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DOI: 10.56871/CmN-W.2023.55.28.006

FEATURES OF GASTROINTESTINAL PATHOLOGY INDUCED BY ALLERGY TO COW'S MILK PROTEIN IN PEDIATRIC PRACTICE (LITERATURE REVIEW)

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For citation: Trapeznikova AYu, Vasilyeva AG. Features of gastrointestinal pathology induced by allergy to cow's milk protein in pediatric practice (literature review). Children's medicine of the North-West (St. Petersburg). 2023;11(4):57-64. DOI: https://doi.org/10.56871/CmN-W.2023.55.28.006

Received: 21.09.2023 **Revised: 21.10.2023** **Accepted: 11.12.2023**

Abstract. According to statistics from all types of atopy in children, food allergies occupy the first place in terms of prevalence. In turn, cow's milk is a food product that most often acts as an allergen. Not rarely, gastrointestinal diseases become one of the manifestations of allergy to cow's milk protein. Currently, it is customary to distinguish the following clinical forms of gastrointestinal pathology induced by allergy to cow's milk protein: specific IgE-mediated reactions and non-IgE-mediated reactions, as well as their combination — mixed-type reactions. In routine pediatric practice, however, non-IgE-mediated forms still remain poorly recognized. This is due to a variety of factors: a variety of clinical manifestations, the lack of reliable methods of laboratory diagnostics, a non-obvious association with time and a causal relationship with an allergen. The article reflects modern views on the features of the clinical course and diagnosis of gastrointestinal pathology induced by allergy to cow's milk protein.

Key words: *children; esophagitis; gastritis; enterocolitis; proctocolitis; allergy to cow's milk protein.*

ОСОБЕННОСТИ ГАСТРОИНТЕСТИНАЛЬНОЙ ПАТОЛОГИИ, ИНДУЦИРОВАННОЙ АЛЛЕРГИЕЙ К БЕЛКУ КОРОВЬЕГО МОЛОКА, В ПЕДИАТРИЧЕСКОЙ ПРАКТИКЕ (ОБЗОР ЛИТЕРАТУРЫ)

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Для цитирования: Трапезникова А.Ю., Васильева А.Г. Особенности гастроинтестинальной патологии, индуцированной аллергией к белку коровьего молока, в педиатрической практике (обзор литературы) // Children's medicine of the North-West. 2023. Т. 11. № 4. С. 57–64. DOI: https://doi.org/10.56871/CmN-W.2023.55.28.006

Поступила: 21.09.2023 **Одобрена: 21.10.2023** **Принята к печати: 11.12.2023**

Резюме. По статистике из всех видов атопий у детей первое место по распространенности занимает пищевая аллергия. В свою очередь коровье молоко — продукт питания, который чаще всего выступает аллергеном. Нередко одним из проявлений аллергии к белку коровьего молока становятся гастроинтестинальные заболевания. В настоящее время принято выделять следующие клинические формы гастроинтестинальной патологии, индуцированной аллергией к белку коровьего молока (БКМ): специфические IgE-опосредованные реакции и не-IgE-опосредованные, а также их сочетание — реакции смешанного типа. Однако в рутинной педиатрической практике не-IgE-опосредованные формы по-прежнему остаются плохо распознаваемыми. Это обусловлено многими факторами: разнообразие клинических проявлений, отсутствие достоверных методов лабораторной диагностики, неочевидная ассоциация со временем

и причинно-следственной связью с аллергеном. В статье отражены современные взгляды на особенности клинического течения и диагностики гастроинтестинальной патологии, индуцированной аллергией к белку коровьего молока.

Ключевые слова: *дети; эзофагит; гастрит; энтероколит; проктоколит; аллергия к белку коровьего молока.*

INTRODUCTION

Over the last years, there has been an increase in gastrointestinal diseases induced by cow's milk protein allergy (CMPA) worldwide as this pathology is highly represented [1, 2]. According to the World Allergy Organization (WAO), cow's milk proteins (CMPs) as well as chicken egg proteins are the most important triggers of food allergy in infants and young children [3]. The use of milk formulas for infant feeding plays an important role in the formation of CMPA. However, exclusively breastfed children may also develop clinical manifestations of CMPA due to the penetration of food proteins into breast milk. CMPs can be found not only in dairy products made of cow's milk, but also in some probiotics, oral polio vaccine, diphtheria-pertussis-tetanus vaccine, and some inhalers used in the treatment of bronchial asthma, such as Fluticasone/Salmeterol or Lanimavir [4].

The first clinical signs of CMPA manifest within the period from 10 days to 10 months of life, 3.5 months on the average. Typically, symptoms appear within the first week after the introduction of products containing CMPs (95% of cases). It has been proven that the use of milk formulas containing CMPs during can the development of the first symptoms in 60% of patients. Various forms of gastrointestinal pathology appear in 32–60% of children, skin manifestations occur in 5–90% of children [5], anaphylactic reaction may develop in 0.8–9% of cases [6, 7].

Currently, it is accepted to distinguish the following variants of CMPs [8]:

1) specific IgE-mediated:
- immediate gastrointestinal hypersensitivity;
- oral allergic syndrome;

2) eosinophilic diseases (mixed IgE and non-IgE-dependent):
- eosinophilic esophagitis;
- eosinophilic gastritis;
- eosinophilic gastroenteritis;
- eosinophilic enterocolitis;

3) non-IgE-mediated reactions:
- food protein-induced enterocolitis syndrome;
- food protein-induced proctocolitis;
- protein-induced protein-losing enteropathy.

The peculiarity of the gastrointestinal form of CMPA manifestation is the diversity of a clinical picture since any part of the gastrointestinal tract (GIT) may be involved in the pathological process [9]. Gastroesophageal reflux (GER), nausea, vomiting, diarrhea, bloody stools, and stabbing pains in the abdominal region may be among the first manifestations of IgE-mediated CMPA. The specific clinical picture and association with the allergen contributes to rapid differentiation of this pathology [10]. However, non-IgE-mediated reaction is also a common pathology and can account for up to 50% of all CMPA cases in pediatric practice. The clinical picture in this form of pathology is varied, and the symptoms usually increase slowly, which can make the diagnosis difficult. It is also characterized by decreased appetite, pale skin, infantile colic, possible development of bleeding from the upper GIT, GER, development of chronic diarrhea or constipation, blood and/or mucus in feces [11]. In the present article, common variants of IgE and non-IgE-mediated reactions of gastrointestinal pathology induced by CMPA are discussed.

ESOPHAGEAL LESIONS

Gastroesophageal reflux. CMPA (often non-IgE-mediated variant) may manifest with GER symptoms such as crying, signs of regurgitation, vomiting and sleep disturbance. It is noted that persistent regurgitation is a common non-specific symptom of CMPA in children. According to the literature, CMPA has been documented in 50% of children with persistent GER. Possible manifestations of CMPA include decreased physical development, diarrhea or rectal bleeding on the background of any symptoms of atopy [12]. Diagnosis of this pathology in pediatric practice is difficult as it requires daily esophageal impedance-pH-metry and endoscopy of the upper GIT [13]. In order to eliminate these symptoms, it is recommended to use formulas based on protein hydrolysate or amino acids, or eliminate products containing CMPs in the diet of a nursing mother for 2–4 weeks [14].

Eosinophilic esophagitis (EoE) is a chronic, slowly progressive immune-mediated disease of the esophagus characterized by marked eosinophilic

inflammation of esophageal mucosa, development of submucosal fibrosis, clinically manifested by swallowing disorders (dysphagia, esophageal obstruction by a food clump, vomiting of swallowed food, etc.) [15]. From the pathophysiological point of view, EoE is a chronic Th2-associated esophageal disease characterized by the development of marked eosinophilic inflammation (more than 15 eosinophils in the field of view on a high-resolution microscope with ×400 magnification) in the esophageal mucosa and submucosal fibrosis, clinically manifested by esophageal dysfunction such as difficulty in eating, vomiting, choking, refusal to eat in children and dysphagia in adolescents and adults.

The nature and severity of complaints may vary depending on the age of a patient and duration of the medical history since EoE is a slowly progressive disease [16, 17]. Children of the first years of life have nonspecific symptoms which include regurgitation, nausea and vomiting during meals, difficulty with swallowing certain foods (seafood, eggs, nuts, etc.), abdominal pain, and physical retardation (rarely). Adolescents' complaints are similar to GER: heartburn, pain behind the sternum, the need to chew food for a long time and wash it down with water. Esophagogastroduodenoscopy (EGDS) in patients with EoE reveals nonspecific signs of active inflammation throughout the esophagus: edema and contact vulnerability of the esophageal mucosa, whitish exudate (eosinophilic microabscesses), longitudinal grooves. In addition to the above mentioned, signs of submucosal fibrosis may be found in adolescents and adult patients: multiple concentric rings ("tracheal" or "cat" esophagus), strictures and narrowings of the esophagus [18].

Histologic study includes examination of biopsy specimens using a high-resolution microscope (×400), staining with hematoxylin and eosin. To obtain correct histologic results, biopsy should be performed in at least 6–8 sections from the distal and mid/proximal esophagus. The biopsy specimen should include the epithelium to its entire depth and the intrinsic mucosal lamina. These recommendations are induced by inflammatory changes in EoE which are focal and equally involve both distal and proximal parts of the esophagus [19].

GASTRIC LESIONS

Isolated gastric involvement in CMPA is rare; however, in some cases, the occurrence of prolonged vomiting may contribute to the development of hemorrhagic gastritis in patients. Endoscopic examination of the upper GIT with biopsy of gastric mucosa is a necessary tool to confirm the diagnosis. The study of such biopsy specimens may show eosinophilic infiltration of the mucosa. The etiologic diagnosis is made in accordance with clinical guidelines for the diagnosis of CMPA. The elimination diet prescribed usually yields positive results with complete spontaneous resolution of symptoms within one week [20].

It should be noted that cow's milk has long been used to alleviate clinical symptoms of peptic ulcer disease or GERD due to its acid-neutralizing features. However, the high calcium and protein content significantly increases hydrochloric acid production by gastric parietal cells. As confirmed by an endoscopic study [21], patients with peptic ulcer disease who followed a dairy-free diet had better ulcer scarring results than those who consumed milk.

LESIONS OF SMALL INTESTINE AND COLON

Exudative or protein-induced protein-losing enteropathy is a rare clinical syndrome involving a loss of serum proteins through the GIT [22]. In infancy, this pathology corresponds to a mixed IgE and non-IgE-immune-mediated food allergy characterized by villous atrophy that leads to enteric protein loss, causing hypoproteinaemia/hypoalbuminaemia, diarrhea, peripheral and cavity edema, and, consequently, malabsorption symptoms. Laboratory diagnosis may show signs of anemic syndrome, eosinophilia, hypoalbuminaemia, increased fecal α1-antitrypsin (α1AT), increased specific IgE, and a positive reaction in the prick-test [23]. The pathogenesis is based on the inability of GIT mucous membranes (not only intestine, but also esophagus and stomach) to retain tissue proteins. Serum protein levels reflect the balance between synthesis, metabolism, and protein loss. Exudative enteropathy is characterized by increased protein loss through the GIT compared to synthesis. Whereas albumins are characterized by a long half-life (20 days), it is hypoalbuminaemia that reflects hypoproteinaemia. Laboratory elevation of fecal α1AT is a marker of protein loss through a digestive system [24]. The diagnosis is based on the effects of the elimination diet prescribed as clinical improvement usually occurs within 3–4 days, however, it may take several weeks for complete elimination of symptoms [25, 26].

Food Protein Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated disease. It manifests in infancy at 1–4 weeks of age, beginning with recurrent prolonged vomiting that occurs approximately in 1–4 hours after a meal. Vomiting is often accompanied by pallor, diarrhea, and lethargy. The delayed acute onset and the absence of cutaneous and respiratory symptoms indicate a systemic reaction of the body which differs from an anaphylactic reaction [18]. The most common causes of this pathology are CMPs, soy and cereals. A pronounced loss of weight and a decreased physical development rate arise with a prolonged chronic course of the disease. FPIES is often misdiagnosed as acute viral gastroenteritis, sepsis, or acute surgical pathology, leading to incorrect therapeutic tactics.

A carefully collected medical history plays a special role in the diagnosis of FPIES. In the vast majority of patients with acute FPIES, a single episode is sufficient to make the diagnosis and identify the syndrome's causative products. If the diagnosis is unclear after careful history taking, an oral provocation test should be used as the gold standard for clarification.

There are major and minor diagnostic criteria which make it possible to suspect the disease [28]. Major criteria: vomiting within 1–4 hours after ingestion and absence of classic IgE-mediated allergic skin or respiratory symptoms. Minor criteria: 1) second (or more) episode of recurrent vomiting after eating the same food; 2) recurrent episodic vomiting in 1–4 hours after ingestion; 3) lethargy with any reaction; 4) pallor with any reaction; 5) need for emergency department admission for any reaction; 6) need for intravenous administration with any reaction; 7) diarrhea in 24 hours (usually 5-10 h); 8) hypotension; 9) hypothermia.

To diagnose FPIES, a patient must have a major criterion and at least three minor criteria presented. In case only one episode of FPIES is noted, a diagnostic oral provocation test should be strongly recommended to confirm the diagnosis, as viral gastroenteritis is common in this age group [29].

Proctocolitis induced by food proteins (eosinophilic proctocolitis, allergic proctocolitis) is a transient and benign manifestation of non-IgE-induced GIT lesions. Protein-induced proctocolitis prevalence remains unknown, however it accounts for 0.16 to 64% among all rectal bleeding in infants [30]. It is more common in breastfed infants (60%) and resolves when the mother eliminates CMPs and soy proteins from her diet [31].

The pathogenesis of proctocolitis induced by food proteins remains inconclusive. The main pathophysiologic mechanism is eosinophilic inflammation: at least 10 eosinophils per field of view are found in biopsy specimens of the colonic mucosa. At the same time, according to C. De Brosse et al. [32], eosinophils (on average 16–20 cells in the field of view) are also detected in healthy children GIT (the control group), especially in the colon.

The main clinical symptom of the disease is diarrhea with blood and, sometimes, mucus in feces. An objective examination of a patien shows no hyperemia and fissures in the perianal area. Some children have colic-like abdominal pain, increased gas and painful defecation. As a rule the volume of feces is small, consequently dehydration does not develop. The pathology does not disturb general condition and development of children [32]. These symptoms may appear in 12 hours after ingestion of a causative allergen and may increase further if the allergen continues to be in daily meals. Adherence to an elimination diet can relieve diarrhea and hematochezia within 2–3 days.

Currently there are no generally recognized standard clinical criteria for diagnosing enterocolitis induced by food proteins. In clinical practice, the diagnosis is made in case the symptoms resolved on the background of the elimination diet and then they have returned after reintroduction of the trigger product. Eosinophilia in peripheral blood occurs in 44% of patients. In rare cases, hypochromic anemia and minor thrombocytosis may be observed in laboratory tests [32].

Endoscopic examination of the upper GIT and histologic diagnosis of biopsy material are necessary for differential diagnosis with other conditions causing rectal bleeding. The histological picture is characterized by colitis with eosinophilic infiltration of the intrinsic lamina and muscular layer of the colonic mucosa (more than 6 eosinophils in the field of view) with the formation of eosinophilic crypt abscesses and erosions [32].

The oral provocation test is the "gold standard" for the diagnosis of proctocolitis induced by food proteins. Re-introduction of the suspected product after 4-8 weeks of elimination may be performed at home and shall be documented in a symptom diary in case visible blood in the feces appear. If there is no blood, a fecal occult blood test is recommended [33].

CONCLUSIONS

Gastrointestinal pathology induced by allergy to cow's milk proteins is common in pediatric practice. Due to the variety of clinical forms and manifestations, the diagnostic search is often difficult and should be primarily based on a thorough collection of a patient's medical history. Disappearance of symptoms and their appearance during a provocative oral test should also alert a physician. A coordinated approach is required among allergists, gastroenterologists and nutritionists, nurses and caregivers since the diagnosis is difficult. Further research on the prevalence, pathophysiology, diagnostic markers, and treatment of this pathology is also needed in order to improve patient care.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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ЛИТЕРАТУРА

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