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The Importance of Urocytokines in Glomerulonephritis in School-Aged Children

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ABSTRACT

Glomerulonephritis is a multifactorial disease and is characterized by a high rate of increase in the incidence and disability of the child population in modern populations. Despite extensive study, the development and progression of chronic glomerulonephritis (CGN) remains one of the leading problems in nephrology.

Glomerulonephritis (GN), being a multifactorial pathology, is characterized by a high rate of increase in the incidence and disability of the child population in modern populations [3] and occupies a leading position in terms of frequency, severity, poor prognosis among other diseases of the urinary system [4, 8, 9, 10].

Primary glomerulonephritis is a heterogeneous group of primary immuno-inflammatory diseases of the glomeruli proper of the kidneys with different clinical and morphological patterns, course and outcome. The course of glomerulonephritis is manifested by different clinical variants: nephritic syndrome, pure nephrotic syndrome or with hematuria and / or arterial hypertension, isolated urinary syndrome, hematuria, hematuria with proteinuria, not reaching the level of nephrotic syndrome. According to the morphological variant, GN is classified as: minimal changes, membranous, focal-segmental glomerulosclerosis, mesangial-oproliferative, membranous-proliferative, extracapillary with crescents. According to the nature of the course of primary glomerulonephritis, there are: acute, rapidly progressive, chronic [7, 10].

In the development of various forms of GN, the importance of bacterial infection, especially nephritogenic strains of P-hemolytic streptococcus group A [4, 8], viruses [4, 10], toxic effects (drugs, heavy metals), and other exogenous and endogenous factors, has been established. It has been shown that bacterial and viral agents are involved in the formation of immune complexes, which are often detected in patients with GN during immunofluorescent studies of nephrobiopsy specimens [3, 4].

The clinic, course and progression of GN are determined by its morphological substrate [2, 6, 8]. The severity of individual clinical symptoms affects the course and outcome of the disease.

Acute glomerulonephritis with nephritic syndrome (AGN) is an acute diffuse immune-inflammatory lesion of the glomeruli of the kidneys that occurs after a bacterial, viral or parasitic disease. Acute poststreptococcal GN is characterized by hematuria (urine of the color of "meat slops"), proteinuria of varying severity, short-term abacterial leukocyturia, arterial hypertension, and edema are not excluded (in some cases). There are hypervolemic circulatory disorders due to increased water-sodium resorption of the tubules. The debut of the hematuric form of glomerulonephritis may not differ from acute poststreptococcal glomerulonephritis. Currently, it is difficult to clinically differentiate the manifestation of the chronic form and the development of acute glomerulonephritis [4].

Membranous GN is characterized by subepithelial deposits, thickening of the glomerular basement membrane, and usually no significant proliferation of endothelial or mesangial cells. Membranous glomerulonephritis is characterized by isolated proteinuria, incomplete nephrotic syndrome or nephrotic syndrome with microhematuria, less often macrohematuria and/or arterial hypertension [3].

Glomerulonephritis with focal segmental glomerulosclerosis (FSGS) in children and adolescents is diagnosed in 7-15% of cases as a variant of primary glomerulonephritis. Immune, circulatory, and metabolic disorders play a role in pathogenesis. Immunity dysfunction in the system of T-lymphocytes with hyperproduction of interleukins is important. A certain role in the development and progression of FSGS is given to hyperlipidemia and lipiduria, an imbalance between the synthesis and degradation of the extracellular glomerular matrix, in particular, an increased synthesis of extracellular matrix components. The main manifestation of FSGS is massive proteinuria, leading to the development of a symptom complex of nephrotic syndrome. Asymptomatic proteinuria in 50% of cases is the initial manifestation of FSGS with the development of incomplete nephrotic syndrome in combination with hematuria (25-80%) and/or arterial hypertension (25-50%) [7; 8].

Membranoproliferative GN is a variant of glomerulonephritis characterized by nephrotic syndrome, hematuria and arterial hypertension or nephritic syndrome with specific morphological changes. In pathogenesis, the leading role is given to circulating and fixed immune complexes with activation of the complement system along the classical or alternative pathways; the role of autoimmune mechanisms and hereditary defects in the complement system is also assumed [2].

Mesangioproliferative GN is characterized by proliferation of mesangial cells, accumulation of mesangial matrix, damage to the vascular wall, primarily the endothelium and basement membrane of capillaries, glomeruli, as well as tubules and interstitial tissue.

Rapidly progressing GN is manifested by a clinical and morphological symptom complex, which is an ultra-high activity of glomerulonephritis, rapidly progressive renal failure with the development of terminal uremia in terms of several weeks to several months, a morphological picture of proliferative extracapillary with epithelial and fibrinoid crescents [3].

GN often has a progradient course due to the development of forms resistant to ongoing therapy. At the same time, the causes of the progression of the disease require study. The available studies are aimed at studying the role of the nature of the infection, the state of the immune system, and the complex interactions of genetic factors. Currently, the state of the tubulointerstitial tissue of the kidneys in the progression of glomerulonephritis is considered a paramount indicator [10].

Experimental and clinical studies of recent years have established the leading role of biologically active compounds - cytokines in the development and progression of glomerular inflammation [3, 5]. Cytokines are proteins produced predominantly by activated cells of the immune system,

lacking specificity for antigens and being mediators of intercellular communications in the immune response, hematopoiesis, inflammation, and intersystem interactions [4, 7].

Achievements of modern immunology have made it possible to establish that dysregulation of the cytokine network is an integral part of almost all studied autoimmune diseases [4, 5, 7]. It has now been established that cytokines are universal regulators of the functional activity of immunocompetent cells, are involved in the infectious and inflammatory process at the level of the immune mechanisms proper and the effector link, largely determining the severity and outcome of the pathological process. Through cytokines, the depth, nature, duration of inflammation and the immune response of the body are regulated. However, the degree of participation of these biological markers in the development and progression of kidney damage has not been sufficiently studied so far. Despite the large number of experimental studies, in the clinical setting, comprehensive studies of cytokine interactions in glomerulopathies (especially in children) are extremely few in the available literature, and their results are very contradictory.

Immune mechanisms of kidney damage play a special role in the pathogenesis of CGN [7]. After the initial damage to the kidneys, activation of infiltrating immune and resident cells of the organ tissue and the release of a large number of inflammatory mediators occur [4, 7]. Complement activation, synthesis of chemokines, various cytokines and growth factors, attraction of circulating leukocytes, release of proteolytic enzymes, activation of the blood coagulation cascade, formation of lipid mediator substances are observed. Activation of resident cells in the kidneys leads to a further increase in destructive changes and the synthesis of extracellular matrix components. Remodeling of the glomeruli and interstitial matrix is promoted by hemodynamic factors - adaptive intraglomerular hypertension and hyperfiltration, nephrotoxic effect of proteinuria, impaired apoptosis. With prolonged inflammation, glomerulosclerosis and interstitial fibrosis develop, which underlie the progression of renal failure [6].

Immune-inflammatory processes, according to modern concepts, play a leading role in the progression of CGN. With prolonged tissue damage, aggressive elements accumulate in the blood (pro- and anti-inflammatory, prosclerotic and proapoptotic mediators [6], which have a direct effect on target cells. In the kidney, they are represented by mesangial, proximal tubular cells, macrophages (monocytes), fibroblasts and myofibroblasts.

In the future, inflammatory mediators and non-immune mechanisms - hemodynamic and metabolic, arterial hypertension, hyperfiltration - acquire an important role.

In the development of glomerular damage, cellular elements of the blood play an important role - macrophages-monocytes, neutrophils and platelets, which, thanks to adhesive molecules, penetrate into the focus of glomerular inflammation after activation, interact with the capillary endothelium and other structures of the glomerulus [7].

In connection with the loss of glomeruli with the progression of the disease, the development of hyperfiltration in the remaining glomeruli is noted. The consequence of this is an increase in intraglomerular pressure, as a result of which the functioning renal parenchyma is increasingly damaged. With the development of hyperfiltration in the remaining intact nephrons (with their gradual failure), proteinuria increases, which contributes to increased production of aggressive anti-inflammatory cyto- and chemokines, loss of podocyte function, and ischemic changes in the kidney. The central factor in the ongoing changes is angiotensin II (AT II), which has pronounced proinflammatory and prosclerotic properties [5, 8].

AT II, having a prosclerotic effect, is involved in the regulation of the synthesis of chemoattactic factors, such as monocytic chemoattractant protein 1 (MCP-1). Fibroblast growth factors, connective tissue growth factor, transforming growth factor ß, and insulin-like growth factor 1 also have a prosclerotic effect [7].

Plasminogen inhibitor plays an important role. AT II increases the expression and synthesis of extracellular matrix proteins such as fibronectin, laminin, and collagen. Under the influence of AT II, fibroblasts, turning into myofibroblasts, occupy the periglomerular and peritubular spaces, and contribute to the expansion of the matrix into the tubulointerstitial zone.

Proteinuria plays an important role in the progression of nephropathy [4, 6, 8]. Increased protein penetration into the tubular epithelium causes increased production of inflammatory mediators such as endothelium-1, MCP-1, the monocyte chemotactic cytokine RANTES, and osteopontin. An increase in proteinuria affects the state of podocytes, since protein accumulation in them has a toxic effect on their functional state [2]. When the protein accumulates in podocytes, the actin-associated synaptopodin molecule is lost, which leads to the loss of cell differentiation [4]. Currently, there are more and more works showing that a decrease in the level of glomerular filtration correlates mainly with the degree of tubulointerstitial damage, while the severity and duration of these changes determine an unfavorable prognosis in patients with various forms of glomerulonephritis. The pathogenesis of the development of tubulointestinal changes in the kidneys consists of a number of mechanisms, such as proteinuria, tubular ischemia, hypoxia, the influence of protein and enzyme factors, cytokines, growth factors, etc. [163]. Many studies have shown that the primary damaging effect on tubular epithelial cells is, first of all, high proteinuria, which often accompanies glomerular diseases.

Cytokines, in particular interleukins, play a special role in the development and progression of chronic glomerulonephritis.

Interleukins are pluripotent substances of a protein nature with multiple biological effects. Being the initial link in the activation of the immune response, they determine the effectiveness and type of immune response to infectious and non-infectious agents, and are directly involved in the regulation of immunological defense [9].

It has been established that any damage to the cells of the kidney parenchyma, including the components of proteinuria, leads to the production of inflammatory mediators by them [6]. Under the influence of pro-inflammatory cytokines, such as IL-ip and TNF-a, the production of monocyte chemoattractant protein 1 (monocyte chemoattractant protein-1, MCP-1) is stimulated, which ensures the influx of leukocytes and monocytes into the area of damage and the formation of an inflammatory infiltrate [10]. The main sources of MCP-1 in urine are tubular epithelial cells. This chemokine is also expressed by mononuclear cells and vascular endothelial cells [5]. MCP-1 is a chemoattractant that ensures the migration of mononuclear cells to the site of inflammation, and an inflammatory mediator that activates resident cells. In cell culture, MCP-1 changes the phenotype of parietal epithelial cells, mesangial glomerular cells (activates them), interstitial fibroblasts (stimulates collagen synthesis), and tubular cells (induces transdifferentiation into myofibroblasts) [8]. Under the influence of MCP-1, vascular smooth muscle cells proliferate, secrete pro-inflammatory cytokines, which contribute to the progression of renal disease due to vascular damage [4, 5]. The involvement of MCP-1 in the processes of interstitial fibrosis and glomerulosclerosis [5] has been established by its effect on the production of transforming growth factor (3, the main profibrogenic cytokine) by tubular epithelial cells [3, 11]. The role of MCP-1 in atherogenesis has been shown [7].

In the study of urine of patients with glomerulonephritis, an increase in the level of MCP-1 was revealed, which correlates with the degree of activity of tubulointerstitial damage and fibrosis. The role of MCP-1 in congenital obstructive nephropathy and renal vasculitis has been studied [4].

However, the role of MCP-1 in the progression of kidney disease in children remains poorly understood. At the same time, the relevance of clarifying the role of MCP-1 in the pathogenesis

of glomerulonephritis is due to the possibility of developing new therapeutic drugs - MCP-1 inhibitors [1].

Another powerful mediator of inflammation is IL-8, which belongs to the group of chemokines. Produced under the influence of bacterial endotoxins and cytokines, mainly under the influence of tumor necrosis factor (TNF) and IL-1, as well as IL-3. IL-8 producing cells are macrophages, lymphocytes, epithelial cells, fibroblasts, epidermal cells. It is involved in creating a gradient for chemotaxis of phagocytic cells, and also causes the appearance of specific receptors in endothelial cells that react with monocytes and neutrophils and stop these cells in capillaries located in the area of inflammation. The main function of IL-8 is to act as a chemoattractant for neutrophils, macrophages, lymphocytes, and eosinophils. In addition to this biological action, IL-8 enhances the adhesive properties of neutrophils by altering the expression of integrins and other compounds with adhesive properties to endothelial cells and subendothelial matrix proteins, which indicates its main role in mediating the inflammatory response [2].

Elevated IL-8 levels are associated with acute and chronic inflammatory conditions. The participation of the cytokine IL-8 in the development of infectious and inflammatory processes has been most studied. In acute myocardial infarction, IL-8, along with IL-6, is one of the main mediators of the acute phase of the response. IL-8 is an important mediator of the inflammatory process in the lungs, a potential marker of bacteremic pneumonia. Simultaneous study of the level of IL-8 and C-reactive protein (CRP) during the initial examination of newborns made it possible to reduce the frequency of irrational antibiotic therapy [4, 8].

IL-8 plays an important role in wound healing, tumor growth and in rheumatoid arthritis, especially high numbers are noted during an exacerbation. An elevated level of IL-8 in the blood is determined in hepatocellular carcinoma [9].

The possible significance of IL-8 as a marker of autoimmune damage is discussed [7].

There are separate publications on the increase in the level of IL-8 in the blood of patients with systemic inflammation, including bronchial asthma [173], primary progressive multiple sclerosis, and Behçet's disease. An increase in the level of IL-8 in human peripheral blood often precedes development of atherosclerosis and cardiovascular diseases, as well as type II diabetes mellitus.

IL-8 mediates the activation and migration of neutrophils, and also initiates the inflammatory process caused by the ingestion of a foreign protein - an allergen. The level of IL-8 was studied in microbial-inflammatory diseases of the urinary tract, in chronic prostatitis [28], the study of the level of IL-8 was used to assess the activity of pyelonephritis, to determine the state of the renal tissue in vesicoureteral reflux. IL-8 plays an important role in the regulation of local immunity of mucous membranes, in particular, the bladder mucosa [3].

In the study of the cytokine profile in patients with chronic renal failure, a significant increase in the levels of interleukin 8, tumor necrosis factor a and transforming growth factor ß was found [10].

The problems of predicting the course of glomerulonephritis, the need to monitor morphological changes in the renal tissue necessitate continued research that reveals pathochemical changes in the kidney tissue.

Currently, the relationship between biochemical and immunological parameters in chronic glomerulonephritis in children has not been sufficiently studied. The problem of diagnosing and determining the degree of activity of the inflammatory process, the search for minimally invasive, alternative to nephrobiopsy, methods for diagnosing the state of the renal tissue is an urgent one.

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