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Immunological Status of Children Infected with *Helicobacter pylori*

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Abstract. Chronic gastritis and duodenitis at the children, associated with Helicobacter pylori infection, carried out by violations in a cellular link of immunity: lymphocytosis, imbalance of subpopulations T-cells with reduction of absolute CD_{3+}, CD_{4+} - lymphocytes, increasing of absolute measures CD_{8+} - and CD_{16+} - lymphocytes. Increasing content of B - lymphocytes, maintenance of IgG and IgM in the peripheral venues blood demonstrates activation of a humoral link on the background of oppression of T - cellular immunity. In the peripheral blood had been shown increase of phagocyte activity of neutrophils, amount of highly active cells, level of the circulating immune complexes.

Introduction

To the leading factors at the etiology and pathogenesis of chronic gastritis and a duodenitis (CHGD) at the children's and teenagers age should carry out hereditary, hyperacidity and peptic, psychological and infectious (Helicobacter pylori — H. pylori) [1,2]. Increasing level of prevalence of digestive system diseases is observed during teenagers' period of life. At that time fast growth of the child is followed by decreasing mass of lymphoid organs. Rising secretion of hormones leads to the oppression of a cellular immunity and stimulation of humoral link of immunity, which causes character of the chronic processes in a digestive tract. Numerous researches of immunological status at the H. pylori – as an associated infection are conducted at the children and adults with chronic gastritis (CHG). On the other hand, it is well - known that duodenitis, and ulcer of a duodenum are induced by H. pylori infection [3, 4, 5]. Literary review, focused on the condition of cellular immunity at the chronic gastritis is ambiguous. Cells, taking part in the congenital immune reactions, included cytotoxic lymphocytes, such as the natural killers (CD_{16+}) and T-cells. T-lymphocytes are the main factors of adaptive immunity and distinguish a wide range of antigens to the bacteria, viruses or other microorganisms, which causing diseases [6]. Despite induction of the mixed pro-inflammatory answers of T-cells, immune system is an incapable to remove H. pylori from the organism, which leads to the constant colonization [7, 8, 9]. At the children with CHG one of the researchers demonstrated rising of T-lymphocytes in a peripheral blood [10]. Proponents of this theory have been shown depression of T-lymphocytes in the blood [11]. Some research carried out the significant trend to the depression of T- lymphocytes, which correlated with increasing duration of illness and severity of an inflammation [12].

There was revealed increasing of CD4+ at the children with H. pylori (+), and H. pylori (–) gastritis. Tendency to decrease ratio of CD4+/CD8+ is considered to be adverse [13]. At the experimental animals and patients with CHG was observed lowest proliferative answer of lymphocytes in the peripheral blood, and lowest production of interleukin 2 and gamma interferon, that indicates about reduction of regulatory activity subpopulation of T – helper's lymphocytes [14, 15, 16, 17, 18].

At the same time was established raised production of interleukin 4 and interleukin 6 by lymphocytes, which characterized function of T – helpers Th_2 type [19]. The research works about humoral link of immunity are also contradictory. Opponent researchers demonstrated increasing content of IgA, IgM, IgG in the blood. Proponent researchers revealed decreasing of these indicators, sometimes – increasing concentration of IgM and IgG at the constant value of IgA [20,

21, 22]. H. pylori infection activates an inflammatory answer at the human body, which leads to recruitment of macrophages, neutrophils and lymphocytes [23].

In general, it testifies about regulatory imbalance in a T-system of immunity, decreasing of the cellular and stimulation of the humoral mechanisms of immunity among infected with H. pylori [24, 25].

Object and Methods of Research

In the research were involved 89 children (45 girls and 44 boys), among them 67 children with chronic H. pylori (+) gastritis, duodenitis. The first group included 35 persons in the aggravation stage of disease, the 2nd group –30 persons in the remission stage. The given patients received treatment and undergo medical examination in the gastroenterology department of the regional children clinical hospital. Duration of the gastrointestinal pathology was varied from 1 to 6 years among the examined patients. Control group was focused on the 24 patients, which covered 11 boys and 13 girls carried out from the gastroenterology department of the regional children clinical hospital. At the given group of children the somatic pathology was absent after medical examination.

Diagnostic of H. pylori - associated infection was assessed by ELISA analyses (USA), using immunological enzyme method (IEM) to determine antibody IgG to H. pylori in the blood.

Estimation T–cell system immunity was carried out with a definition population and subpopulation of lymphocytes in the blood and the next determination ratio of CD_{4+}/CD_{8+} and CD_{3+}/CD_{19+}. In order to study humoral immunity was assessed determination quantity of IgA, IgM, IgG in the blood, using quantitative IEM method. Amount of the circulating immune complexes (CIC) was assessed by V. Hashkov method (1978). Functional activity of neutrophils was carried out in the spontaneous nitro blue tetrazolium test (NBT) with the reaction of recovery.

To compare results obtained with different groups of children, statistical analysis was performed using STATISTICA 6.1 license program. For analyses the data of results were calculated arithmetic average (M), standard deviations (σ) and standard error of the average (±m). Before performing the statistical criteria, we checked a hypothesis about normal law of distribution the random variables (Kolmogorov – Smirnov criteria, Lillifors and Shapiro - Wilkie). Parametrical t-criterion Student was applied to compare results between groups of research, by the data of experiment. There were performed two levels of statistical significance between results of research $p < 0.05$; $p < 0.01$.

Results of Research

State of systemic immunity among the first group of children was characterized by relative and absolute lymphocytosis (table 1), decreasing percentage and quantity of CD_{3+}, CD_{4+} and increasing of the relative and absolute contents of cytotoxic lymphocytes (CD_{8+}). Decreased content of CD_{4+} (helper) on a background of increased content of CD_{8+} (suppressor) carried out to the reduced ratio of CD_{4+}/CD_{8+}. Relative and absolute content of natural killers (CD_{16+}) was significantly increased.

Key role in the reactions of humoral immunity provided B– cells (CD_{19+}), which main function is synthesis of the specific antibodies. Analysis of the cellular immunity at the patients in the first group revealed statistically significant increasing of the absolute amount of B – lymphocytes, compared with control group. Ratio CD_{3+}/CD_{19+} (T/B lymphocytes) was significantly reduced at the children in the first group.

Against an increased content of CD_{19+}-cells, was revealed compensatory activation of T-suppressors, which protected a human body from undesirable consequences of immune responses. At the same time, the relative content of CD_{19+}-cells was significantly increased at the children with chronic gastritis and duodenitis in a stage of remission, compare with a similar indicators in control group ($p_{control}<0.01$).

Changing indicators of cellular immunity in the second group of patients was characterized by lower level of the absolute and relative contents of CD_{3+}- and CD_{4+}- cells, comparing with control group ($p_{control}$ <0.01), and increased relative indicators of CD_{8+} - and CD_{16+} - lymphocytes.

One of the numerous indicators of humoral autoimmune shifts is increased level of circulating immune complexes (CIC).

Table 1. Indicators of cellular immunity in the groups of examined children (M±m)

Indicators		Groups		
		1 (n=35)	2 (n=30)	3 (n=24)
Leukocytes	(10^9/l)	7.37±0.11 $p_{control}$,p_1<0.01	6.01±0.06 $p_{control}$<0.05	6.19±0.05
Lymphocytes	(%)	38.20±1.30 $p_{control}$,p_1<0.01	25.76±0.61 $p_{control}$<0.01	27.16±0.31
	(10^9/l)	2.11±0.07 $p_{control}$,p_1<0.01	1.33±0.04 $p_{control}$<0.01	1.55±0.02
CD_{3+} T-lymphocytes	(%)	48.64±0.82 $p_{control}$<0.01 p_1=0.36	47.76±0.51 $p_{control}$<0.01	53.56±0.39
	(10^9/l)	0.85±0.05 $p_{control}$<0.01 p_1=0.80	1.06±0.02 $p_{control}$<0.01	1.41±0.02
CD_{19+} B-lymphocytes	(%)	22.14±1.09 $p_{control}$=0.26 p_1=0.18	20.63±0.25 $p_{control}$<0.01	19.03±0.32
	(10^9/l)	0.46±0.03 $p_{control}$,p_1<0.01	0.42±0.01 $p_{control}$=0.51	0.32±0.01
CD_{4+} T-helper	(%)	29.26±0.66 $p_{control}$, p_1<0.01	39.76±0.63 $p_{control}$<0.01	45.90±0.63
	(10^9/l)	0.57±0.03 $p_{control}$,p_1<0.01	0.41±0.02 $p_{control}$<0.01	0.68±0.02
CD_{8+} T-suppressor	(%)	27.18±0.37 $p_{control}$,p_1<0.01	23.60±0.21 $p_{control}$<0.01	22.23±0.32
	(10^9/l)	0.49±0.02 $p_{control}$,p_1<0.01	0.38±0.01 $p_{control}$=0.17	0.32±0.01
CD_{16+} T-killer	(%)	21.97±0.41 $p_{control}$,p_1<0.01	21.26±0.09 $p_{control}$<0.01	19.70±0.44
	(10^9/l)	0.41±0.05 $p_{control}$<0.01 p_1=0.78	0.40±0.22 $p_{control}$<0.01	0.29±0.01
CD_{4+}/CD_{8+}		1.63±0.08 $p_{control}$<0.01 p_1=0.10	1.79±0.06 $p_{control}$<0.01	2.11±0.05
CD_{3+}/CD_{19+}		2.49±0.16 $p_{control}$<0.01 p_1=0.41	2.35±0.05 $p_{control}$<0.01	2.75±0.06

Note. $p_{control}$ – reliability of differences in comparison with control group; p_1– reliability of differences between indicators in the 1st and 2nd groups.

The highest CIC was observed among the patients with CHGD in a stage of aggravation, in comparison with control group, which indicating about significant antigenic loading on the human body (table 2).

Table 2. Indicators of the humoral immunity in the groups of examined children (M±m)

№ groups	Indicators			
	CIC (units of optical density)	Immunoglobulins (g/l)		
		A	M	G
1 (n=35)	6.19±0.24 $p_1<0.01$ $p_{control}<0.01$	1.56±0.05 $p_1<0.01$ $p_{control}<0.01$	1.63±0.06 $p_1=0.37$ $p_{control}<0.01$	14.52±0.49 $p_1<0.01$ $p_{control}<0.01$
2 (n=30)	4.13±0.11 $p_{control}<0.01$	1.40±0.04 $p_{control}<0.01$	1.45±0.03 $p_{control}<0.01$	13.01±0.28 $p_{control}<0.01$
3 (n=24)	2.67±0.08	1.88±0.07	1.09±0.06	9.34±0.42

Note. $p_{control}$ – reliability of differences in comparison with control group; p_1– reliability of differences between indicators in the 1st and 2nd groups.

Concentration of Ig G, M classes in a blood plasma among children in the first group was significantly higher, than in the control group. There was observed the highest content of IgG – 14.52±0.49 g/l (9.34±0.42 g/l in control group, $p_{control}<0.01$). Content of IgM was 1.63±0.06 g/l, against 1.09±0.06 g/l in the control group ($p_{control}<0.01$). Concentration of IgA was significantly reduced, in comparison with control group. At the patients in the second group was observed significantly increasing contents of Ig G, M classes, on a background of reduced content of IgA.

At the children in the first group was observed increasing of the neutrophils oxidase activity in a spontaneous nitro blue tetrazolium test (hereafter – NBT – test), comparing with the control and second group (table 3).

Table 3. Functional activity of neutrophils (M±m)

Indicators	Research groups		
	1 (n=35)	2 (n=30)	3 (n=24)
NBT–test spontaneous (%)	50.23±2.69 $p_1<0.01$ $p_{control}<0.01$	21.1±0.83 $p_{control}<0.01$	10.97±0.23
Cytochemical activity of neutrophils (conventional units)	1.05±0.11 $p_1<0.01$ $p_{control}<0.01$	0.61±0.02 $p_{control}<0.01$	0.37±0.02

Note. $p_{control}$ – reliability of differences in comparison with control group; p_1– reliability of differences between indicators in the 1st and 2nd groups.

Therefore, it is testified about activation of the humoral mechanisms of immunity at the children with CHGD in a stage of aggravation. The same violations observed at the children in the stage of remission.

Discussion

H. pylorus causes one of the most widespread chronic infection, which is located at the mucous membrane of a stomach about 50% population in the world [26, 27]. H. pylori do not interfere into the mucous membrane of a stomach, but its attachment to the epithelial cells in mucous membranes causes the cellular and immune reactions in the organism of its owner. It provokes chronic inflammatory answer, such as recruitment of neutrophils, T-lymphocytes, lymphocytes, plasmatic cells and macrophages, which are caused damage of the gastric epithelium, as a result of their activity [28, 29].

Infection is primary got at the children's age and remains throughout the whole life at the absence of treatment [30]. Immune answer of the child to the infection could play a crucial role at the development of diseases of digestive tract at the adult age [31]. H. pylori cause chronic diseases and changes of the immune answer; therefore, it is important to observe the child during different age periods [32].

In the research were involved 89 children (45 girls and 44 boys), among them 67 children with chronic H. pylori (+) gastritis, duodenitis. The first group included 35 persons in the aggravation stage of disease, the 2nd group –30 persons in the remission stage. Control group was focused on the 24 patients without the somatic pathology.

In the investigation was shown, that chronic H. pylori (+) gastritis and duodenitis at the children was connected with decreasing content of CD_{4+} (helper) on a background of increased content of CD_{8+} (suppressor). As the result of this, ratio of CD_{4+}/CD_{8+} was decreased. On the other hand, the research work of proponents demonstrated increased content of CD_{4+} cells in the peripheral blood and tendency to increase ratio CD_{4+}/CD_{8+} at the absence of essential distinctions in the contents of T-lymphocytes (CD_{3+}) and CD_{8+} (suppressors) [10].

CD_{8+} cells are provided cytotoxic reactions, and oppress proliferation and functional activity of T-helpers and B-lymphocytes, thereby limited immune answer, which could be destructive. Similar changes show tension and inferiority of the cellular immune protection. Decrease of the relative and absolute quantity of T-lymphocytes demonstrated poor protective forces of an organism and development of hypoimmune state.

Unlike the majority of bacterial pathogens, which temporarily cause a virulent disease and removed to an adaptive immune answer, specific to the given pathogen, H. pylori successfully reflects the immune answer. Colonization could remain for the decades or the whole life. Therefore factors of bacterial virulence together with factors of its owner, define diseases severity. Role of CD_{4+} cells have a crucial importance to the immune answer of an infection [18].

B-cells have a several functions, but primary play a central role in the humoral immunity, producing antibodies on the response to anti-gene stimulation. Increased content of B-lymphocytes demonstrates activation of humoral link of immunity at the given pathology, against oppression of the cellular immunity.

Increasing the absolute and relative amount of CD_{16+}- lymphocytes had been shown an increased aggression of immune system cells, promoted to the development of cellular immune pathological reactions. Increasing a suppression activity is considered as the reaction of organism, directed to the suppression of inflammatory processes.

One of indicators of the humoral autoimmune shifts is increased level of CIC. Determination of CIC in the blood is considered as a probable possibility of development and progressing of immunopathological process in an organism.

At the normal conditions, immune complexes, which formed in a bloodstream, should be phagocytized and destroyed. Increasing of CIC in the peripheral venous blood at the children with chronic gastritis and duodenitis testified about ineffectiveness of the compensatory mechanisms, which reduce formation of autoantibodies. The given clinical picture is typically found out during process of aggravation.

Reaction of humoral immunity to H. pylori is typical for IgG. It is focused on a high-immunogenic anti-gene epitop, located in the lipopolisakharid H.pylori. The similar answers of IgA and IgM are less specific [33, 34, 35, 36].

In our research was found out significantly increased levels of Ig classes G, M, however level of IgA was reduced. This fact testified, firstly, about high tension of the humoral mechanism of protection organism of patients, which were ill with chronic gastritis and duodenitis, mainly expressed at the children, on a background of the aggravation process [37].

Increased of the spontaneous NBT –test indicated about a high reduction potential of each cell, as the result of increasing levels of CIC [38,39].

Conclusions

Chronic gastritis and duodenitis at the children, associated with Helicobacter pylori, was accompanied by disturbances in the cell-mediated immunity: lymphocytosis, an imbalance of T-cells subpopulations with decreasing absolute values of CD_{3+} -, CD_{4+} - lymphocytes, increasing absolute values of CD_{8+} - and CD_{16+} - lymphocytes.

High levels of B - lymphocytes, increasing of IgG and IgM contents in the peripheral venous blood suggests about activation of the humoral immunity, on a background of T - cell immunity depression.

Determination high titers of circulating immune complexes in the blood of patients with chronic gastritis and duodenitis demonstrated role of immune reactions in the pathogenesis of an upper gastrointestinal tract pathology, which increased in a stage of aggravation of the disease.

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