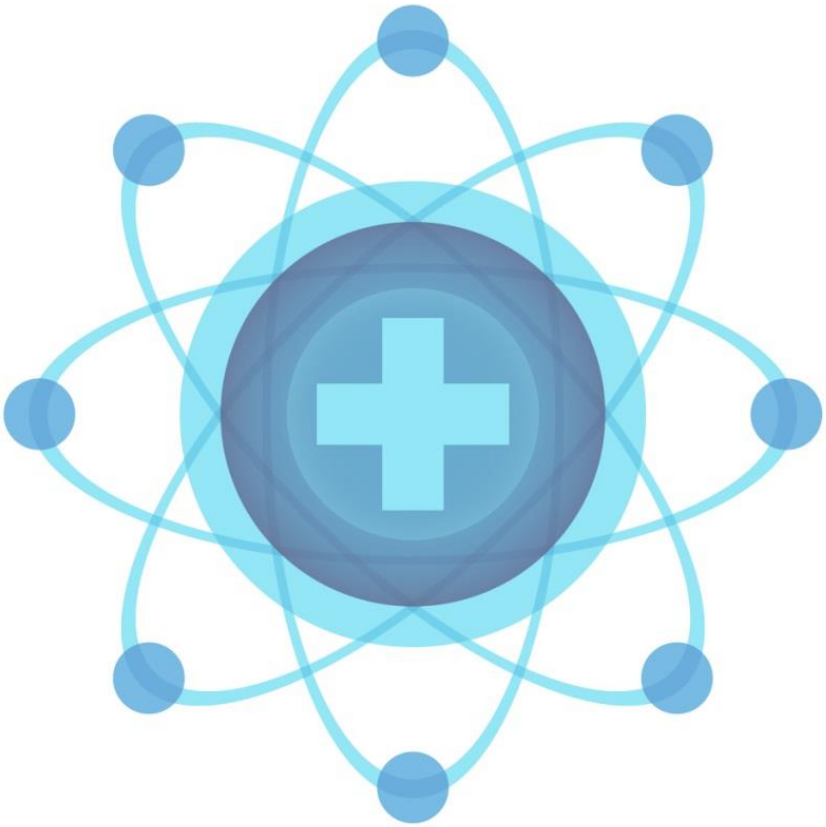

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DIAGNOSTIC ROLE OF IMMUNOLOGICAL AND BIOCHEMICAL PARAMETERS IN THE GASTROINTESTINAL FOOD ALLERGY IN CHILDREN

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Abstract.

Studies have shown that the gastrointestinal form of food allergy in children is often combined with diseases of the gastrointestinal tract associated with Helicobacter pylori infection. The aim of the study was to study the relationship between the immunological and biochemical parameters of blood and saliva in the gastrointestinal form of food allergy in children, depending on the Helicobacter pylori infection. To study the effect of concomitant pathology on the course of food allergy and non-invasive diagnostic methods, 63 patients from 3 to 10 years of age with gastrointestinal allergy were examined. For early non-invasive diagnosis and differentiation of gastrointestinal allergy in children, depending on the Helicobacter pylori infection, it is advisable to determine the concentration of IgE in saliva and diastasis in urine. The authors conducted a study of immunological and biochemical parameters in biological media in the gastrointestinal form of food allergy in children. The study proved an increase in the concentration of IL-8, TNF-α, IgE and a decrease in sIgA in saliva in patients with gastrointestinal allergy, regardless of the association with Helicobacter pylori; it was proved that the quantitative insufficiency of CD8+ T cells in Helicobacter pylori-associated gastrointestinal allergy is an informative factor in the development of chronic diseases of the gastrointestinal tract with a high risk of

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developing an autoimmune mechanism. It was also revealed that IgE in saliva and urine diastasis are informative indicators of early and non-invasive diagnosis, differentiation of gastrointestinal allergy in children, depending on the infection with Helicobacter pylori. In patients with Helicobacter pylori-associated gastrointestinal allergy, a strong positive relationship of Helicobacter pylori infection with saliva IgE and urine diastasis was established, which was not typical for gastrointestinal allergies without Helicobacter pylori infection.

Keywords: Allergy, Helicobacter pylori, gastrointestinal food allergy, correlation, children, non-invasive diagnosis, saliva

Introduction

Food allergy (FA) is characterized by polymorphism of clinical manifestations and complex immunological mechanisms. It has a high and uneven prevalence in various regions of the world, due to specific dietary traditions and the peculiar impact of environmental factors on the child's body [1].

Recent scientific works prove the importance of the microbiocenosis of the gastrointestinal tract (GIT) in the process of allergy formation, that the prevalence of Helicobacter pylori infection significantly differed between children with and without allergies, and also revealed the role of the interaction of genetic (family history of allergies) and environmental (type of birth, breastfeeding, previous antibacterial therapy) factors in the development of allergies [2, 3, 4].

In recent years, many studies have been conducted indicating that specific microorganisms can cause diseases even away from the main focus of infection, which also proves the importance of Helicobacter pylori in various extra-gastric diseases [5].

Sang Pyo Lee's research has shown that Helicobacter pylori infection has a pathogenetic link to allergic diseases. Helicobacter pylori can provoke the release of

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histamine from basophils and, apparently, also suppresses the allergic reaction of the immune response through T-helper cells [6].

In children with allergic pathology, due to the atopic tendency of the immune response, the synthesis of IgE-antibodies to Helicobacter pylori is increased, which is manifested by their increased level and high frequency of detection with an exacerbation of the allergic process against the background of a decrease in the level of IgE - antibodies. The production of IgE-antibodies to Helicobacter pylori is a kind of protective reaction of the body in conditions of chronic infection of the mucous membranes. The protective effect of IgE-antibodies to Helicobacter pylori is also confirmed by their detection in insignificant concentrations, but with a high frequency of cases in the sera of practically healthy children. The presence of these antibodies indicates a predisposition to the Th2 response, which is characteristic of mucosal immunity, which provides asymptomatic persistence of the microorganism in the gastrointestinal tract [7].

Children differ from adults regarding Helicobacter pylori infection in many aspects. Helicobacter pylori causes some extra-intestinal diseases along with gastrointestinal diseases. Although among these diseases in children, symptoms such as recurrent abdominal pain are not specific. A reliable way to detect Helicobacter pylori is a crucial issue that is still being actively discussed. The tests used to diagnose infection are grouped into invasive and non-invasive methods. Non-invasive tests include a urea breath test, fecal antigen test, serological examination, and molecular diagnostic approaches. The use of the endoscopic method is a prerequisite for all invasive methods and creates difficulties in children, as it is a complex procedure and requires the participation of the patient. For this reason, non-invasive tests are widely used in children [8]. Taking into account the above, it can be confidently stated that at present, it is extremely difficult to conduct a differential diagnosis between non-IgE-mediated gastrointestinal allergies (GIA) and functional disorders of the gastrointestinal tract [9].

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Although knowledge of the various characteristics of Helicobacter pylori infection has been expanded since its discovery, much remains to be done to better understand its underlying mechanisms. In addition, new diagnostic methods should be better understood in order to reduce health care costs and provide patients with less invasive diagnostic alternatives [10,11].

The purpose of the study was to study the relationship of immunological and biochemical parameters of blood and saliva in the gastrointestinal form of FA in children, depending on Helicobacter pylori infection.

Materials and methods of research. To study the effect of concomitant pathology on the course and prognosis of FA, 63 sick children from 3 to 10 years of age with GIA were examined, who were undergoing inpatient examination and treatment at the Bukhara Regional Children's Multidisciplinary Medical Center. The patients were divided into 2 groups: 32 children with Helicobacter pylori-associated GIA and 31 children with GIA without Helicobacter pylori. All patients were examined for general, biochemical tests of blood (bilirubin, ALT, AST, urea, diastasis) and urine (general analysis of urine, diastasis in urine). Antibodies to Helicobacter pylori in the blood were determined by ELISA (Human, Germany). Immunological studies were carried out by studying the indicators of humoral immunity (IgA, IgM, sIgA, IgE) and cytokines (IL-8, TNF-α) in peripheral blood serum and saliva by the ELISA method (Vector Best JSC, Russia), according to the attached instructions.

Statistical analysis of the obtained results was carried out using the methods of variation statistics. The reliability of the differences in the mean values was estimated on the basis of the Student's test (t) with the calculation of the error probability (P) when checking the normality of the distribution and the equality of the general variances (F – Fisher's test). The data was considered reliable under the condition that $t \geq 2$, and $P<0.05$.

The correlation analysis was performed using Spearman (Rs) and Pearson (r) methods. The relationship criteria were evaluated on the Cheddock scale: $0.1 < r <$

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0.3: weak; 0.3 < r < 0.5: moderate; 0.5 < r < 0.7: noticeable; 0.7 < r < 0.9: high; 0.9 < r < 1: very high;

Results and discussion. The study of the factors of humoral immunity of the blood in patients with GIA showed a characteristic imbalance in the composition of immunoglobulins in GIA, depending on the Helicobacter pylori infection (Table 1).

Table 1.

The concentration of immunoglobulins in children with food allergies

Blood parameters	Control group (n=30)	GIA with Helicobacter pylori (n=32)	GIA without Helicobacter pylori (n=31)
Ig A (g/l)	3,1 ± 0,5	8,8 ± 1,2*	1,36±0,17*
Ig M (g/l)	2,2 ± 0,5	3,5± 0,8	1,91±0,19
Ig G (g/l)	14,8 ± 1,0	21,5±1,0*	9,54±0,43*
Ig E (IU/ml)	22,0 ± 1,2	25,0±1,1	88,67±4,84***

Note: * - differences relative to the control group data are significant (* - P<0,05, ** - P<0,01, *** - P<0,001)

Analysis of the results of blood tests in patients with GIA associated with Helicobacter pylori showed a significant increase in the concentration of Ig A-8.8 ± 1.2 g/l versus 3.1 ± 0.5 g/l in the control and IgG-21.5±1.0 g/l versus 14.8 ± 1.0 g/l in the control (P < 0.05).

Comparative characteristics of the content of immunoglobulins in the blood of patients with GIA without association with Helicobacter pylori revealed opposite shifts in the ratio of the studied immunoglobulins. It was characterized by a significant decrease in the concentration of IgA to 1.36±0.17 g/l and IgG to 9.54±0.43 g / l (P<0.05) compared with the data of the control group.

The IgM concentration had an unreliable tendency to increase relative to the control in GIA associated with Helicobacter pylori and vice versa, in GIA without

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association with Helicobacter pylori, it tended to decrease against the background of a significant increase in the level of Ig E-88.67±4.84 IU/ml versus-22.0 ± 1.2 IU/ml in the control.

In the study, patients with GIA without association with Helicobacter pylori showed a significant 4-fold increase in Ig E-88.67±4.84 μl compared to the control parameters-22.0 ± 1.2 μl (P<0.001).

The study of secretory immunity in patients with GIA showed a significant decrease in sIgA in both follow-up groups (Table 2).

Table 2.

The concentration of immunoglobulins and cytokines in the saliva of GIA in children

Parameters of saliva	Control group (n=30)	GIA with Helicobacter pylori (n=32)	GIA without Helicobacter pylori (n=31)
Ig A mg%	1,1 ± 0,04	0,3 ± 0,02***	0,6±0,04***
Ig E mg%	1,2 ± 0,05	21,5±1,29***	27,9±1,82***
IL-8 pg/ml	16,2 ± 0,6	95,3±6,12***	57,3±3,26***
TNF-α pg/ml	21,2 ± 1,0	60,8±8,63**	41,6±3,2***

Note: * - differences relative to the control group data are significant

(* - P<0,05, ** - P<0,01, *** - P<0,001)

It was noted a significant decrease in sIgA 3.7 times (0,3 ± 0,02 mg%) with GIA associated with Helicobacter pylori and 1.83 times (0,6 ± 0.04 mg%) with GIA no Association with Helicobacter pylori against benchmarks and 1.1 ± 0.04 mg% (P<0.001).

The concentration of sIgE is increased as in GIA Association with Helicobacter pylori (up to 21.5 ± 1,29 mg%) , and in its absence (up to 27.9 ± 1.82 mg%) vs control - 1,2 ± 0,05 mg% (P<0.001).

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In order to introduce non-invasive manipulations in the practice of pediatric allergy and improve the methods of non-invasive diagnosis of FA in children, cytokines in saliva were studied. The results showed a significant increase in the level of IL-8 and TNF-α in saliva in GIA in children, regardless of Helicobacter pylori infection.

IL — 8 is known to be produced by monocytes, fibroblasts, and endothelial cells. It acts as a neutrophil activator, because it is a chemokine, i.e. an endogenous chemoattractant. It stimulates the directional movement of various types of white blood cells. IL-8, TNF-α, and other cytokines produced by macrophages during the early inducible response are pro-inflammatory cytokines. Their action completely determines the development of the inflammatory process that develops when the antigen is introduced into the macroorganism. The study showed an increase in IL-8 by 5.8 times (95.3 ± 6.12 pg/ml) in GIA associated with Helicobacter pylori and by 3.53 times (57.3 ± 3.26 pg/ml) in GIA without association with Helicobacter pylori in relation to the control - 16.2 ± 0.6 pg / ml.

A significant increase in the concentration of TNF–α in saliva was found in patients with GIA, regardless of Helicobacter pylori infection. In GIA associated with Helicobacter pylori, TNF-α increases to 60.8±8.63 pg / ml, and in GIA without association with Helicobacter pylori to 41.6±3.2 pg/ml versus control - 21.2 ± 1.0 pg/ml ($P<0.01$).

Correlation analysis helps to predict the possible values of one indicator, knowing the value of the other, which is very important when performing non-invasive diagnostic manipulations with high accuracy and significance.

During the exacerbation of GIA in patients without Helicobacter pylori, the linear correlation coefficient showed a strong positive relationship between blood and saliva IgE ($r=0.80$) and an inverse strong relationship between saliva sIgA and blood IgE ($r=-0.78$)

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Based on the results of the study, it can be stated that the increase in the concentration of IgE in both blood and saliva is accompanied by a decrease in the level of sIgA in saliva in children with GIA. The established relationships between salivary and blood immunoglobulins allow early and accurate non-invasive diagnosis of GIA, which, due to the presence of a correlation, is sufficient to study IgE in saliva.

It is known that IL-8 is a pro-inflammatory cytokine and plays a huge role in the innate immune system. IL-8 stimulates the secretion of histamine by basophils and is one of the stimulators of angiogenesis [4]. In our studies in patients with Helicobacter pylori unassociated GIA, an average positive relationship was found between saliva IL-8 and blood IgE (r=0.49), and between saliva IL-8 and saliva IgE (r=0.39). There is also an average negative feedback in the saliva of IL-8 with sIgA (r=-0.45). Consequently, in saliva, an increase in IgE is accompanied by an increase in IL-8 and a decrease in sIgA.

Studies on Helicobacter pylori infection in GIA showed a weak negative association of saliva IL-8 with blood Helicobacter pylori (r=-0.29).

Of interest was the study of the relationship between blood Helicobacter pylori and other blood parameters in GIA. In this respect, weak positive relationships were found between the content of Helicobacter pylori and white blood cells (r=0.27), and TNF-α of saliva (r=0.27). The average positive association of blood Helicobacter pylori with blood AST was also revealed (r=0.39). The average positive association of urine diastase with saliva sIgA (r=0.40) and negative association with saliva IgE (r=-0.50) was also revealed.

It should be noted that there is a positive relationship between saliva and blood IgA (r=0.47), while saliva sIgA has a strong negative relationship with blood IgM (r=-0.59).

The established pattern makes it possible to predict Helicobacter pylori infection by the level of diastasis in the urine, which proves the possibility of limiting non-invasive diagnostics and reducing the financial costs of tests.

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In studies in patients with Helicobacter pylori-associated GIA, a strong positive relationship was established between Helicobacter pylori infection and saliva silencing (P=0.83), blood IgE (P=0.71), and blood IdM (P=0.56), which was not typical for GIA without Helicobacter pylori infection.

A characteristic moderate positive relationship of Helicobacter pylori in the blood with blood leukocytes (r = 0.28), blood eosinophils (r = 0.38) and with blood AST (r = 0.26) was also established in the presence of a moderate negative relationship with urine diastasis (r = - 0.26).

In contrast to the correlations in Helicobacter pylori unassociated GIA, the association of GIA with Helicobacter pylori infection shows an average positive association of TNF-α saliva with IL-8 saliva (P=0.44) and a weak positive association of TNF-α saliva with IgA in the blood (P=0.20). Consequently, in studies on the correlation relationships of immuno-biochemical parameters, it was found that saliva immunoglobulin and urine diastasis are more informative indicators for the urgent and non-invasive diagnosis of GIA.

Thus, for early non-invasive diagnosis and differentiation of GIA in children, depending on Helicobacter pylori infection, it is advisable to determine the concentration of salivator IgE and diastase in the urine.

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