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FEATURES OF FORMATION OF GASTROINTESTINAL FORM OF FOOD ALLERGY IN EARLY CHILDREN

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ABSTRACT

The aim of the study was to study the features of the formation of the gastrointestinal form of food allergy in young children. There were 109 patients under observation, aged from 1 month to 3 years, who received treatment in the department of gastroenterology. All children underwent an immunological study to determine the lymphokine-producing ability of T-lymphocytes to allergens.

In this study, we wanted to determine the role of regulatory cells TGF-β1 and IL-10 in non-IgE associated forms of gastrointestinal food allergy in young children. Considering that, according to many authors, food protein-induced enterocolitis syndrome and allergic enteropathy are not attributed to IgE-associated forms of food allergy, it was important for us to evaluate the effect of TGF-β1 and IL-10 on the clinical manifestations of allergic enterocolitis in children.

The data obtained indicate that the cytokines of the TGF-β1 and IL-10 groups in gastrointestinal forms of food allergy act as regulators of inflammatory reactions. The regularities of the influence of the levels of transforming TGF-β1, IL-10 on the activation of the process in gastrointestinal forms of food allergy, more pronounced when the underlying disease is associated with increased IgE values, have been established.

KEYWORDS: Allergic enteropathy, TGF-β1, IL-10, gastrointestinal, IgE

抽象的

本研究的目的是研究幼儿食物过敏胃肠道形式的形成特点。留观患者109**例**，**年**龄1**个月至**3岁，均在消化内科接受治疗。所有儿童都接受了免疫学研究，以确定 T **淋巴**细胞对过敏原的淋巴因子产生能力。

在这项研究中，我们想确定调节细胞 TGF-β1 **和** IL-10 **在幼儿非** IgE **相关形式的胃**肠道食物过敏中的作用。考虑到根据许多作者的说法，食物蛋白诱导的小肠结肠炎综合征和过敏性肠病

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不归因于 IgE **相关形式的食物**过敏，因此评估 TGF-β1 **和** IL-10 对临床表现的影响对我们来说很重要儿童过敏性小肠结肠炎。

获得**的数据表明**，**食物**过敏的胃肠道形式的 TGF-β1 **和** IL-10 组的细胞因子充当炎症反应的调节剂。已经确定转化 TGF-β1、IL-10 **水平**对胃肠道食物过敏过程激活的影响规律，当潜在疾病与 IgE 值增加有关时，这一规律更为明显。

关键词：过敏性肠病，TGF-β1，IL-10，**胃**肠道，IgE

INTRODUCTION

The trend of the last century has been an increase in allergic diseases among children; in every third case (34.2%) they are manifested only by gastrointestinal manifestations [1]. Clinical manifestations of gastrointestinal forms of food allergy have various forms of manifestation, are difficult to diagnose, which increases the frequency of complications and depends on the pathogenetic mechanisms of the development of the disease: IgE associated, non-Ig E-associated and mixed etiology

In recent years, the recognition of non-IgE-associated food hypersensitivity has been increasing [2], but requires further study. In the pathogenesis of food allergy, more and more attention is paid to a new regulatory subpopulation of T cells - type 3 T helper cells. The marker cytokine of this subpopulation is TGF-β1, IL-10 and TNF-α, the undoubted positive role of secretory IgA, which is produced by intestinal plasma cells and thus prevents the entry of antigens into the body. In European countries and North America, the prevalence of food allergies among children is 12% [5]. In Sicherer studies, food allergy manifests itself as gastrointestinal manifestations in 50% of patients. A high prevalence of food allergy has also been reported in Asian countries. So, in India it was 1:96, in Iran 1: 118, in Turkey 1:87, in China 3.8%. Of interest is a study from the United States describing the dependence of the incidence of allergic diseases on the race. It was found that food allergies are more common and polyvalent among representatives of the Negroid race [8].

In Uzbekistan, we studied the prevalence, clinical manifestations of food allergy depending on the type of feeding, regional features of combined forms of allergy in children with hereditary burden [3,4], without studying the pathogenetic mechanisms of the formation of gastrointestinal forms of food allergy in children. Directly atopic, that is, IgE-mediated, includes only immediate gastrointestinal hypersensitivity and oral allergic syndrome. The rest of the forms (non-IgE and mixed forms) are manifested in the form of allergic enteropathy and proctocolitis, food protein-induced enterocolitis syndrome (FPIES), eosinophilic esophagitis, eosinophilic enteritis and are based on cellular reactions. The grouping of these diseases, based on the leading immunological mechanism, is of practical importance. In these diseases, the T-cell response is activated, the combination of an increase in the level of TNF-α by antigen-specific T cells and TGF-β1 leads to an increase in the permeability of the mucous membrane of the small intestine. The importance of regulatory T cells and the production of immunosuppressive cytokines such as IL-10 and TGF-β1 for the prevention of the development of IgE-mediated allergic

immune reactions and hyperreactivity is especially emphasized [11] Describes the role of the regulatory cytokine TGF-β1 in suppression of T cells and protection of the mucous barrier of the small intestine from the penetration of foreign agents [13]. In addition, TGF-β1 stimulates the synthesis of collagen, fibronectin and extracellular matrix protein by altering the expression of integrins, which is very important for reducing intestinal permeability and its barrier function. The results obtained suggest that it is the decrease in the protective role of TGF-β1 against the destruction of the barrier of the mucous membrane of the small intestine by T cells that may play a role in the pathogenesis of enterocolitis syndrome induced by food proteins.

The purpose is to study: to study the peculiarities of the formation of the gastrointestinal form of food allergy in young children.

MATERIALS AND METHODS

There were 109 patients under observation, aged from 1 month to 3 years, who received treatment in the department of gastroenterology. Of these, boys accounted for 52.2% (57), girls - 47.8% (52). Of the examined patients, 72 were diagnosed with food protein-induced enterocolitis syndrome and 37 with allergic enteropathy. To establish the diagnosis of food allergies, clinical-anamnestic, paraclinical (general blood test, coprology, feces for latent bleeding, total protein), and immunological (total IgE, IgE specific to food antigens by enzyme immunoassay, determination of lymphokine-producing ability of T-lymphocytes) were used to allergens) research. The essence of the test for "determining the lymphokine-producing ability of T-lymphocytes to allergens" is to detect and determine the concentration of lymphotoxin in the supernatant of T-lymphocyte cultures obtained after stimulation of cells with food antigens. In the case of a positive reaction, a change in the wavelength of the test sample of lymphoid cells (allergen-stimulated test) occurs on the spectrophotometer in comparison with the control (non-stimulated) sample. The amount of lymphotoxin is expressed in conventional toxic units [7]. When making the diagnosis of food protein-induced enterocolitis syndrome, the following criteria developed by Sicherer [12] were also taken into account: 1) repeated exposure to the culprit food product caused vomiting or diarrhea for the next 24 hours, without any other reasons for this; 2) symptoms are limited only to the gastrointestinal tract; 3) the exclusion of a causally significant product from the diet causes resolution of clinical symptoms within 24 hours. When making a diagnosis of allergic enteropathy, intestinal colic, frequent and loose stools, regurgitation were taken into account; vomiting, bloating after eating food allergy triggers. The physical development of patients was assessed according to the WHO criteria (2016).

RESULTS AND DISCUSSION

Each group of patients, depending on the established diagnosis, was divided into 2 subgroups according to the content of IgE in blood serum. Thus, of 72 patients with food protein-induced enterocolitis syndrome, 46 (63.9%) had an increased IgE level, the average value of which was 128.3 ± 30.0 IU / L, among patients with allergic enteropathy there were 20 (54.1 %), and the average value is 67.1 ± 19.1%. It should be noted that in the subgroup of children with enterocolitis syndrome induced by

food proteins with high IgE values, the time from the onset of the disease to the establishment of an accurate diagnosis was 19.4 ± 3.5 months, in the other subgroup it was 10.1 ± 2.4 months. We assume that this is due to the difficulties in diagnosing the acute course of enterocolitis syndrome induced by food proteins, since the clinical manifestations resemble intestinal infection, sepsis, as noted by other authors [6, 11]. The leading cause of allergy development in the observed children was cow's milk proteins (100%). At the same time, monovalent allergy was more often observed in patients with elevated IgE values. So, in the syndrome of enterocolitis induced by food proteins, sensitization to one product was present in 47.4%, and in the subgroup of children with low IgE values in 35% of cases. The values of specific IgE to cow's milk proteins were clinically significant and amounted to 1.13 ± 0.4 U for enterocolitis syndrome induced by food proteins and 0.9 ± 0.1 for allergic enteropathy. In case of polyvalent allergy, the causes of food allergy in the syndrome of enterocolitis induced by food proteins were most often beef, eggs, chicken meat, less often gluten, soy and citrus fruits. With allergic enteropathy, approximately the same picture was observed (Table 1)

Table 1. Frequency of occurrence of causal allergens by nosology (%).

Products	Food protein-induced enterocolitis syndrome		Allergic enteropathy	
	IgE-associated n = 46	IgE-unassociated n=26	IgE-associated n=20	IgE-unassociated n=17
	abs	%	abs	%	abs	%	abs	%
Gluten	8	17,3	2	6,5*	2	10	2	11,7
Cow's milk	46	100	26	100	20	100	17	100
Soy	7	15,2	2	6,5*	2	10	4	23,5*
Eggs	11	23,9	11	42,3	5	25	7	41,1
Citrus	6	13	6	23	6	30	3	17,6*
Beef	11	23,9	6	23	6	30	1	5,8*
Chiken	11	23,9	7	26,9	1	5	7	41,1*

Note: * - reliability of data between subgroups (P <0.05)

Attention is drawn to the fact that it was in the group of children with food protein-induced enterocolitis syndrome with high IgE levels that clinical signs characteristic of the acute course of the disease were observed: lethargy (13%), pallor and lethargy (17.3%). Especially more often in patients with enterocolitis syndrome induced by food proteins, vomiting was noted, and in the subgroup with increased IgE values - in 58.6% of cases, with normal values 3.8 times less often (15.2%). With allergic enteropathy, we did not observe such a dependence, vomiting was found in 15.7% of cases in patients with high IgE values and in 17.1% with normal IgE values. One of the frequent clinical manifestations of the disease was transparent mucus in the feces, meeting with the same constancy in the syndrome of enterocolitis induced by food proteins and allergic enteropathy, but with increased IgE

values, there was a slight predominance of this symptom, respectively 69.5% and 61.5% in the syndrome of enterocolitis induced by food proteins, with allergic enteropathy, the opposite was observed: 35.0% and 64.7%. Visible blood in the stool was observed only in patients with food protein-induced enterocolitis syndrome in 5 (6.9%) patients, regardless of IgE values. Latent bleeding was found irrespective of IgE values in 9 children (12.5%) with food protein-induced enterocolitis syndrome and in 7 (18.9%) children with allergic enteropathy. In patients with food protein-induced enterocolitis syndrome, a lag in mass-height index below 3 standard deviations was found in 4 patients (5.6%), weight loss by 2 standard deviations - in 9 (12.5%), it is typical that in the subgroup in patients with high IgE values, the delay in physical development was 2 times more common, 15.2% and 7.6%, respectively. TGF-β1 values were increased in all groups of patients, a higher level of TGF-β1 was found in the subgroup with high IgE values, respectively 42.01 ± 7.5 pg \ ml and 25.4 ± 6.3 pg \ ml ($P < 0.05$), with allergic enteropathy these values were lower and amounted to 33.7 ± 15.4 pg / ml in the first subgroup and 30.2 ± 2.8 pg / ml in the second. It should be noted that children in the control group had TGF-β1 (mean value 0.26 ± 0.1 ng / ml). IL-10 values among patients with food protein-induced enterocolitis syndrome had different values depending on the IgE level. Thus, in the subgroup of children with food protein-induced enterocolitis syndrome with increased IgE values, IL-10 values were 42.8 ± 14.2 pg \ ml, and with low Ig E values - 25.4 ± 6.3 pg \ ml, among patients with allergic energy, these figures were 52.4 ± 16.6 pg / ml (with increased IgE values) and 15 ± 3.5 pg / ml (with normal IgE values). In the control group, the level of IL-10 was 10.7 ± 2.3 pg / ml.

There has been an increase in the prevalence of food allergy in recent decades. There are many reports that new eating habits, together with epigenetic factors, may be responsible for this trend. Sensitization is the first step in food allergy, characterized by the production of IgE specific antibodies, inflammatory cytokines and the realization of clinical signs of the disease. Cow's milk protein allergy is one of the leading food allergies, affecting about 2.5% of children under 3 and from 3 to 6% of children under 4 years of age. Although many children outgrow their cow's milk protein allergy, persistence of symptoms of cow's milk protein allergy has been reported [13]. Usually, the prognosis is good with the development of tolerance by 3 years, although recent studies have shown serious consequences in patients with IgE-associated cow's milk protein allergy [14].

In this study, we wanted to determine the role of regulatory cells TGF-β1 and IL-10 in non-IgE associated forms of gastrointestinal food allergy in young children. Taking into account that, according to many authors, food protein-induced enterocolitis syndrome and allergic enteropathy are not attributed to IgE-associated forms of food allergy, it was important for us to evaluate the effect of TGF-β1 and IL-10 on the clinical manifestations of allergic enterocolitis in children. In general, we found a fairly frequent occurrence of an increase in IgE in our patients in 63.9% with food protein-induced enterocolitis syndrome and in 54.1% of cases with allergic enteropathy. Our data coincide with the results of Japanese researchers, according to which increased IgE values were observed from 19 to 50% in the syndrome of enterocolitis induced by food proteins, depending on the cluster of the disease.In contrast to the data obtained by us and

Japanese researchers, European scientists noted an increase in IgE significantly less often in 4 25% [15].

Indicators of TGF-β in our studies demonstrated a significant increase in this indicator in children with enterocolitis syndrome induced by food proteins, more noticeable with increased IgE values (42.01 ± 7.5 IU / ml), at the same time, it is characteristic that in the subgroup with normal IgE values, increased TGF-β1 values were found in all patients, and the mean values reached 21.2 ± 11.2 pg / ml. In patients with allergic enteropathy, the TGF-β1 values were approximately the same in both subgroups, slightly higher in the subgroup of children with increased IgE values. IL-10 indicators in patients with food protein-induced enterocolitis syndrome had the same orientation as TGF-β1, and in patients with allergic enteropathy in the subgroup of children with high IgE values, the indicators were 5 times higher than those in the control group, in the other subgroup (with normal IgE values) reached normal values. In general, the data obtained suggest that the innate immunity is preserved in patients of both groups, since a decrease in TGF-β1 production due to inadequate stimulation of innate immunity by the intestinal microflora can significantly reduce oral tolerance. Other authors also report this [16].

CONCLUSION

The data obtained convincingly indicate that the cytokines of the TGF-β1 and IL-10 groups in gastrointestinal forms of food allergy act as regulators of inflammatory reactions.

The regularities of the influence of the levels of transforming TGF-β1, IL-10 on the activation of the process in gastrointestinal forms of food allergy, more pronounced when the underlying disease is associated with increased IgE values, have been established.

REFERENCES

1. Zakharova I.N., Berezhnaya I.V. Food allergy in children: what is the reason for its growth? // Medical Council. 2018. No. 17. P. 156-162

2. Varlamov E.E., Pampura A.N., Okuneva T.S. Interrelation of the profile of sensitization to cow's milk proteins with the severity of clinical manifestations of atopic dermatitis and the presence of multiple food proteins intolerance in young children. Pediatrics. Journal named after G.N. Speransky 2018; (2): 36.

3. Borisova E.Yu., Lavrova AE, Tolkacheva NI, et al. Features of the cytokine profile in children with gastrointestinal tract pathology with food allergies at different age periods.// Cytokines and inflammation. 2015.Vol. 14.No. 1.P. 91-95Макарова С.Г., Галимова А.А.,

4. Fisenko A.P. et al. Markers of persistence of cow's milk protein allergy: results of a 5-year follow-up. //Pediatrics. Journal named after G.N. Speransky. 2020.Vol. 99. No. 2. S. 88-95

5. Dementyeva EA, Gurina OP, Blinov AE, et al. Study of the subpopulation composition of lymphocytes in atopic dermatitis in children // Materials of the IX scientific-practical conference "Vorontsov readings". St. Petersburg, 2016.S. 53-54

6. Davletova Z. Zh. Clinical features of food allergy in young children, depending on the type of feeding. Abstract for the degree of candidate of medical sciences. Tashkent, 2007.S. 85

7. Kamilova A.T., Geller S.I., Mirzamukhamedov D.M. The syndrome of enterocolitis induced by food proteins in young children: a description of 18 cases. // Questions of Pediatric Dietetics. 2015.Vol. 13.No. 4.P. 56-62Evasovic J.M., Singer CA. Regulation of IL-17A and implications for TGF-31 comodulation of airway smooth muscle remodeling in severe asthma. Am J Physiol Lung Cell Mol Physiol. 2019; 316(5): L843-L868.

8. Flom J.D., Sicherer S.H. Epidemiology of cow's milk allergy. Nutrients 2019;11(5):1051. DOI: 10.3390/nu11051051.

9. Scott H. Sicherer, MD, and Hugh A. Sampson, MDFood allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol 2014;133:291-307.

10. Ginkel C.D., van der Meulen GN, Bak E et al. Retrospective observational cohort study regarding the effect of breastfeeding on challenge-proven food allergy.// Eur J Clin Nutr.– 2018 Feb 19.

11. Meyer R., Chebar Lozinsky A., Fleischer D.M. et al. Diagnosis and management of non-IgE gastrointestinal allergies in breastfed infants-An EAACI Position Paper. Allergy 2020;75(1):14–32.

12. Meyer R. Nutritional disorders resulting from food allergy in children. Pediatr Allergy Immunol. 2018;29(7):689–704. doi: 10.1111/ pai.1296

13. Pensabene L., Salvatore S, D'Auria E, Parisi F.1, Concolino D , Borrelli O, Thapar N, Staiano A,Vandenplas Y,Saps M. Cow's Milk Protein Allergy in Infancy: A Risk Factor for Functional Gastrointestinal Disorders in Children? //Nutrients 2018, 10, 1716; doi:10.3390/nu10111716

14. Vandenplas Yvan, Zakiudin Munasir, Badriul Hegar, Dewi Kumarawati, Ahmad Suryawan, Muzal Kadim, Julistio Tb Djais, Ray Wagiu Basrowi, Deni Krisnamurti, A perspective on partially hydrolyzed protein infant formula in nonexclusively breastfed infants // Korean J Pediatr. 2019; 62 (5): 149-154.

15. Benlounes N., Candalh C., Matarazzo P., et al. The time-course of milk antigen-induced TNF-alpha secretion differs according to the clinical symptoms in children with cow's milk allergy. J Allergy Clin Immunol 1999; 104:863

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