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Cytokine Profile in Patients with Glomerulonephritis Depending on the Clinical Course

Eshbekov M. A.
Samarkand State Medical University

Khamdamov B. Z., Khamdamov A. B.
Bukhara State Medical Institute

Askarov T. A .
Tashkent Pediatric Medical Institute

Abstract: **Relevance.** In recent years, convincing data have been obtained proving the link between the development of GN and "immune dysregulation", primarily concerning T-lymphocytes. Experiments have shown the damaging effect on glomeruli of a cell-mediated mechanism (Th1-type) of an adaptive immune response associated with the activity of IFN-γ.Thus, it seems that cytokines play an important role in the pathogenesis of GN. However, only isolated studies are known on the study of pro- and anti-inflammatory cytokines circulating in the blood in patients with various forms of GN.

The purpose of study. To study the features of the immunopathogenetic mechanisms of the effect of immune system mediators on the development of various clinical forms of glomerulonephritis

Results and conclusions. According to the final values of cytokine levels, it should be noted that in patients with nephrotic GN, the minimum values of IL-1β, RAYL-1β and IL-8 levels detected at the beginning of treatment remained. In patients with nephrotic form, only the level of IL-10 remained high for a long time, the average value of which, as at the beginning of treatment, had a minimal value relative to the indicators of other groups of patients. In addition, with nephrotic GN, the lowest values of IFN-γ were recorded at the end of treatment. The cytokine profile of patients with hypertension at the end of treatment combined with that of patients with nephrotic GN with a reduced value of IL-8 relative to other groups of patients. With mixed GN, high values of IL-1β, IL-10, IFN-γ and IL-1β/RAYL-1β were found.

Keywords: glomerulonephritis, clinic, cytokines, interleukins.

Relevance. Glomerulonephritis (GL) is a steadily progressive disease, in the pathogenesis of which immunological disorders play a leading role (1,3,5)..

The effect of cytokines on cells is carried out: autocrine – on cells that secrete this cytokine; paracrine – on cells around the secreting cell; endocrine-remotely – on cells of any other organs and tissues after cytokines enter the circulating bloodstream. The formation and release of cytokines is a short–term and tightly regulated process; it is also characteristic that the production of one cytokine affects the activity of a number of others (2,4,6). Cytokines are local mediators, so it makes sense to determine their levels in biological fluids (serum, urine, plasma,

cerebrospinal and synovial fluids, etc.). Additional information about the state of the immune system can be obtained by studying the properties of blood cells to produce cytokines in vitro. In vitro studies, mononuclears are a successful model, mainly due to their availability (whole blood can be used for research). Serum cytokine levels reflect the current functional state of the immune system and the development of protective reactions, reflecting the synthesis of cytokines by the body's cells in vivo. Determination of cytokine levels in vitro shows the functional state of cells (7,9,11).

In recent years, convincing data have been obtained proving the link between the development of GN and "immune dysregulation", primarily concerning T-lymphocytes. Experiments have shown the damaging effect on glomeruli of a cell-mediated mechanism (Th1-type) of an adaptive immune response associated with the activity of IFN-γ (8,10,12). Thus, it seems that cytokines play an important role in the pathogenesis of GN. However, only isolated studies are known on the study of pro- and anti-inflammatory cytokines circulating in the blood in patients with various forms of GN. Thus, an increase in TNF-α, IL-2 levels and a decrease in IL-6 and IL-10 were described in children with nephrotic GN in the acute stage of the disease (13,15,16). Other researchers also confirmed an increase in IL-2 serum levels in adult patients with nephrotic GN. However, there is currently no holistic understanding of the role of cytokines circulating in the blood in the development of nephrotic syndrome (NS) in adult patients with GN, as well as other clinical forms of GN – hypertensive, urinary (latent) and mixed.

The aim of the study. To study the features of the immunopathogenetic mechanisms of the effect of immune response mediators in various clinical forms of glomerulonephritis.

Materials and methods. Our study involved 103 patients with GN, aged 16 to 58 years (average age 35.6±2.8). The average duration of GN in the examined patients was 3.8±1.1 years. The diagnosis was established on the basis of the results of a clinical examination, data from laboratory and instrumental research methods. Depending on the clinical form of GN, patients were divided into four groups: group I (n=28) – patients with latent form of GN; group II (n=25) – patients with nephrotic form of GN; group III (n=25) – patients with hypertensive form of GN; Group IV (n = 25) – patients with a mixed form of GN.

To determine the cytokine content in the blood serum of the studied groups, a three–stage "sandwich" method was used - this is a type of three-phase ELISA. The concentration of interleukin-IL-1β, IL-8, IL-10, IFN-γ was determined using a set of reagents from the company Vector-Best (Novosibirsk).

Results and discussion.

To identify the pathogenetic role of various immunological factors in the pathogenesis of GN, we determined the level of a number of different cytokines (IL-1β, IL-8, IL-10, IFN-γ) in the blood serum of patients with GN during inpatient treatment (1st-2nd and 14th-15th days) and practically healthy people.

A comparative analysis of patients with GN at admission to the hospital revealed a difference in the level of the studied cytokines from the indicators of the control group. Differences were observed in the level of all studied cytokines: IL-1β – 6.5 times, IL-8 – 2.4 times, IL-10- 2.7 times, IFN-γ – 8.6 times. The level of RAYL-1β was also increased, and differed from the level of the control group by 7.2 times. Such dynamics of cytokine levels persisted until the end of inpatient treatment (day 14-15). And according to the level of RAIL-1β and IFN-γ, a significant decrease in the dynamics of inpatient treatment was revealed.

The next step in our study was to study the cytokine status of patients depending on the clinical form of GN (Table 1.). A comparison was made between the indicators of one single form with the indicators of the combined group, which combines all other forms of GN. So, in the tab.1 presents the indicators of patients with latent form and the combined group, including nephrotic, hypertensive and mixed forms of GN.

The latent form of GN was characterized by low levels of proinflammatory cytokines - IL-1β, its receptor antagonist and IL-8 both at the beginning and at the end of treatment, and the initial indicators of anti-inflammatory cytokines (IL-10 and IFN-γ) were at a fairly high level. In the latent form of GN, the expression level of IL-1β and RAYL-1β increased unidirectionally, as can be judged by the integral indicator, which is equal to the ratio of these cytokines (IL-1β/RAYL-1β) within the control digits, as well as in patients of the comparison group, that is, in the combined group of other forms of GN, an increase was observed The level of IL-1β prevailed over the degree of production of RAIL-1β, and as a result, the average value of this integral indicator - IL-1β/RAIL-1β was 2.89 times higher than this indicator in the control group. There were no significant changes in cytokine status during inpatient therapy in patients with latent GN.

Table 1. Cytokine content in patients with latent GN

Cytokines, pg/ml	Days of illness	The control groupn=20	The latent form of GNn=28	Other forms of GNn=75	P
IL-1β	1-2й	1,7±0,2	10,8±1,6	19,2±2,5	<0,05
	14-15й		7,1±1,1	24,6±3,1	<0,05
IL-8	1-2й	2,4±0,3	2,5±1,1	5,1±2,1	>0,05
	14-15й		2,8±1,2	5,6± 1,2	>0,05
IL-10	1-2й	2,5±0,8	4,8±1,7	3,8±1,5	>0,05
	14-15й		2,7±1,4	3,7±1,1	>0,05
RA IL-1β	1-2й	43,2±6,7	380,3±24,6	412,9±31,8	<0,05

In patients with nephrotic GN, changes in cytokine levels were the opposite of the changes that were detected in patients with latent form of the disease - the levels of IL-1β, RAYL-1β and IL-8 were higher than in patients with other forms of GN, and the level of IL-10 was lower (Table 2.). The content of IFN-γ in patients with nephrotic GN at the end of treatment was lower compared with the value of this cytokine in patients with other forms of the disease.

Table 2.Cytokine content in patients with nephrotic GN

Cytokines, pg/ml	Days of illness	Control group n=20	The nephrotic form of GNn=25	Other forms of GNn=78	P
IL-1β	1st-2nd	1,7±0,2	107,1±21,6	11,2±2,5	<0,05
	14th-15th		72,1±19,1	12,4±3,1	<0,05
IL-8	1st-2nd	2,4±0,3	6,8±1,2	4,1±1,8	>0,05
	14th-15th		5,7±1,1	3,9± 1,2	>0,05
IL-10	1st-2nd	2,5±0,8	2,8±0,7	4,1±1,5	>0,05
	14th-15th		2,7±1,1	2,9±1,1	>0,05
RA IL-1β	1st-2nd	43,2±6,7	780,3±24,6	462,9±31,8	<0,05
	14th-15th		567,4±27,5	393,3±31,8	<0,05
IFN- γ	1st-2nd	6,3±0,7	73,1±33,5	75,2±12,6	<0,05
	14th-15th		44,7±26,7	52,4±6,4	<0,05

In patients of the general group, the increase in the levels of IL-1β and RAIL-1β was equivalent, as a result of which the integral indicator (IL-1β/RAIL-1β), reflecting their balance, did not exceed the control indicators.And in patients with nephrotic GN, this integral indicator was more than 3.2 times higher than in the general group, and 4.5 times higher than in the control group.

Patients with hypertonic GN were characterized by low levels of IL-8 and IL-10 before treatment and a high index of Ra-IL-1ß (Table. 3.).

Table 3.Cytokine content in patients with hypertensive form of GN

Cytokines, pg/ml	Days of illness	The control groupn=20	Hypertensive form of GNn=25	Other forms of GN n=78	P
IL-1β	1st-2nd	1,7±0,2	14,1±21,6	14,2±2,5	<0,05
	14th-15th		22,3±11,5	25,7±3,1	<0,05
IL-8	1st-2nd	2,4±0,3	4,7±1,2	5,2±1,8	>0,05
	14th-15th		5,2±1,1	3,8± 1,3	>0,05
IL-10	1st-2nd	2,5±0,8	2,8±0,7	4,6±1,5	>0,05
	14th-15th		2,7±1,1	2,9±1,1	>0,05
RA IL-1β	1st-2nd	43,2±6,7	512,3±24,6	442,9±31,8	<0,05
	14th-15th		767,4±27,5	386,3±31,8	<0,05
IFN- γ	1st-2nd	6,3±0,7	58,1±33,5	65,2±12,6	<0,05
	14th-15th		57,7±26,7	52,4±6,4	<0,05

The mixed form of GN was characterized by high levels of IL-8 before treatment and high levels of IL-1β, IFN-γ and IL-10 after treatment compared with those of patients in the general group.And there was also a decrease in IL-8 expression with an increase in the integral index of IL-1β /RAYL-1β after treatment (Table 4.).

Table 4.Cytokine content in patients with mixed GN

Cytokines, pg/ml	Days of illness	The control group n=20	Mixed form of GN n=25	Other forms of GN n=78	P
IL-1β	1st-2nd	1,7±0,2	24,1±21,6	14,2±2,5	<0,05
	14th-15th		37,3±11,5	18,7±3,1	<0,05
IL-8	1st-2nd	2,4±0,3	8,7±1,2	5,1±1,8	>0,05
	14th-15th		5,4±1,1	3,9± 1,3	>0,05
IL-10	1st-2nd	2,5±0,8	3,9±0,8	4,2±1,5	>0,05
	14th-15th		4,7±1,1	2,9±1,1	>0,05
RA IL-1β	1st-2nd	43,2±6,7	507,3±21,6	462,9±21,8	<0,05
	14th-15th		467,4±22,5	376,3±19,8	<0,05
IFN- γ	1st-2nd	6,3±0,7	38,1±13,5	55,2±12,6	<0,05
	14th-15th		62,7±16,7	48,4±6,4	<0,05

The next stage of our study was to study the cytokine status of patients with various clinical forms of GN (Table 5.). Analysis of the presented data showed that each clinical form was

characterized by the dynamic activity of a separate cytokine. Thus, the nephrotic form was characterized by the lowest levels of IL-8, the highest levels of this cytokine were in the mixed form. The latent form was characterized by the maximum level of IL-10, the lowest values of this cytokine were in nephrotic and hypertensive forms. High values of IL-1β and RAYL-1β were observed in the nephrotic form of GN, low values in the urinary form of GN. The IFN-γ index had differences only in the latent form of GN and was higher than in patients with other forms of the disease.

Table 5.Cytokine content in patients with various forms of GN

Cytokines, pg/ml	Days of illness	The latent form of GN n=25	The nephrotic form of GN n=25	Hypertension is a form of GN n=78	Mixed form of GN n=25
IL-1β	1st-2nd	10,8±1,6	107,1±21,6	14,1±21,6	24,1±21,6
	14th-15th	7,1±1,1	72,1±19,1	22,3±11,5	37,3±11,5
IL-8	1st-2nd	2,5±1,1	6,8±1,2	4,7±1,2	8,7±1,2
	14th-15th	2,8±1,2	5,7±1,1	5,2±1,1	5,4±1,1
IL-10	1st-2nd	4,8±1,7	2,8±0,7	2,8±0,7	3,9±0,8
	14th-15th	2,7±1,4	2,7±1,1	2,7±1,1	4,7±1,1
RA IL-1β	1st-2nd	380,3±24,6	780,3±24,6	512,3±24,6	507,3±21,6
	14th-15th	367,4±27,5	567,4±27,5	767,4±27,5	467,4±22,5
IFN- γ	1st-2nd	83,1±23,5	73,1±33,5	58,1±33,5	38,1±13,5
	14th-15th	54,7±26,7	44,7±26,7	57,7±26,7	62,7±16,7

The cytokine profile of patients with various clinical forms of GN, as well as their integral indicators characterizing the balance between different groups of cytokines, had significant differences among themselves, which once again proves the pathogenetic heterogeneity of clinical forms of GN, which is reflected not only in the clinical picture and therapeutic measures, but also in the prognosis of the disease.

Conclusions:

1. High production of IL-1β and IL-8 against the background of reduced production of IL-10, associated with activation of Th2 cell activity and impaired functioning of the pituitary-thyroid system according to the hypothyroid type, cause the formation of the nephrotic form of GN.

2. A moderate increase in the production of the proinflammatory cytokine IL-1β, combined with an increase in IL-10, as well as the predominance of Th1 cell activity with a balance of changes in the pituitary-thyroid system are responsible for the asymptomatic course of GN.

3. Reduced production of IL-10 and IL-8, combined with a minimum level of activity of the humoral and cellular components of the adaptive immune response and subclinical hypothyroidism, contribute to the formation of a hypertensive form of GN.

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