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Phenotypes And Endotypes Of Cow Milk Allergy In Children.

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ABSTRACT

216 infants with cow's milk allergies were examined for the analyze the clinical and immunological features of the cow's milk allergy in infants. We studied the state of humoral immune status (immunoglobulins A, M, G, total IgE and cytokines (IL-2, IL-4, IL-6, IL-8, TNFα) in serum, saliva, and coprofiltrate. It was used the sandwich ELISA enzyme-linked immunosorbent assay. Clinical and laboratory analysis allowed us to identify the skin, gastrointestinal and mixed phenotype of CMA in children, Ig E positive and Ig E negative endotype. Our study showed that each of the studied CMA phenotypes was characterized by the development of a cytokine disbalance at the systemic and local level. We detected the most pronounced changes in the fecal level of cytokines and immunoglobulins in children with the gastrointestinal CMA phenotype. This confirms the role of local allergic inflammation in the pathogenesis of food allergy; it necessitates studying the fecal level of biomarkers to optimize diagnostic and therapeutic approaches

Keywords: local immunity, intestinal epithelial barrier, phenotypes and endotypes, cow milk allergy, children

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INTRODUCTION

Currently, allergic diseases are one of the most common forms of pathology and they are becoming epidemic-wide [1, 2]. According to various authors, about 4-17% of all children suffer from food allergies, a large proportion of them are children of the first year of life [2, 3]. In studies conducted in different countries of the world, it was shown that regardless of the place of residence, the first place among the causally significant allergens in young children was cow's milk [3,4]. The heterogeneity of the clinical symptoms of cow's milk allergy (CMA), differences in the severity and course of the disease, and the different effects of the standard treatment regimens make it necessary to isolate individual phenotypes and endotypes of CMA, which will explain the clinical, pathophysiological, functional features of each individual patient and choose a personalized one therapy [3, 5]. To study the pathogenetic features of the course of CMA with the formation of various clinical phenotypes, we searched for endogenous factors in the implementation of the allergic process [3, 6]. Cytokines are currently considered as a universal biological communication system. They initiates and regulates inflammatory, immune, metabolic processes, interacting at subcellular, cellular, organ and systemic levels, and thus determine the effectiveness and type of immunological response, including the severity of clinical manifestations [7-9].

The purpose was to analyze the clinical and immunological features of the cow's milk allergy in infants, depending on the phenotype of the disease.

MATERIAL AND METHODS

It was studied 216 children with cow's milk allergies, aged from 1.5 to 12 months (group I). The comparison group (group II) consisted of 30 healthy children who did not have a history of food allergy symptoms. We studied the state of humoral immune status (immunoglobulins A, M, G, total IgE and cytokines (IL-2, IL-4, IL-6, IL-8, TNFα) in serum, saliva, and coprofiltrate. It was used the sandwich ELISA enzyme-linked immunosorbent assay.

All patients gave written consent to participate in the study. The study was carried out taking into account the requirements of the Helsinki Declaration of the World Association "Ethical Principles of Scientific Medical Research with Human Participation" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order No. 266 of the Ministry of the Russian Federation of June 19, 2003.

Statistical processing of the material was carried out using specialized software packages for research ("Excel-2010" and "Statstica 10.0" for Windows)

RESULTS

An immunological study of saliva in patients with CMA showed significantly low values ($p < 0.01$) of SIgA levels (0.301 ± 0.006 g/l), responsible for the local immunity system, when compared with children in the control group (0.531 ± 0.031 g/l). IgE in saliva in children with CMA did not differ from the norm. IgM (5.506 ± 0.211 g/L) and IgG (9.624 ± 0.412 g/L) in CMA children significantly exceeded the contral group dates (4.915 ± 0.211 g/L and 0.084 ± 0.032 g/L, $p < 0.05$). When studying the level of systemic cytokines, a slight increase in the level of pro- and anti-inflammatory cytokines was revealed, while the prevalence of anti-inflammatory cytokines in the blood serum was noted ($p > 0.5$). An analysis of the data revealed a significant ($p < 0.05$) change in the studied markers in coprofiltrates in all CMA patients. The level of TNF-α in children with CMA was increased by more than seven times compared with healthy children (31.04 ± 1.31 and 4.08 ± 0.84, respectively, $p < 0.05$). The content of IL-4 in children with CMA was almost 3 times higher than in the control group (15.01 ± 2.64 and 5.67 ± 1.14, respectively, $p < 0.05$). There was a decrease in secretory IgA in coprofiltrate in children of CMA group (23.82 ± 3.87 and 29.32 ± 1.14, respectively, $p < 0.05$).

Clinical and laboratory analysis allowed us to identify the cutaneous, gastrointestinal and mixed phenotype of CMA in children with the formation of Ig E positive and Ig E negative endotype. The skin phenotype (SF, n = 72, 33.3%) was characterized by an isolated lesion of the skin, the absence of complaints from the gastrointestinal tract and other body systems. The Ig E positive endotype prevailed among this phenotype and was determined in 54 children (75% among children with the CMA skin phenotype), the average level of total Ig E was 27.16 +3.68 kUA/L. The gastrointestinal phenotype (GIF, n = 46, 21.3%) was characterized by an isolated lesion of the gastrointestinal tract, the absence of changes in the skin integument and other body systems. This

phenotype was predominantly represented by Ig E negative endotype (33 people, 71.7% among children with GIF), Ig E positive endotype was determined in 13 children with GIF (28.26%), the average level of total Ig E was 34,71 + 5,92 kUA/l. The mixed phenotype (MF) prevailed in our study, n = 98 (45,4%) and was characterized by a combination of skin and gastrointestinal manifestations, of which 7 children (3,2% of all children with CMA) along with symptoms of skin lesions and gastrointestinal tract revealed respiratory manifestations not associated with the layering of an acute respiratory disease. The Ig E positive endotype was predominant; it was determined in 81 children with MF CMA (82.7%), the average level of total Ig E was 21.58 + 5.24 kUA/l.

We recorded a change in the fecal level of immunoglobulins and cytokines in all children with CMA, regardless of the clinical phenotype. SF and MF were characterized by an increase in fecal production of Ig M and G, against a background of a slight increase in Ig E and a moderate decrease in secretory Ig A. In these patients, a moderate increase in the content of anti-inflammatory cytokines (IL 4 and IL13) was noted against a background of a decrease in the production of pro-inflammatory cytokines (IFN-γ, IL8) and increased TNF-α. We detected the most pronounced changes in the fecal level of cytokines and immunoglobulins in children with the gastrointestinal phenotype CMA.

DISCUSSION

The human gastrointestinal tract is composed of several organs with a complex cellular and functional structure. Our study showed that each of the studied CMA phenotypes was characterized by the development of a cytokine disbalance of varying severity at the systemic and local level. The Ig A production decrease, IFN-γ synthesis inhibition, TNF-α and IL-4 increases were observed in patients with CMA. It indicates the activation of the Th2 type of immune response. In this case, the skin phenotype was characterized by more pronounced changes in the serum (systemic) level of cytokines and immunoglobulins; in children with a gastrointestinal phenotype, significant violations of the salivary and fecal level of the determined markers were revealed. Attention is drawn to the active participation in the pathological process of pro-inflammatory TNF-α: serum TNF-α was 6,4 times higher than the control group of children, salivary 1,4 times, fecal more than 2 times. He was considered the most powerful pro-inflammatory cytokine [10]. It is initiates the immune response in the form of a delayed-type hypersensitivity reaction, activates macrophages, starts the synthesis of other cytokines, increases the permeability of the endothelial layer, which in turn leads to an increase in the migration of leukocytes, neutrophils, macrophages, i.e. is a key link in the inflammatory process[8, 11]. The level of IL-4 was also significantly changed in all studied biological fluids: the serum level exceeded the indices of the control group of children by 11,2 times, salivary by 5,6 times, and fecal by 2 times[9, 12]. Hyperproduction of pro- and anti-inflammatory cytokines was accompanied by significant damage to the mucous membrane, migration of a large number of lymphocytes and macrophages to the focus of allergic inflammation [11, 13]. Pro-inflammatory cytokines (IL-1, IL-8, TNF) bind to receptors on other macrophages, lymphocytes and endothelial cells, which leads to increased permeability, increased expression of adhesive molecules and the development of clinical manifestations [7, 9].

CONCLUSIONS

The dynamics of the cytokine in coprofiltrate, saliva and blood serum reflects the current state of the immune system and local protection and, in combination with other indicators, has diagnostic value in determining the localization and degree of activity of allergic inflammation, forming a clinical phenotype of the disease. The significant decrease of secretory Ig A and INF-γ and the increase of fecal levels of Ig E, IL-4, IL-8, IL-13, TNF-α were found. This confirms the role of local allergic inflammation in the pathogenesis of food allergy, and necessitates studying the fecal level of biomarkers to optimize diagnostic and therapeutic approaches.

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