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FEATURES OF CYTOKINE PROFILE OF BLOOD SERUM IN CHRONIC KIDNEY DISEASE IN CHILDREN

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Abstract

Objective: to study the diagnostic and prognostic significance of determining the cytokine status of blood serum in children with various nosological forms of kidney disease.

Patients And Methods. We observed 255 children with various kidney diseases [with urolithiasis (UL) - 16, with inflammatory kidney diseases (IKD) - 174, with glomerulopathies (GN) - 65]. In all groups of subjects, children with stage 1 and 2 CKD predominated (100, 97.5 and 95.4%, respectively). The control group consisted of 50 practically healthy children. All subjects were tested for serum levels of TNF-α, TNF-RI and TNF-RII, IL-10, TGF-β1 and TGF-β3, IL-2, IL-2-SR).

Results. Increased serum TNF-α levels can be considered a highly specific marker of acute pyelonephritis chronization, while decreased TNF-RII concentrations can be considered indicators of complete clinical and laboratory remission of pyelonephritis. Increased TNF-α and TNF-RI can also be considered a marker of autoimmune inflammation. Deficiency of IL-2, IL-10, and TGF-β3 with increased IL-2 R in the blood should be used as a marker of inflammatory and autoimmune kidney diseases, and increased TGF-β1 as an early marker of nephrosclerosis development, especially in patients with glomerulonephritis. A more than 4-fold increase in TNF-α/IL-10 makes it possible to position it as an additional diagnostic criterion for the inflammatory and autoimmune process in the kidneys. Increased urinary excretion of TNF-α against the background of decreased IL-10 with the maintenance of stably high concentrations of TGF-β1 is a marker of inflammation and fibrosis in inflammatory kidney diseases and glomerulonephritis. Timely nephroprotective therapy aimed at inhibiting the progression of CKD and its complications should also include modulation of the cytokine status.

Keywords: Cytokines, chronic kidney disease, children.

Introduction

The involvement of cytokines in the pathogenesis of various kidney diseases has been confirmed by the results of a number of studies in recent years [12-17]. It has been shown that cytokines can be synthesized by proximal tubule epitheliocytes, subsequently exerting a para- or autocrine effect on target cells, stimulating the processes of cellular proliferation, differentiation, growth and secretion [18, 19]. Despite the local nature of their action, some of them are found in the systemic bloodstream and biological fluids, which may have diagnostic value in kidney diseases [20, 21].

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However, the majority of studies are currently devoted to cytokines in individual groups or nosological forms of kidney diseases without an emphasis on the stage of ckd and without comparing the studied indicators depending on the primary disease [12-17].

The aim of the study is to investigate the diagnostic and prognostic significance of determining the cytokine status of blood serum in children with various nosological forms of kidney disease.

PATIENTS AND METHODS

A total of 255 children with various kidney diseases were observed. The control group consisted of 50 practically healthy children. The patients were divided into 3 groups: group 1 - 16 children with urolithiasis (ul) and dysmetabolic nephropathy (dmn) without infection, group 2 - 174 children with microbial inflammatory kidney diseases (mickd), group 3 - 65 children with glomerulopathies (gn). Among the children with mickd, there were 165 observations with acute and chronic pyelonephritis and 9 with cystitis. The development of the microbial inflammatory process in the urinary system was caused by the following factors: congenital malformations of the urinary system - 40, including vesicoureteral reflux - 11, hydronephrosis - 10, duplication of the kidneys - 9, renal cysts - 3, renal hypoplasia - 3, pyelourethral stenosis - 2, pelvic dystopia - 2; dmn - 80; neurogenic urinary bladder (nub) - 26 children. Depending on the stage, various pathologies were identified in ckd. At stage 1 - these are dmn and nub (the average age of children is 9.1 years), at stage 2 - congenital malformations of the urinary system (presented above) and dmn (the average age of children is 6.8 years). Moreover, in patients with ckd stage 2, a combination of several factors was noted in 70% of cases. At stage 3. - vur, reflux nephropathy (16-year-old boy and 13-year-old girl), at stage 4 - hydronephrosis of both kidneys (1-year-old boy), at stage 5 - cystic dysplasia of both kidneys (15-year-old boy).

The duration of the disease in all groups of observed patients was more than 3 months. Each child was assigned a stage of CKD according to the National Kidney Foundation-K/DOQI classification (2003) in accordance with the level of SCF calculated using the Schwartz formula (2009) [22, 23] (Table 1). Children with stages 1 and 2 of CKD predominated. Therefore, the cytokine profile indicators of children with CKD stage C3-5 (CKD) were used only to assess the inflammatory index (II), which was calculated as the ratio of pro- and anti-inflammatory cytokines [13, 14]. The average age of the examined children: Group 1 - 10.7 ± 2.7 years, Group 2 - 8.7 ± 0.7 years, Group 3 - 9.1 ± 1.1 years, $p > 0.1$. In terms of gender, boys predominated in Groups 1 and 3 (87.5 and 60%, respectively), while girls predominated in Group 2 (83.3%).

All subjects underwent quantitative determination of the following cytokines in the blood serum: TNF-α (tumor necrosis factor a), TNFRI and TNFRII (tumor necrosis factor I and II receptor), IL-10 (interleukin-10), TGFβ1 and TGFβ3 (transforming growth factor-β types 1 and 3), IL-2 (interleukin-2), IL-2-SR (interleukin-2 soluble receptor). Blood was collected from each child in the morning on an empty stomach, then the blood samples were stored at -76 °C. The study was conducted by the sandwich method of solid-phase enzyme immunoassay, using specific reagents from R&DDiagnostics Inc (USA) in accordance with the manufacturer's recommendations. The results were recorded using a Multiscan enzyme immunoassay analyzer (Finland). The number of indicators was calculated by constructing a calibration curve using a computer program and expressed in pg/ml or ng/ml. Blood samples were examined in a licensed laboratory of non-infectious immunity chemistry of the Federal State Budgetary Scientific Institution G.B. Elyakov

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Pacific Institute of Bioorganic Chemistry, Far Eastern Branch of the Russian Academy of Sciences (Head of Department, Doctor of Chemical Sciences, Professor P.A. Lukyanov).

Table 1 Distribution of patients depending on the stage of CKD

Stages of CKD	Diseases of the urinary system (abs., %)					
	DMN and UL (n=16)		MVPZ (n =174)		GN (n	=65)
	Abs	%	Abs	%	Abs	%
C1	13	81,3	145	83,3	56	86,2
C2	3	18,7	25	14,4	6	9,2
C3	0	0	1	0,6	2	3,1
C4	0	0	2	1,1	1	1,5
C5	0	0	1	0,6	0	0
Total	16	100	174	100	65	100

Statistical analysis of the obtained data was performed using the Statistica 10 application package (StatSoft, USA), Microsoft Excel 10. Nonparametric statistics and qualitative data analysis were used to evaluate cytokine indices (Mann-Whitney U-test, two-sided p-value, calculation of the correlation criterion value R, median and quartiles). Parametric statistics were used to evaluate the cytokine profile of blood in children of group 3 (CG3): mean values of features (M), errors of mean values (± mx), Student's t-test was used to evaluate the statistical significance of the obtained results in the calculations. To determine the clinical significance of the TNF-α indicator, ROC analysis (Receiver Operator Characteristic) was used - a linear regression method with the construction of ROC curves, which allows assessing the quality of the model (diagnostic feature - its sensitivity and specificity), using the Med Calc program. In this case, the AUC (Area Under Curve) indicator was taken into account. The quality of the test was judged by the expert scale for AUC values. The null statistical hypothesis of the absence of differences and relationships was rejected at $p < 0.05$.

RESULTS

Tumor necrosis factor alpha (tnf-alpha) is a proinflammatory cytokine synthesized mainly by monocytes and macrophages [20, 21]. In our study, all patients with kidney disease had higher blood tnf-a levels than healthy children, and they were significantly higher in children with mvd and gn (table 2). An interesting fact is that all patients with kidney disease also had significantly higher urine tnf-a levels (our own studies) than healthy children, with the highest levels found in the group of patients with glomerulonephritis [24], which coincides with data from other researchers [14, 25-27]. I.i. zhiznevskaya et al. (2014) showed that the debut of glomerulopathies, regardless of their further course, was characterized by a high level of tnf-alpha, which indicates the severity of the inflammatory immunopathological process in the kidneys in the pathology under study [14]. When performing binary logistic regression analysis and constructing a roc curve for the tnf-a indicator, the location of the curve in the upper left corner was determined both in children with mvd and in children with gn. The auc interval under the curve for these observation

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groups was almost the same (0.8). This proves that the quality of the model (according to the expert scale) is very good.

It is known that multiple TNF activities are realized through two types of receptors - type 1 and type 2 [20]. Soluble receptors bind and neutralize TNF-α. The TNFRte blood index in all patients is higher than in healthy children, but no significant differences were found between all groups of children, with the highest TNFRfy in children with glomerulonephritis being 1.3 times higher than in the control group. TNFRII in the blood of all observed sick children (groups 2-4) is lower than in healthy children. The lowest TNFRII blood index was found in the group of children with MVZP, which is statistically significant ($p<0.05$) (Table 2). When analyzing the content of TNF-α in the blood of children with acute (n=35) and chronic pyelonephritis (n=80) (PN) in the dynamics of the disease, a reliable increase was revealed in acute pyelonephritis compared with the indicators in the control group (n=22) (21.87 ± 5.23 and 4.28 ± 0.67 pg/ml, respectively; $p \leq 0.005$). A significant increase in TNF-α was established in children with chronic pyelonephritis during exacerbation of the disease (n=43), partial (n=10) and complete clinical and laboratory remission (n=27) compared to the control group (26.25 ± 4.77; 19.44 ± 3.51; 17.52 ± 3.47 pg/ml, respectively, $p \leq 0.001$).

In studies by O.G. Bykova (2013, 2014), an increase in TNF-α in the blood of children at all stages of chronic pyelonephritis was also statistically proven [16, 29].

When analyzing the indicators of soluble receptor II of tumor necrosis factor-α, a significant reliable decrease in soluble receptor II of tumor necrosis factor-α in the blood of patients with acute pyelonephritis was revealed (1381.81 ± 167.79 pg/ml; $p\leq 0.002$) compared to the indicator of the control group (2897.94 pg/ml). In chronic pyelonephritis, a reliable decrease in the sTNFRII level in the blood of patients at all stages was also determined, with a more significant decrease noted in the active stage (1766.37 ± 118.11 pg/ml; $p \leq 0.02$). In the stage of partial clinical and laboratory remission, the sTNFRII indicator was 1813.83 ± 155.49 pg/ml ($p < 0.05$) and in complete clinical and laboratory remission - 1993.24 ± 159.46 pg/ml ($p < 0.05$) compared with the control group (2897.94 pg/ml) (Fig. 2).

Table 3 The content of IL-2 and its soluble receptor in the blood serum of children with kidney diseases

Indicator	Healthy children	Children with ICD and DMN	Children with MVZP	Children with GN	Significance level (p)
	1	2	3	4	
IL-2, pg/ml	(n=50) 9,0 (3,7-19,9)	(n=2) 7,1 (6,3-7,8)	(n=21) 0,4 (0,3-62,2)	(n=16) 10,4 (0,3-970,5)	p1- p_3<0,001 p_3- p_4<0,05
IL-2 R, pg/ml	(n=50) 356,4 (207,3-564,1)	(n=2) 544,3 (325,1-763,4)	(n=21) 436,2 (180,7-971,9)	(n=16) 458,4 (307,3-861,2)	

Interleukin-2 (IL-2) is a soluble glycoprotein, which is a proinflammatory cytokine, a mediator of immunity and inflammation. It is produced by T cells in response to antigenic and mitogenic stimulation [20]. In our study, IL-2 in the blood of patients with MVD was significantly lower compared to the group of healthy children ($p < 0.001$). However, the level of IL-2 R receptor is higher in all children with kidney diseases compared to the control group (Table 3). In our previous studies, the IL-2 indicator in the urine of all patients was significantly lower compared to the group of healthy children ($p < 0.05$). The lowest indicator was found in children with metabolic disorders. However, the level of IL-2 R receptor in the urine was significantly higher in children with MVD and children with GN compared to the group of healthy children. The highest statistically significant indicator was registered in children with MVZP, which is quite natural ($p<0.05$) [24]. IL-10 belongs to the group of anti-inflammatory cytokines [20]. In our study, the IL-10 indicator in the blood of sick children of all groups was significantly lower than in the control group (Table 4). The most reliably significant low IL-10 indicator in the blood was found in the group of children with MVZP ($p<0.001$). The obtained data coincide with the data of other researchers [12, 15].

We studied anti-inflammatory cytokines in the blood: TGF-β1 and TGF-β3. It was found that the level of TGFβ1 cytokine in patients of the 4th group was significantly (and consistently) higher than in children of the control group ($p<0.05$). Interestingly, the level of TGFβ3 cytokine in children with metabolic diseases was also higher than in healthy children. In children with MVD and GN, the TGF-β3 indicator in the blood was significantly lower compared to children of the control group (see Table 4). It is known that when determining inflammation biomarkers, it is necessary to study not only the level of cytokines, but also their ratios, which allows us to assess the relative deficiency or hyperproduction of the studied mediators [15]. In our study, we used the cytokine inflammatory index (II), which was calculated as the ratio of pro- and anti-inflammatory cytokines. Thus, when assessing the TNF-a/IL-10 index, its reliably high level was determined in all patients, especially in children with MVD (3rd observation group), the index was higher (1.41±0.19, n=50) than in healthy children (0.13±0.02, n=50), $p<0.001$ (Table 5).

Table 4 Content of anti-inflammatory cytokines in blood serum in children with kidney diseases

Indicator	Healthy children	Children with ICD and DMN	Children with MVZP	Children with GN	Significance level (p)
	1	2	3	4	
IL-10, pg/ml	(n=50) 36,7 (20,7-60,1)	(n=8) 14,5 (6,4-25,8)	(n=78) 10,0 (1,9-26,8)	(n=24) 12,6 (6,8-38,1)	p_1– p_2<0,05 p_1– p_3<0,001 p_1– p_4<0,01
TGF-β_1, ng/ml	(n=50) 15,1 (12,4-36,8)	(n=2) 18,5 (13,9-22,9)	(n=12) 18,2 (12,2-22,3)	(n=13) 35,5 (22,3-43,6)	p_1- p_4<0,05
TGF-β_3, pg/ml	(n=50) 112,2 (106,0-126,4)	(n=8) 123,3 (46,7-291,5)	(n=74) 63,6 (19,3-110,7)	(n=13) 52,1 (29,9-92,8)	p_1- p_3<0,05 p_1- p_4<0,05

Table 5 TNF-a/IL-10 inflammatory index

Indicator	Healthy children	Children with ICD and DMN	Children with MVZP	Children with GN	Significance level (p)
	1	2	3	4	
TNP-α/ИЛ-Ю	0,13±0,02 (n=50)	0,56±0,2 (n=9)	1,41±0,16 (n=76)	0,9±0,19 (n=23)	p_1- p_2<0,05 p_1- p_3<0,001 p_1-p_4<0,01 p_2- p_3<0,01 p_3- p_4<0,05

DISCUSSION

The main biological effect of il-2, due to which it was called the lymphocyte growth factor, is to stimulate the proliferation of various cell types [20]. Il-2 stimulates cell division of both helper t-lymphocytes, which synthesize it in response to antigen stimulation, and killer t-lymphocytes, which act in an autocrine and paracrine manner. In addition, il-2 stimulates the production of antibodies in b-lymphocytes, and the production of proinflammatory cytokines, phagocytosis, and bactericidal activity in monocytes [20, 21]. A number of studies have shown that high concentrations of il-2 are observed in lymphocytes of patients with idiopathic nephrotic syndrome, with the level of il-2 being elevated during exacerbation and remaining normal during remission [14, 28]. It has been proven that the disruption of the cellular immune response due to the altered function of virus-infected b-lymphocytes and monocytes is important in the development of kidney damage in chronic herpesvirus infection. Thus, sharply reduced production of il-2 was detected in children with herpes infection and membranous nephropathy [29]. In our study, il-2 in the blood of patients with mvd was significantly lower compared to the group of healthy children ($p < 0.001$). However, the level of its receptor il-2 r was higher in all children with kidney diseases, but no reliable differences were found. We found a positive correlation between tnf-α and il-2 r ($r = 0.51$) in the blood of children with gn. Thus, inflammatory and autoimmune reactions in il-2-deficient children can be explained by a decrease in cellular immunity, the development of lymphoproliferation and autoimmune disorders. An increase in the il-2 r level can be attributed to inflammation markers [20].

It was found that the IL-10 level in the blood of healthy children was significantly higher than that of the observed patients with kidney diseases. In our previous study, the IL-10 level in the urine of sick children of all groups was also lower than that of healthy children. The most reliably significant low IL-10 level in the urine was found in the group of children with MVD ($p<0.05$), which is natural, given the pathogenesis of these diseases [24]. This is understandable given the known data on the properties of this cytokine: IL-10 is an anti-inflammatory cytokine that suppresses the production of proinflammatory cytokines and is a significant inhibitor of cellular immunity [20, 21]. We have found a positive correlation between IL-10 and IL-2 ($R = 0.91$) in the blood of children with MVD, which proves the role of deficiency of IL-10 and IL-2 cytokines in reducing the cellular immune response in patients with kidney disease.

TGF-β is an anti-inflammatory cytokine, a protein that controls proliferation, cell differentiation and other functions of most cells. The family of transforming growth factors (TGF) in humans

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includes 3 main ones: TGF-β1, TGF-β2, TGF-β3 [20]. Cytokines of the TGF family have various biological effects: changes in cell proliferation, in most cases - suppression; increased formation of the extracellular matrix due to activation of the synthesis of its components and suppression of degradation; immunosuppressive effect [20]. With the development of pathology, TGFβ1 is the main mediator of fibrosis formation and probably in the group of patients with GN, where it is significantly higher in the blood than in healthy children ($p < 0.05$), this cytokine can be considered an early marker of nephrosclerosis development. The TGF-β3 index is significantly reduced in children with microbial inflammatory kidney diseases and in children with GN compared to healthy individuals ($p<0.05$). This is understandable given the known data on its properties: TGF-β3 is an anti-inflammatory cytokine that suppresses the production of proinflammatory cytokines and is a significant inhibitor of cellular immunity [20, 21]. We have found a strong positive correlation between IL-10 and TGF-β3 ($R = 0.88$) in the blood of children with MVD. In our own studies conducted earlier, we found that the level of cytokine TGFβ1 in the urine of patients in groups 3 and 4 was significantly (and consistently) higher than in children in the control group (U221/0.035, $p<0.05$ and 169/0.033, $p<0.05$, respectively) [24]. Interestingly, the level of cytokine TGFβ3 in the urine of children with metabolic diseases was significantly higher than in healthy children, which requires further research and discussion [25].

CONCLUSION

An increase in the tnf-α indicator in the blood serum is recommended to be considered as a specific marker of immune inflammation, as well as acute pyelonephritis and its transition to the chronic stage, i.e. Tnf-α can be considered a universal cytokine involved in various pathogenetic processes in kidney diseases in children. A decrease in tnf-rii can be attributed to a marker of complete clinical and laboratory remission of pyelonephritis. An increase in tnf-α-ki can be considered as a marker of autoimmune inflammation. Deficiency of il-2, il-10 and tgfβ3 with an increase in il-2 r in the blood should be used as a marker of bacterial-inflammatory and autoimmune kidney diseases, and an increase in tgfβ1 - as an early marker of the development of nephrosclerosis, in particular, in patients with glomerulonephritis. An increase in the tnf-α/il-10 ratio by more than 4 times makes it possible to position it as an additional diagnostic criterion for the microbial inflammatory and autoimmune process in the kidneys. An increase in the excretion of tnf-α in the urine against the background of a decrease in il-10 with the maintenance of stably high concentrations of tgfβ1 is a marker of inflammation and fibrosis in microbial inflammatory kidney diseases and glomerulonephritis. In our earlier experimental studies, we determined the same data on these cytokines in the urine [24].

Thus, pathological processes underlying CKD are accompanied by changes in the level of pro-inflammatory and anti-inflammatory cytokines. Hyperproduction and deficiency of cytokines in renal dysfunction contribute to the intensification and development of inflammation of various types, fibrosis and nephrosclerosis. Prevention of unfavorable outcomes and early diagnosis (stages 1-2) of CKD in children is one of the pressing problems of pediatric nephrology. Timely nephroprotective therapy aimed at slowing down the progression of CKD and its complications should also include correction of the cytokine status.

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