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The Cytokine Profile at Children with Juvenile Forms of Arthritis

ABSTRACT

Research of cytokine profile at 76 children with various forms of juvenile arthritis aged from 0 till 16 years is conducted. Average values of levels of pro-inflammatory cytokine (TNF-α, IFN-γ and IL-6) is ten times exceed the limit of the normal range. High level of pro-inflammatory cytokine of IL-1β significantly correlates with a hereditary loading of patients, and high levels of anti-inflammatory cytokine of IL-10 are observed at patients with the juvenile ankylosing spondylitis (JAS).

Keywords: cytokine, juvenile forms of arthritises

INTRODUCTION

Juvenile arthritis (JA) is one of the most common and most debilitating rheumatic diseases at children. JA disease ranges from 2 to 16 per 100 thousand of children's population under the age of 16 years. Prevalence of JA in different countries ranges from 0.05 to 0.6%. The prevalence of JA in children under 18 years reached 62.3 in Russia. The primary disease - 16,2 per 100 thousand including teenagers - 116.4 and 28.3 and children under the age of 14 - 45 8 and 12.6 [2].

The juvenile rheumatoid arthritis is the multifactory constitutional inveteratephlogotic immune autoaggressive disease with the primary affect of supporting-motor apparatus. The main **aim** of the pathogenesis of JRA is the activation of cellular and humoral parts of immune autoaggressive process.

It is expected that entheticor changed self-antigen is understood and processed by macrophage which present as T-lymphocytes. The interaction of antigen-presenting cells with T-lymphocyte stimulates the cytokine synthesis, causing a cascade of pathogenic changes with the development of systemic manifestations of the disease and progressive inflammation in joint cavity. In this case systemic appearances of JRA (fever, rash, lymphadenopathy, weight loss, etc.) are associated with increased synthesis and the activity of tumor necrosis factor (TNF-α) and interleukin (IL-6, IL-1) [4]. Early diagnosis and treatment of juvenile idiopathic arthritis in children is one of the most urgent problems of pediatrics, the etiological factors of development which

has not been established till nowadays. Among the possible reasons underlying pathological process, discusses the infectious nature of the disease, trauma, stress, immunogenetic predisposition. The aim of our research is the evaluation of cytokine profile in patients with different forms of juvenile arthritis.

METHODS AND MATERIALS

We studied 76 children (aged 1 to 16 years) with juvenile seronegative arthritis (reactive arthritis, spondylitis, juvenile arthritis, etc.), passing stationary inspection treatment in cardiorheumatological unit of the republican hospital No. 1 in national center of medicine. The average age of children was 9.88 ± 4.25 years. Among the examined children: Yakut nationality was 66, Russians - 11, Evenks – 3.The age structure of the children examined by us strongly varied, however 18.8% from them appeared 13-years, 10,0% - 7 years etc. Note that, this pathology in 42.5% of cases was found in children of 12-16 years, i.e. during adolescence. The distribution by sex showed the predominance of boys (60%) of girls (40%), which corresponded to the literary data [3].

A B C

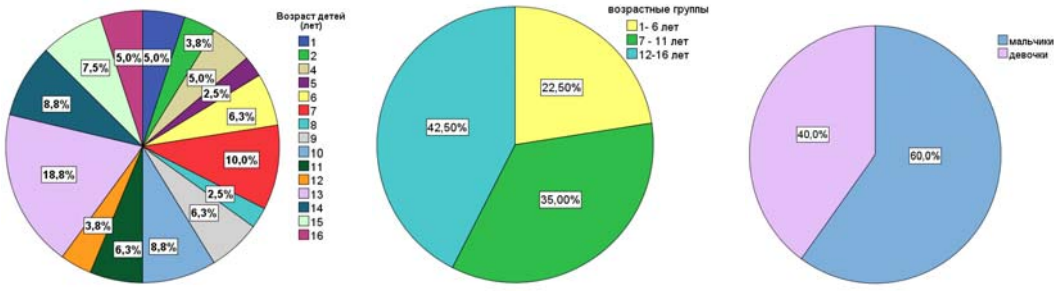

Figure 1.Distribution of the studied children on age (A), age groups (B) and a sex (C).

Concentration of anti-inflammatory (IL-4, IL-10) and pro-inflammatory cytokines (IL-6, IL-1β, IFN-γ and TNF-α) in blood serum determined by method of an enzyme immunoassay with application of sets of the reagents released by JSC Vektor-Best (Novosibirsk, Russia) by the enclosed instructions, results expressed in pg/ml.

All sick children were conditionally divided by diagnosis into 3 groups: 1 group consisted of children with psoriatic arthritis (PA) (n=1), juvenile rheumatoid arthritis (JRA) (n=14); 2 group consisted of the children with reactive arthritits (RA) (n=24), juvenile idiopathic arthritis (JIA) (n=2), the last group – children with the juvenile ankylosing spondylitis (JAS) (n=16).All of the received quantitative results are subjected to statistical analysis using the package «SPSS.17.0"company StatSoftInc (USA) 2001. The equality of sample means was tested by the parametric Student t-test (in the case of a normal distribution) and non-parametric U-Mann-Whitney test for independent samples (if different from the normal distribution).Data are expressed as M (average mean) ± m (standard error of the mean). The method of correlation analysis of the data with the calculation of coefficients and Spearman rank correlation was used for identifying the relationship between the studied parameters. For the threshold significance we took size p with a value <0.05.

RESULTS

The average values of the investigated cytokines indicate a different character of changes (Table 1). In carrying out the average mean of children and cytokines to normal values of healthy individuals, the greatest degree of improvement observed in the level of pro-inflammatory cytokines TNF-α (12.42 in time), IFN-γ (in time 11.17), IL-6 (a 9.41-fold) and IL-1β (1.73 times).

Table 1

Average value of concentrations of cytokine at sick children in comparison with the normal values of conditionally healthy persons (JSC Vektor Best)

Cytokine (pg/ml)	Indicators of the studied group				Indicatorsofhealthyperson	
	Minimum	Maximum	Averagevalue	Standarddeviation	Rangesofnorms	Averagevalue
IL-4	1,06	11,94	**2,44**	2,21	0-13	0
IL-6	3,44	252,7	**18,82**	34,78	0-16	2
IL-10	1,54	11,58	**3,61**	1,57	0-31	5
IL-1β	1,26	70,70	**2,78**	7,96	0-11	1,6
TNF-α	2,09	71,93	**6,21**	8,66	0-6	0,5
IFN-γ	14,63	90,63	**22,34**	10,83	0-10	2

Level shift of anti-inflammatory cytokines is characterized by increasing of IL-4 and decreasing of IL-10B 1.38 times. Thus, in children with juvenile forms of arthritis increased average proinflammatoryof cytokines TNF-α, IFN-γ and IL-6 as well as reduced levels of anti-IL-10.

Table 2

Cytokine level in the age groups of children with juvenile forms of arthritis

Cytokine (pg/ml)	Age groups		
	1 1-6 years (n=17)	2 7-11 years (n=28)	3 12-16 years (n=31)
IL-4	2,4 ± 0,37	2,01 ± 0,16	2,83 ±0,55
IL-6	**16,1 ± 4,0**	**12,79 ± 2,99**	**25,16 ± 8,80**
IL-10	3,9 ± 0,4	3,82 ± 0,37	3,25 ± 0,21 (p^{1-3}=0,089)
IL-1β	**1,78 ± 0,05**	**1,95± 0,11**	**3,99 ±2,15**
TNF-α	5,32 ± 0,45	7,17 ± 2,5	5,91 ± 1,03
IFN-γ	22,32 ± 1,87	25,16 ± 3,02	20,05±0,98

There was comparative analysis of the level of cytokines in different age groups, which have not identified any statistically significant differences between groups (Table 2).According to the

level of anti-inflammatory cytokine IL-10 decreasing tendency (p = 0.089) observed in the age group (12-16 years) compared with the first group (1-6 years) children. It should be noted that the average value of pro-inflammatory cytokines IL-6, IL-1β has the maximum level in the same third age group (12-16 years).Perhaps such obvious changes may be associated with features of puberty, when the immune system becomes vulnerable due to hormonal imbalance and disruption of regulatory functions of the hypothalamic-pituitary-adrenal system. The imbalance between the overproduction of pro-inflammatory cytokines mainly macrophage nature, such as TNF-α, IL-1β, IL-6 and anti-inflammatory cytokines IL-4 induces a chronic inflammatory process [5].

Correlation analysis was performed in a total sample of patients between levels of cytokines in serum and by range parameters as personal data, the diagnosis, the number of affected joints, positive for HLA-B27, duration of disease, articular syndrome, limitation of motion of the joints, the nature of disease onset (gradual, sharp) factors (respiratory infections, hypothermia, trauma, vaccinations, allergies), the presence of family history, swelling and pain.

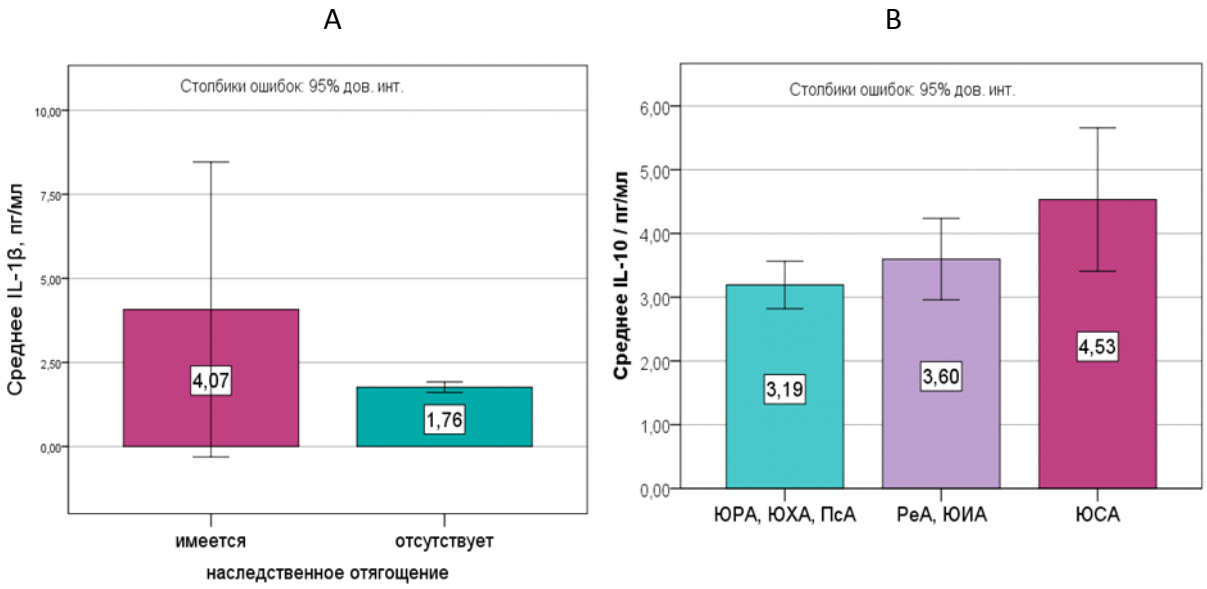

Figure 2.The dependence of the levels of IL-1βfrom hereditary loading (A) and IL-10 from the juvenile form of arthritis (B)

The results showed a correlation of the pro-inflammatory cytokine IL-1β (r = - 0,408; p = 0,000) with the presence of hereditary loading (Figure 2A). At children with hereditary loading of rheumatic diseases (parent questionnaire covering 3 generations), the level of this cytokine (2.15 ± 4.07 pg / ml) was significantly higher (p = 0.000) compared with children without burdeness (1.76 ± 1.76 pg / ml).Another correlation was established between the level of anti-inflammatory cytokine IL-10 (r = 0,314; p = 0,006) and conventional groups, ranked by diagnosis. The minimum value of the average level of IL-10 has been installed in one group (3,19 ± 0.18 pg / ml). In group 2, it was (3.60 ± 0.31 pg / ml), and the maximum level observed in group of patients 3 (4.53 ± 0.52 pg / ml). A statistically significant difference (p = 0.027) observed while comparing the groups 1 and 3. It's known that the main function of IL-10 - inhibition of cytokine production by T-helpers of the first type (TNF-β, IFN-γ), and activated macrophages (TNF-α, IL-1, IL-12). Most likely, rising of this cytokine has protective-compensatory mechanism to suppress inflammation.

Thus, the preliminary results of the analysis of the cytokine profile of children with juvenile forms of arthritis indicate rising of pro-inflammatory cytokines, more of TNF-α, IFN-γ and IL-6. High levels of the pro-inflammatory cytokine IL-1β significantly correlates with hereditary loading of patients, and high levels of anti-inflammatory cytokine IL-10 are observed at patients with juvenile ankylosing spondylitis (JAS).

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