undiagnosed [12,13].

Asthma is a chronic inflammatory disease of the respiratory system, which is caused by bronchial hyperreactivity and is manifested by recurrent symptoms of wheezing [5, 11]. Asthma is one of the diseases that significantly reduces the quality of life, as well as contributing to early disability and mortality in children [10, 24, 57, 58,6 7].

According to the literature, there is a combined pathology of the digestive organs in 76.9 % of children with asthma. More severe asthma and control of symptoms are found in children with the presence of concomitant digestive system disease. With more severe lesions of the gastrointestinal mucosa there is a more profound impact on the severity of the asthma than with milder changes in the mucosa according to Bolbot Yu.K. and Kalichevskaya M. V. Therefore, it is extremely important to properly diagnose and promptly treat the concomitant upper digestive system pathology in patients with asthma [3].

It is known that a certain number of inflammatory and dystrophic processes of the digestive tract increase the "antigen-antibody" reaction 3-5 fold with the formation of a "shock body" in the organism. The basis of 20 % of digestive tract diseases is an allergic component [14,20], while 30-60 % have a combination of respiratory and food allergies.

As a result of studies conducted among the Ohio

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children's population, R.Noel et al. [1] in 2003 established the frequency of eosinophilic esophagitis (EE) as 1 case per 10,000 per year [15].

It was first described in 1970, and in the early 1990's it was named as separate medical disorder, and since that time the frequency of diagnosis of this disease has increased [7, 26, 36, 74, 76].

EE is often associated with asthma, and 80 % of patients with EE are atopic. The prevalence of both diseases is greatest in the western world [76]. EE is found 3 times more often in girls than boys [50].

In recent years, there has been a significant increase of incidence of gastrointestinal symptoms in children of food allergy. Food allergies occupy an important place among diseases of the digestive system in children and its prevalence is increasing. This increasing prevalence while causing more morbility is developing more undestanding of the disease among doctors and improving diagnostic techniques [7, 26, 61]. Unfortunately, today the basic algorithms for diagnosis and treatment of this disease in children are not yet well developed. There are no satisfactory protocols or methodological recommendations that can be used by pediatricians, family doctors and pediatric gastroenterologists with their patients [6].

In 50% of children with EE there are other manifestations of allergy, such as bronchospasm, eczema and allergic rhinitis [6, 61].

There are several factors involved in the development of allergic reactions in the esophagus. First of all, the esophagus is the gateway for sensitizing the body to different allergens. The next is that diseases such as esophagitis, diverticulitis or ulcers are triggering factors in the development of general or local allergic reactions which increase the frequency of allergies elsewhere. And the esophagus also turns into a "shock organ" with corresponding functional and organic changes of varying severity [11].

In some literary sources, the question is called an asthma esophagus [76]. There are some pathogenetic peculiarities between the asthma and EE. Therefore, at present, the urgent study of similar and distinctive features of these diseases continues. Consequently, EE and asthma are chronic immunological diseases characterized by inflammatory changes in the mucous membrane and submucosal membrane with characteristic eosinophilic infiltration [76], which leads to dysfunction of the organs. The mucous membrane of the respiratory tract in the asthma, as well as the mucous membrane of the esophagus with EE, can be visualised endoscopically and appear normal which does not exclude the final diagnosis. In asthma and EE, there is a chronic restructuring of tissue architecture due to a long inflammatory process. In comparison there can be complete restoration of tissues with treatment in the early stages of the disease. Toxic proteins derived from eosinophils make up most of the major proteins. Eosinophilic neurotoxin and eosinophil cationic protein can be found in the mucous membrane in both diseases and cause thickening of the basement membrane [45, 52]. With the use of corticosteroid drugs, the elimination diet, and avoidance of contact with the allergen there is a positive improvement in the asthma and EE. Consequently, the few common features between asthma and EE cause the presence of common pathogenetic links in the development of the disease in various organs [76].

Asthma and EE occur at any age, but both of these diseases often have their very beginning in childhood and adolescence. There are no pathognomonic symptoms for combined pathology of asthma and EE; therefore, the diagnosis does not always occur at the onset of the disease. Between the appearance of the first symptoms of EE and the final diagnosis there is usually a delay [60]. Children with combined diseases lose the opportunity to have a high quality of life [68].

Since most patients with asthma and EE have atopy, seasonal exacerbations are a common symptom [33,42]. It is found in combination not only with asthma, but also with allergic rhinitis, atopic dermatitis and food allergy [75]. Children with EE in 42-93 % of cases have allergic diseases during treatment and approximately 50-60 % have it in their medical history [27,61].

Asthma and EE macroscopically may have an unchanged gross appearance of the mucous membrane despite dense infiltrate of eosinophils, mast cells and lymphocytes. However, with a prolonged course of EE in the mucous membrane of the esophagus, characteristic ulcers are formed [76]. It is important to remember that an endoscopically intact mucous membrane does not exclude the presence of EE [32].

EE is a chronic immune disease characterized by a pronounced isolated eosinophilic infiltration of the esophagus due to the action of food and air allergens. There may also be an autoimmune aspect of the disease [15, 28, 61]. Most researchers believe that EE is associated with an IgE-dependent mechanism, but other researchers - mostly non-IgE-dependent [17, 54, 66].

The clinical picture of EE in young children differs from the symptoms of older children and is manifested by anxiety, decreased appetite and refusal of food with vomiting, abdominal pain, and poor weight gain [27, 34, 73, 75]. Older children complain of dysphagia, discomfort behind the sternum, pain in the sternum, physical inactivity, nausea, heartburn, feelings of something stuck in the throat, chest pain, and are selective about food choices [39, 43, 44, 59, 69, 70].

During the esophagogastroduodenoscopy (EGD), there is no visual difference between the macroscopic features of the EE and reflux esophagitis. Therefore, without biopsy it is impossible to make the correct diagnosis of EE [6, 31].

EE is not always associated with gastroesophageal reflux [6]. The difference lies in the fact that the EE causes damage of the mucous membrane of the esophagus throughout its length, and in reflux esophagitis it is only in the distal portion.

Endoscopically in EE, swelling, furrows and strictures, rings, exudates and plaques are seen. Swelling manifests as pallor mucous membrane and impaired vascular pattern. The longitudinal muscles of the esophagus are contracted to form concentric rings like the

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trachea has [15, 38, 47]. The tissues are gradually remodeled. Fibrous strictures are formed and fixed rings are found. The presence of the exudate and white spots is similar to the picture of candidal esophagitis, but histologically they are represented by eosinophilic microabscesses. Epithelial edema forms a furrow that has the appearance of vertical lines that run parallel to the axis of the esophagus. The chronic eosinophilic inflammation of the esophagus may lead to strictures and scarring [15, 48]. Also, the strictures associated with EE are more susceptible to reoccurrance than peptic strictures in gastroesophageal reflux disease [5, 61].

The narrowing of the esophagus lumen is a frequent complication of the EE. When passing the endoscope, but not after dilation of the esophagus, the mucous membrane visually resembles corrugated paper as a result of its increased brittleness. The endoscopic signs listed above may not alweys be specific for EE [72].

When conducting a biopsy in a patient with significant EE a rigidness is present. Despite the normal endoscopic picture, complaints of dysphagia in the patient`s history is a direct indication for biopsy and subsequent histological examination of the esophagus mucosa [49]. In order to verify the diagnosis of EE, it is recommended to carry out 2 to 4 biopsies between the distal and proximal esophagus starting 5 cm above the gastroesophageal junction, as well as targeted biopsies in any modified areas of the mucous membrane [64, 75].

In order to calculate intraepithelial eosinophils in areas of maximal inflammation microscopically, it is recommended to use a power of 400x to determine the highest concentration [15].

There are "large" and "small" histological criteria of EE. The "large" include eosinophilic infiltration of squamous epithelium (over 15 eosinophils in basement membrane layer per the field of view on microscope power 400x), or a cluster of eosinophils in the epithelial surface layer with eosinophilic microabscesses (4 or more eosinophils) [35, 47, 61]. Necrotized squamous cells often occur in superficial layers. The "small" histological criteria include chronic inflammatory infiltrate with fibrosis in the lower layers of the esophagus mucosa with intercellular edema, hyperplasia of muscle layers and basal epithelial cells with extension of the papillae of lamina propria [65]. Clayton et al. (2014) in their studies found a large amount of IgG4 in the plasma cells of lamina propria of the esophagus mucosa [41].

The mucous membrane of the esophagus with EE has uneven pathological changes that affect the esophagus throughout its length [27]. Unfortunately, no histological findings are considered specific for EE.

During the study of esophageal mucosa biopsy in EE, eosinophilic infiltration with focal proliferation of T-cells is seen in the mucosa and submucosa and hypertrophy of the papillary and basal zones are detected. The chronic nature of EE causes strictures, rings, furrows and whitish layers with characteristic eosinophilic inflammation of the mucous membrane. Formation of eosinophilic microabsceses occur in the areas of spots and plaques. Eosinophils in the surface layers of the epithelium, extracellular eosinophilic granules, desquamation of the epithelium, hyperplasia of the papillary layer, hyperplasia of the basal layer of the epithelium, extended intercellular spaces, fibrosis/sclerosis of the mucosa, mastocytosis, degranulation of eosinophils, mast cells, and detection of CD8+ T-lymphocytes and B-lymphocytes are also found [6,15,53]. It turns out that the intragastric pH measurement is unchanged in EE, and some authors consider antisecretory therapy to be ineffective [6,11]. With the 400x microscopic view 15-25 eosinophils are visualized in EE. In reflux esophagitis without food allergy, the number of tissue eosinophils in the mucous membrane does not exceed 5 cells. Due to severe damage of the mucous membrane in reflux esophagitis, even the term "cigarette paper" was proposed to describe the appearance of mucous membrane [14].

Improvement of the patient's condition after elimination of food allergens and the use of topical or systemic glucocorticosteroids confirms the diagnosis of eosinophilic allergic esophagitis [14].

It is necessary to pay attention to the patient's medical history to clarify the features of the clinical course of the disease and the effectiveness of therapy, presence of food allergy, and get confirmation of endoscopic and morphological examination of the esophageal mucosa [6].

New criterias for the diagnosis of EE have been developed by experts from 14 countries and published in October 2018. First of all, it is important to pay attention to the long-term presence of the following symptoms of esophageal dysfunction: a sense of food stuck in the throat, eating disorder, heartburn, regurgitation, vomiting, chest pain and abdominal pain, odynophagia (painful swallowing) and other symptoms. The combination with atopic states increase the likelihood of having EE. On biopsy of the esophagus 15 or more eosinophils (about 60 eosinophils per square mm) per field, eosinophilic infiltration must be present in the esophagus [6,51].

Moshko Yu.O. (2009) for the diagnosis, evaluation, and monitoring of EE in addition to the endoscopic biopsy also measured intraesophageal pH, conducted an endosonography and X-ray contrast studies of the esophagus to detect strictures, and to determine the diameter and length of the esophagus [15].

Pathognomonic signs for EE have not yet been found. There are other diagnostic tests for EE. With the use of barium, the appearance of the esophagus may be normal, but may show narrowing of the diameter of the esophagus with rings and isolated strictures [27, 64]. Esophageal manometry is used to establish normal motility. Initial measurement in children may show normal peristalsis but with a longer study ineffective peristalsis of the esophagus is detected. The thickening of all layers of the wall of the esophagus, due to inflammation and edema, can be detected with echoendoscopy [27, 64].

It is necessary to make a differential diagnosis of EE with other chronic esophagitis of different etiologies, including various infections. In recent years, the num-

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ber of infections that cause esophageal lesions has increased. This is due to the spread of acquired immunodeficiency syndrome, since it is believed that infectious esophagitis often develops in immunodeficient conditions. It is found in candidal esophagitis, but also don`t overlook chronic viral lesions of the esophagus, primarily due to herpes simplex virus type I and cytomegalovirus infection [18].

According to the literature, eosinophilia of the esophagus mucosa may be associated also with other conditions such as gastroesophageal reflux disease, eosinophilia of the esophagus (which is sensitive to proton pump inhibitors), eosinophilic gastroenteritis, hypereosinophilic syndrome, Crohn's disease, connective tissue diseases, drug hypersensitivity, both parasitic and fungal infections, and achalasia [46].

The main principles of EE therapy are: an eliminational diet removing foods for which the child has shown hypersensitivity, antihistamines, probiotics [6], and other pharmacotherapy, dilatation of the esophagus [28,35].

According to various authors, the first line medications to improve the histological picture and symptoms of the disease in the treatment of EE are topical glucocorticosteroids, which are prescribed for 8 weeks [28, 40, 62, 75]. When administering inhaled fluticasone orally (without any inhalation) in the form of metered spray, 880 mcg twice daily for 6 weeks, efficacy in reducing the symptoms and eosinophilia of the esophagus mucosa was demonstrated [28, 70]. The maximum effect of its antiinflammatory action is achieved mainly in the proximal esophagus. It is recommended that it not be used within 30 minutes after eating, drinking, or rinsing the mouth to prevent flushing off of the esophagus mucus. To reduce dysphagia and esophageal eosinophilia, budesonide 1 mg metered spray is prescribed twice a day. The dilation of the esophagus (balloon dilatation) does not affect the underlying inflammation, but it is beneficial in the absence of the effects from long-term use of high doses of steroids for symptomatic treatment [28, 75].

At the moment, there are no studies that are comparing the effectiveness of steroid drugs and proton pump inhibitors for the treatment of EE. In the absence of improvement from the use of a therapeutic diet or steroid therapy, it is important to consider therapy with the use of proton pump inhibitors. Proton pump inhibitors are recommended by expert committee opinion for the treatment of this disease, and not for trial therapy or diagnosis [51].

The literature data indicate a lack of efficiency of mast cell stabilizers (sodium cromoglycate, ketotifenum), nonsteroidal anti-inflammatory agents in the treatment of eosinophilic esophagitis [28]. A positive effect of using montelukast (an inhibitor of cysteine leukotriene receptor expression, cys-LT1) [63] or mepolizumab was found [28, 37, 55]. When mepolizumab is used there is a decrease in peripheral and tissue eosinophilia, morphological changes in the esophagus are normalized, and clinical symptoms are eliminated [28, 37].

Some authors report that use of fluticasone propionate results in improvement of both asthma and EE. Clinical remissions were achieved by the end of the first week after taking the drug, and microscopic improvement was seen (with a decrease in the degree of eosinophilic infiltration) when used for 8 weeks [28,71]. Candidiasis of the esophagus was the only complication when using the drug at a dose of 220 mg twice a day applied orally [28, 77].

Thus, existing data indicate that eosinophilic esophagitis is often found combined with asthma, and may affect the degree of control over the symptoms of the disease. However, the current prevalence of this comorbid pathology in children remains unknown. Until now, the risk factors and the leading causative factors and approaches to treatment and prevention are uncertain, which is the subject of further research.

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ASTHMA COMBINED WITH EOSINOPHILIC ESOPHAGITIS IN CHILDREN: MODERN CONDITION OF THE PROBLEM

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Abstract

All over the world allergic diseases are becoming pandemic, as their prevalence is near 50 %. There is a combined pathology of the digestive system in 77 % of children with asthma. There is an allergic component in the basis of 20 % of the digestive tract pathology. And 30–60 % of atopic patients have a combination of respiratory and food allergies. Eosinophilic esophagitis (EE) and asthma have some common pathogenetic characteristics. They are chronic immunological diseases with inflammatory changes in the mucous membrane and submucosa with eosinophilic infiltration leading to organ dysfunction. There is a reorganization of tissue architectonics as a result of a prolonged inflammatory process in both asthma and EE, as compared with the complete restoration of tissues in the early stages of the diseases. Toxic proteins derived from eosinophils (eosinophilic neurotoxin and eosinophilic cationic protein) can be found in the mucosa in both diseases, which also causes a thickening of the basement membrane. Thus, literature data indicate that EE is often combined with asthma, which may affect on the asthma control. The prevalence of this comorbidity in children remains unknown. The risk factors and the main causative factors have not been studied until. Approaches to the treatment and prevention of diseases are the subject of further research.

Key words: asthma, eosinophilic esophagitis, children.

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