

MEDICAL SCIENCES

**FOOD ALLERGY OR FUNCTIONAL DISORDERS OF
THE GASTROINTESTINAL TRACT IN INFANTS:
PRINCIPLES OF DIFFERENTIAL DIAGNOSIS**

Bobrova Vira

MD, PhD, professor of the pediatric department №1
National Medical University named
after O.O. Bogomolets

Proshchenko Yulia

PhD, assistant of the pediatric department №1
National Medical University
named after O.O. Bogomolets

Pylypenko Iruna

Medical headmaster
Kyiv Clinical Hospital of the 1st branch
of the Health Care Center of “Ukrzaliznytsa”

In recent years, worldwide, the level of food allergies (FA) in children has increased [1,2]. Not only hereditary predisposition but also epigenetic factors play an important role in the development of allergies. The active introduction of dyes, flavors and preservatives into the food industry, and antimicrobial drugs into the agricultural industry, the uncontrolled use of antibiotics, antiseptics have a huge impact not only on the immune response and microbiome of a pregnant women, but also on the debut of allergies in the first days and weeks after the birth of a child and the persistence of allergy symptoms during the whole life [3,4].

Food allergy is an unwanted reaction to food with a proven immune-mediated mechanism due to both IgE-dependent and IgE-independent reactions, which is clinically manifested by pathological changes on the part of the skin, respiratory and digestive organs. The most common form of FA in infants is an allergy to cow's milk protein, which occurs with a frequency of 0.5% in infants who receive breast feeding, and in 2-12% of children – who receive artificial feeding [5,6]. Intact bovine alpha-1-casein, which is considered a major allergen in cow's milk, is easily excreted in a woman's milk when she consumes cow's milk and meat products [3,7].

Gastrointestinal manifestations of allergy to cow's milk proteins are quite difficult to distinguish from common functional disorders of the gastrointestinal tract (GIT) in young children [8,9]. For example, infant intestinal colic, regurgitation, diarrhea, constipation can be manifestations of both allergies to cow's milk and functional disorders of the gastrointestinal tract. At the same time, allergy to cow's milk proteins

in children with burdened heredity by atopy often manifests disorders of the gastrointestinal tract from the first weeks and months of life [10,11]. This causes some difficulties in the differential diagnosis of gastrointestinal disorders in infants and gastrointestinal symptoms of FA. Immaturity of the intestine and violation of the digestive barrier that protects the body from antigens are of great importance in the development of FA as well as functional disorders of the gastrointestinal tract in young children. The function of the intestinal barrier is mediated by immune (secretory Ig A and immunoglobulins of other classes, local cellular immune response) and non-immune factors. Among non-immune factors, gastric secretion of hydrochloric acid and proteolytic enzymes play a special role, which cleave proteins to less antigenic molecules by reducing their size and changing their structure. Among the physical barriers, the most important role has peristalsis, which reduces the likelihood of contact of potential allergens with the gastrointestinal mucosa.

With the failure of the gastrointestinal tract barrier function, there is an increase in the permeability of the intestinal mucosa, excessive absorption, prolonged contact of immunocompetent cells with protein antigens and, as a consequence, the development of sensitization [12,13]. Each of these conditions may have a different etiology, but in each case it is necessary to keep in mind the possibility of non-IgE-mediated allergy to cow's milk protein.

Despite the fact that by the three years of life, 90% of patients with a cow's milk protein allergy have a history of milk tolerance, at the age of one, only 50% of children tolerate dairy products. Functional disorders of the gastrointestinal tract usually disappear much earlier. Children's colic and anxiety are reduced to the age of three to four months, regurgitation - up to 6 months [14,15]. Thus, the dynamics of symptoms and long-term consequences of allergies and functional disorders of the gastrointestinal tract are significantly different, which determines the need to develop unified recommendations that are based on the principles of evidence-based medicine. Such regulatory documents include a protocol for the diagnosis and treatment of allergies to cow's milk proteins in young children, developed by a group of experts from the European Society of Pediatric Gastroenterologists, Hepatologists and Nutrition [16].

According to ESPGHAN's 2012 guidelines for the diagnosis and treatment of cow's milk protein allergy in young children, diet therapy has been identified as the only effective treatment, even with normal levels of specific IgE. The duration of diagnostic elimination of cow's milk protein can last up to 2-4 weeks. In artificial feeding, children are prescribed mixtures based on deep protein hydrolysis. In the absence of improvement on the background of feeding hydrolyzed mixtures for 2 weeks it is advisable to transfer the child to an amino acid mixture to eliminate the reaction to residual peptides in the hydrolysates. If the baby is breastfed, it is recommended to exclude cow's milk protein products from the mother's diet.

Discussing the significance of laboratory investigations, European experts point out that determining the level of specific IgE in the serum is not the gold standard [14,15]. Children with gastrointestinal symptoms predominantly have normal level of specific IgE, which does not exclude them from being allergic to cow's milk protein. It should be noted that the results of the examination for specific IgE should always be interpreted in accordance with the clinical picture and the results of dietary diagnosis.

Regarding the role of serological tests in the detection of allergy to cow's milk proteins in children, it should be noted that modern publications provide evidence of the role of antibodies to free light chains of immunoglobulins (Ig-FLC) in the complex of allergy diagnostics. A number of researchers have demonstrated an increase in these markers in experiments on both sensitized animals and in children with allergy to cow's milk proteins in both IgE-mediated and non-IgE-mediated developmental mechanism [14]. The obtained data indicate a possible prospect of using this test in the process of differential diagnosis of gastrointestinal manifestations in infants.

Clinical case report

The child is 8 months old. During the examination, the mother complained of vomiting, anxiety, liquid feces in the child from the first months of life to the present. The baby is naturally fed. From birth, regurgitation and colic, which was regarded by the pediatrician as manifestations of functional gastrointestinal tract disorders. Therefore, therapy was carried out with espumizan, riabal, dompyridone with a slight positive effect. At 6 months after the introduction of milk porridge, the child had a rash on the face, lower limbs, liquid feces, without pathological impurities. The child was examined: the level of total IgE was in normal range, the polymorphism of 13910 ° C / T lactase gene was established. Consultation of a gastroenterologist: functional disorders of the gastrointestinal tract, lactase deficiency. On the recommendation of a gastroenterologist, treatment of mammalak, creon, sorbents, probiotics was carried out without effect. No diet therapy was prescribed.

From the anamnesis it is known that the child has a burdensome family allergy history: the father has allergic rhinitis, the mother has an allergy to seafood.

During the general examination: the child is pale, the skin is dry, papular-vesicular rash on the face, body, popliteal areas of the lower extremities. During the palpation of abdomen bloating was noted, parenchymal organs are not enlarged. Defecation 3 times a day, liquid, without pathological impurities.

Analysis of clinical and anamnestic data suggested that the child had symptoms of FA, namely allergies to cow's milk protein. The tactics of managing this patient: to continue breastfeeding, mother - a hypoallergenic dairy-free diet, an exception to the diet of beef. After the following elimination diet, after 2 weeks, the child's condition improved, defecation twice a day of normal consistency, decreased rash. It was recommended to follow a dairy-free diet up to 3 years old. Weaning start with dairy-free porridge.

Therefore, clinical observation demonstrates that the diagnosis of FA, especially in the early stages, causes significant difficulties and they are associated with the underestimation of clinical manifestations of allergies to cow's milk protein in the first year of life and their interpretation is not correct - functional disorders of the gastrointestinal tract, lactase insufficiency. When it comes to clinical manifestations of lactose intolerance at an early age, they will always be secondary and associated with insufficient synthesis of the enzyme β lactase due to immunological inflammation of the intestine mucosa membrane due to sensitization of cow's milk proteins.

In addition to the variability of the clinical picture, there are certain diagnostic difficulties. The level of general and specific Ig E is not determinative of diagnosis, the last word in diagnosis remains behind the history and effectiveness of the elimination

diet. A typical mistake is also polyprognozja in the treatment with no clinical effect. To treat "functional disorders of the gastrointestinal tract, lactase deficiency" - means to contribute the development of the pathological process in a more severe form. The effectiveness of pharmacotherapy of gastrointestinal disorders in accordance with international guidelines has not been proven.

Thus, in view of the above, it can be concluded that the differential diagnosis between non-IgE-mediated FA and functional disorders of the gastrointestinal tract is extremely difficult. With a higher probability the allergic lesions may indicate a burdensome family allergy history, involving more than one organ system, for example, the digestive system and the skin, in the pathological process. Elimination of the causal allergen is the basis for the diagnosis and treatment of FA.

References:

1. Burks W. A., Tang M., Sicherer S., Muraro A., Eigenmann P. E., Ebisawa M., Fiocchi A. ICON: Food allergy. *J. Allergy Clin. Immunol.* 2012; 129: 906-920.
2. Prescott S. L., Allen K. Food allergy: riding the second wave of the allergy epidemic. *Pediatr. Allergy Immunol.* 2011; 22: 155-160.
3. Ashley S., Dang T., Koplin J., Martino D., Prescott S: Food for thought: progress in understanding the causes and mechanisms of food allergy. *Curr Opin Allergy Clin Immunol.* 2015; 15: 237-242
4. Merras-Salmio L, Aronen ET, Kuitunen M, Pelkonen AS, Mäkelä MJ, Kolho KL. How mothers perceive infants with unspecific gastrointestinal symptoms suggestive of cow's milk allergy? *Acta Paediatr*, 2014, 103: 524-8.
5. . Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*, 2014, 69: 992-1007.
6. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*, 2011 Mar, 127(3): 594-602
7. Fiocchi A, Brozek J, Schünemann H. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. *World Allergy Organ J*, 2010, 3: 157-61
8. Caubet JC, Szajewska H, Shamir R, Nowak-Węgrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. *Pediatr Allergy Immunol.* 2017;28(1):6–17. doi: 10.1111/pai.12659.
9. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Çokura F, et al. Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age. *J Pediatr Gastroenterol Nutr*, 2015, 61: 531-7
10. Canani R.B., Di Costanzo M. Gut microbiota as potential therapeutic target for the treatment of cow's milk allergy. *Nutrients.* 2013; 5: 651-62
11. Lynch S.V., Boushey H.A. The microbiome and development of allergic disease. *Curr Opin Allergy Clin Immunol.* 2016 Apr; 16(2): 165-71
12. Van den Hoogen SC, van de Pol AC, Meijer Y, Toet J, van Klei C, de Wit NJ. Suspected cow's milk allergy in every day general practice: a retrospective cohort study on health care burden and guideline adherence. *BMC Res Notes.* 2014, 7: 507.

13. Werfel T, Asero R, Ballmer-Weber BK, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy*. 2015;70(9):1079–1090. doi: 10.1111/all.12666.
14. Schouten B, van Esch BC, van Thuijl AO et al. Contribution of IgE and immunoglobulin free light chain in the allergic reaction to cow's milk proteins. *J Allergy Clin Immunol*, 2010, 125: 1308-14.
15. Vandenplas Y, Cruchet S, Faure C, et al. When should we use partially hydrolysed formulae for frequent gastrointestinal symptoms and allergy prevention? *Acta Paediatr*, 2014, 103: 689-95.
16. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr*, 2012, 55: 221-9