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The level of cytokine profile in children with infectious mononucleosis epshtein's barb-viral - etiology

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✓ ***Summary***

A comparative study of cytokines in clinically similar groups of patients requiring differential diagnostic search revealed significant differences in the level of indicators. At the height of the disease, the serum of children with infectious Epstein-Barr mononucleosis of viral etiology is characterized by an increase in the content of proinflammatory cytokines IL-1α (1.7 times), IL-β (1.6 times) and INF-γ (4.3 times). In severe infectious mononucleosis, there was a twofold increase in the level of IL-1α and IL-β, a 7-fold increase in the concentration of INF-γ, an increase in the content of IL-1Ra (2.3 times) in the blood serum and the INF-γ/IL-4 coefficient (1.6 times). Correlations were also found between the levels of IL-1α and IL-1Ra (0.49), IL-1a and IL-4 (0.45), IL-1α and INF - γ, (0.64), INF - γ, and IL-4 (0.47), INF - γ, and the number of atypical mononuclears (0.37). Acute bacterial tonsillitis is characterized by a twofold increase in levels of IL-1β and INF - γ, and acute viral hepatitis "B" - much more significant increase in the concentration of IL-Vetta (18 times), increased INF - γ, (2.3 fold) and increased levels of IL-1Ra (1.3 times).

Key words: *infectious mononucleosis, bacterial tonsillitis, hepatitis B.*

Infectious mononucleosis is a widespread infectious disease among children and adults, caused by the Epstein-Barr virus (EBV). The virus is not eliminated from the body, has a tropism for lymphoid and reticular tissues, causing a kind of immune-pathological process, which makes EBV similar to the human immunodeficiency virus. In connection with the introduction of the virus into lymphoid cells, structural changes are formed that affect all parts of the immune system [1,6,7,8,12]. Active proliferation of virus-infected lymphocytes in all organs with lymphoid tissue promotes infiltration and histological changes in these organs (lymph nodes, liver, spleen, etc.). This causes polymorphism of clinical symptoms and complications in EBV infection [2,5,13].

Immune disorders in infectious mononucleosis are complex in nature, they relate to both the cellular and humoral links, entail an aggravation of the course, an increase in complications of the disease, which reflects the essence of infectious mononucleosis as a disease of the immune system [3, 4 , 9,11,14,15]. The analysis of the state of the immune status in relation to changes in the cytokine spectrum in children with infectious mononucleosis has not yet been carried out in the literature available to us, which served as the basis for setting the goal of the study.

The importance of the problem of studying infectious mononucleosis Epstein-Barr-viral etiology is due to the high prevalence, specific tropism of the pathogen to immunocompetent cells, difficulties in differential diagnosis, peculiarities of the course of infection, lack of specific prophylaxis and etiotropic therapy [10]. To date, these issues have been widely studied in children of all age categories and have not been practically studied in adults. Given the variety of clinical forms of the disease, the presence of oncological pathology, the formation of immunodeficiencies of varying severity, in the genesis of which the Epstein-Barr virus plays a key role, the diagnosis of active infection is of particular importance in modern healthcare.

The aim of the research was to study the immunological features of infectious mononucleosis Epstein-Barr virus etiology in children.

Materials and methods

A retrospective analysis of a hospital cohort of patients (a total of 176 sick children) with a diagnosis of "Epstein-Barr virus infection" was carried out, including 72 children with a diagnosis of "infectious mononucleosis Epstein-Barr virus etiology" were included in this study who were treated Bukhara Children's Infectious Diseases Hospital "Specialized Clinical Infectious Diseases Hospital" of Bukhara region for the period 2017-2021.

In the period from 2017 to 2021, on the basis of the Bukhara Children's Infectious Diseases Hospital, data on patients with diagnoses of Epstein-Barr

infectious mononucleosis of viral etiology, acute bacterial tonsillitis and acute viral hepatitis B were analyzed, the features of the course of the disease were studied and clinical and laboratory indicators. Studies of the immune status in patients with infectious mononucleosis were carried out in the laboratory of immunocytokines of the Republican Immunological Scientific Center, the profiles of immunological parameters of the main clinical groups and the control group were studied.

Patient inclusion criteria for the study:

1. age - 12 years and older;
2. clinically and then laboratory-confirmed diagnoses: Epstein-Barr infectious mononucleosis of viral etiology (ELISA, PCR), acute bacterial tonsillitis (bacteriological examination), acute viral hepatitis B (ELISA, PCR);

3.informed consent of the parents of children for the study of immunological parameters.

Criteria of exclusion of patients from the study:

1.age - up to 18 years;

2.the presence of severe concomitant damage to the cardiovascular system, nervous system, urinary system, autoimmune diseases;

3.presence of HIV infection;

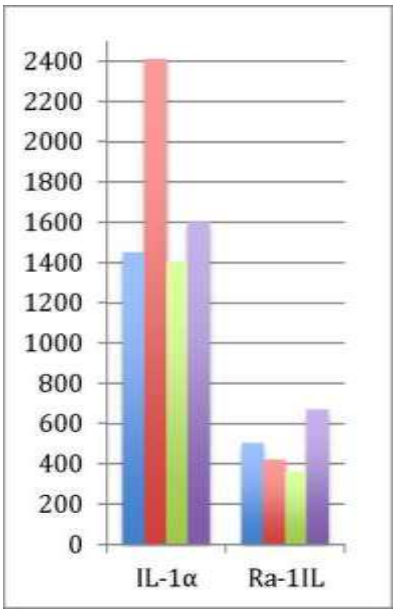
4.the presence of a premorbid background;

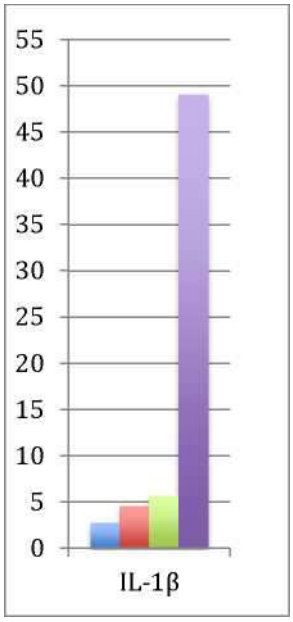
5.the presence of allergic diseases;

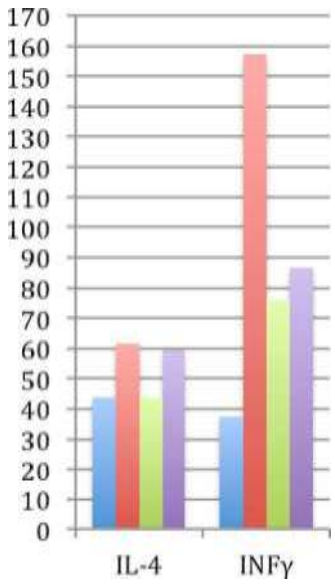
6.other acute viral infections caused by CMV, adenovirus, enterovirus (PCR), as well as reactivation of CMV infection (PCR saliva, blood, ELISA).

Research results and their discussion

Content researchof IL-1α, IL-1β, IL-1Ra, IL-4, INF-γconducted in children of patients with infectious Epstein-Barr mononucleosis of viral etiology, acute bacterial tonsillitis, acute viral hepatitis "B" and relatively healthy children.







Evaluation of the content of cytokines in the group of patients diagnosed with Epstein-Barr infectious mononucleosis of viral etiology revealed a significant increase in serum levels of pro-inflammatory cytokines, while the content of anti-inflammatory IL-1Ra and IL-4 did not differ from those in the group of clinically healthy children (Table 1, picture 1). So, the content ofIL-1α andIL-βexceeded the results of the group of healthy donors by 1.7 and 1.6 times, respectively, and the level of contentINF-γ exceeded the indicators of the control group by 4.3 times($p<0,05$). Coefficientof INF-IL-4was 2,7±0,50 ($p<0,05$), which is 1.3 times higher than in patients with acute bacterial tonsillitis and 2.5 times in patients with acute viral hepatitis "B".

In sick children diagnosed with acute bacterial tonsillitis, the level ofIL-1α andIL-4did not differ significantly from the values of the group of healthy children, IL-1Ratended to decrease, whereas the concentration of IL-βи INF-γ2 times higher than the indicators of the group of healthy children ($p<0,05$). CoefficientofINF- γIL-4was 2,1±0,40, not significantly different from the indicator in patients with infectious mononucleosis.

Table 1.

The level of cytokines in patients with Epstein-Barr infectious mononucleosis

of viral etiology and in the comparison groups

Group \ Indicator	IL-1a, pkg \ ml	IL-1e, pkg \ ml	IL-1Ra, pkg \ ml	IL-4,pkg\ml	INFY, pkg \ ml	INFy/ IL-4
Control (0)	1452,6±226,82	2,7±0,29	502,2±73,82	43,6±5,48	37,1±3,14	1,5±0,25
Infectious mononucleosis (1)	2413,9±304,42	4,5±0,40	419,4±72,93	61,6±7,35	157,3±32,57	2,7±0,50
Acute bacterial tonsillitis (2)	1406,0±256,59	5,6±1,92	358,9±88,98	43,6±4,46	75,8±11,72	2,1±0,40
Acute viral hepatitis “B”(3)	1601,7±356,61	49,1±11,98	667,4±80,66	59,1±9,02	86,5±18,76	1,1±0,15
P_{o-1}	**< 0,05**	**< 0,001**	>0,05	>0,05	**< 0,001**	**<0,05**
P_{1-2}	**< 0,05**	>0,05	>0,05	>0,05	**< 0,05**	>0,05
P_{1-3}	>0,05	**< 0,001**	**< 0,05**	>0,05	>0,05	**<0,01**

Note: P0-1 - reliability of differences in indicators between control groups and IM; P1-2 - reliability of the differences in indicators between the IMand MBT groups; P1-3 - reliability of the differences in indicators between the groups of MI and AVH.

In acute viral hepatitis B, attention is drawn to a sharp increase in the contentIL-β, 18 times relative to the group of clinically healthy children (table 1, figure 1). Also, a characteristic feature of AVH "B" is an increase in the level of IL-1Ra (1.3 times), which may serve as a differential difference of this disease. Along with this, an increase in the contentINF- γ(2.3 times relative to control), while the contentIL-1αand IL-4 was within the indices of the group of healthy donors with a slight tendency to increase. CoefficientINF- γ IL-4significantly lower than the value in the MI group and was 1,14±0,15 (p<0,01).

When analyzing the results obtained, significant intergroup differences were found, which made it possible to determine diagnostically significant cytokine markers of the studied infections in sick children. Thus, a distinctive feature of Epstein-Barr infectious mononucleosis of viral etiology in sick children is a significant increase in the content of IL-1α (1.7 times compared to a group of clinically healthy children) at a normal level of its content in patients with acute bacterial tonsillitis and acute viral hepatitis "B », IL-β (1.6 times) and the maximum increase in INF-γ - (4.3 times). The differential diagnostic criterion for acute viral hepatitis is a significant increase in the level of IL-β (18

times relative to the group of healthy children), INF γ - (2.3 times) and IL-1Ra (1.3 times), and a feature of acute bacterial tonsillitis in adults can be considered a twofold increase in the level of IL-β and INF-γ relative to the group of clinically healthy children.

With obvious intergroup differences in the serum concentration of cytokines in the patients of the three clinical groups, there is a similar pattern of changes in the indicated cytokine profile, as evidenced by an increase in the content of proinflammatory INF-γ, which is most pronounced in MI, as well as the absence of changes in the anti-inflammatory cytokine - IL-4. The INF-γ, IL-4 coefficient in MI was significantly different from the AVH "B" groups ($p < 0.01$) and healthy donors ($p < 0.05$).

When studying the concentration of cytokines, a significant change in the level of all studied parameters was determined depending on the severity forms of Epstein-Barr infectious mononucleosis of viral etiology.

The level of the studied pro- and anti-inflammatory cytokines in moderate MI was slightly lower than the average values in the general group of infectious mononucleosis, but with the preservation of the direction of changes. Severe MI was characterized by a twofold increase in the level of IL-1α and IL-β,7-fold increase in the concentration of INF-γ, an increase in the content of IL-1Ra in the blood serum and the coefficient INF-γ IL-4 (table 2).

Table 2.

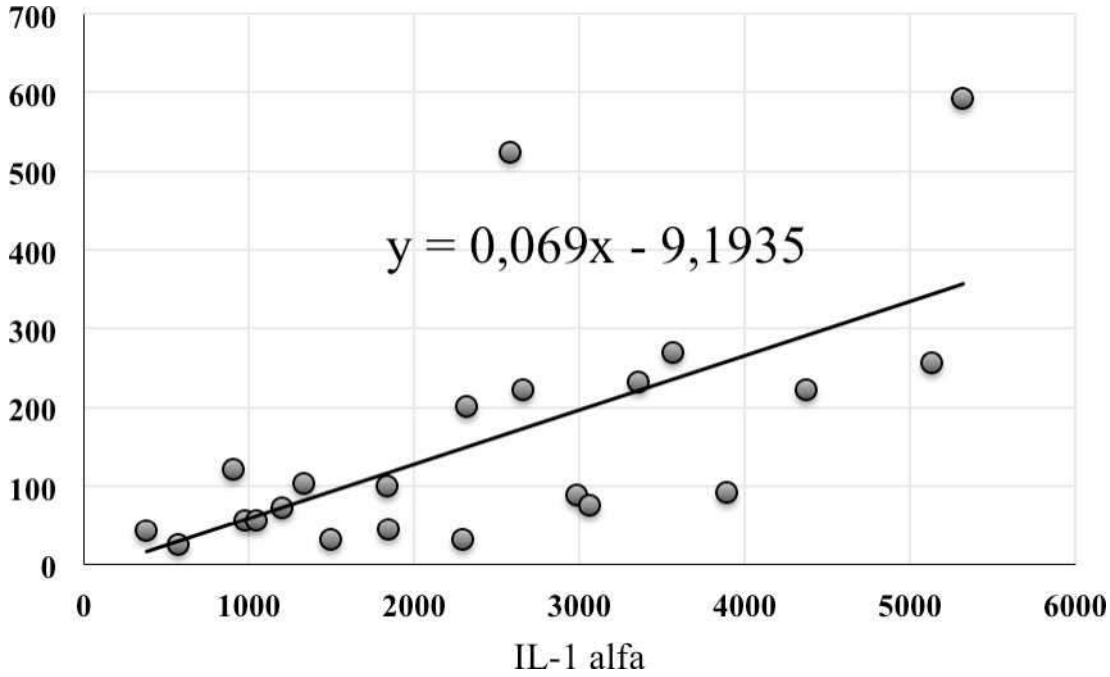
Cytokine levels depending on the severity of infectious mononucleosis

sIndex	IM mean value	IM middle course	IM severe course	Control
IL-1α, pkg \ ml	2413,9±304,42*	2127,4±2,51**#	3027,9±5,24***	1452,6±226,82
IL-β, pkg \ ml	4,5±0,40***	4,0±0,10***#	5,6±0,20***	2,7±0,29
IL-1Ra, pkg \ ml	419,4±72,93	309,8±0,81*#	726,5±4,43**	502,2±73,82
IL-4, pkg \ ml	61,6±7,35	61,1±0,47**#	62,6±0,74**	43,6±5,48
INF γ, pkg \ ml	157,3±32,57***	107,3±0,60***#	264,4±2,10***	37,1±3,14
INF γ IL-4	2,7±0,50*	2,3±0,11**#	3,7±0,27***	1,5±0,25

*Note: p - reliability of differences in indicators between the groups of IM and control, where ****

*- p <0.001; ** - p <0.01; * - p <0.05; # - significant differences in the clinical groups of IM, depending on the severity of the course*

When researching the correlations between the levels of cytokines, the content of atypical mononuclear cells in peripheral blood and the level of aminotransferases (ALT, AST), the following relationships were established: a moderate direct correlation between the levelsIL-1andILα-1Ra(0,49), IL-4 (0,45); more pronounced correlation is observed between levelsIL-1αandINF-γ - 0,64 (picture 2); level INF- γalso correlates with the levelIL-4 (0,47)and the number of atypical mononuclear cells (0.37); the level of aminotransferases does not correlate with the level of any of the cytokines.



Pic.2. Correlation between the level of INF-γ and IL-1α in the acute period of infectious mononucleosis

Thus, a comparative study of cytokines in clinically similar groups of patients requiring differential diagnostic search revealed significant differences in the level of indicators. At the height of the disease in the blood serum of sick children with Epstein-Barr infectious mononucleosis of viral etiology, an increase in the content of pro-inflammatory cytokines IL-1a (1.7 times), IL-β

(1.6 times) and INF-y (4.3 times times).In a severe course of infectious mononucleosis, a twofold increase in the level of IL-1α and IL- β,7-fold increase in the concentration of INF-γ, increase in the content of IL-1Ra (2.3 times) in blood serum and the ratio INF-γ / IL-4 (1.6 times).Correlation relationships were also established between the levelsIL-1α andIL-1Ra(0,49), IL-1aandIL-4 (0,45), IL-1aandINF- γ(0,64), INF- γ andIL-4 (0,47), INF-andγthe number of atypical mononuclear cells (0,37). Acute bacterial tonsillitis is characterized by a 2-fold increase in levelsIL-1eandINF γ -, and acute viral hepatitis "B" - by an order of magnitude more significant increase in the concentration of IL-vetta (18 times), increased INF-γ (2.3 times) and an increase in the level of IL-1Ra (1.3 times).

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