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The Role Of Polymorphic Genes Of Matrix Metalloproteinases (MMPS) And Their Tissue Inhibitors In The Development Of Renal Dysfunction In Chronic Glomerulonephritis In Children

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ABSTRACT

In children, glomerulonephritis is a disease characterized by rapid progression and complication caused by an irreversible process of the renal glomeruli. Currently, methods of molecular diagnostics have begun to actively develop, which not only complement traditional research methods, but also provide insight from the point of view of molecular pathophysiology. It is expected that a key role in the diagnosis of kidney disease is played by the identification of genes and their changes in the course of the disease, which predict the course of the disease. Changes in chromosomal polymorphic genes of matrix metalloproteinase and its tissue inhibitors, as well as how this change manifests itself in chronic glomerulonephritis, were determined in the prognosis of the disease.

KEYWORDS

Chronic glomerulonephritis, matrix metalloproteinase, tissue inhibitor.

INTRODUCTION

Chronic glomerulonephritis is one of the most severe kidney diseases in children, which is characterized by the frequent development of complications and the progression of the course of the disease. The incidence of chronic glomerulonephritis over the past 10 years has been steadily progressing and accounts for 36.76% of all kidney diseases. Diseases of the urinary system, according to the WHO, currently occupy the 2nd place among the main forms of renal pathology inherent in childhood. Glomerulonephritis ranks second in the structure of kidney diseases in children admitted to the nephrology department. The

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urgency of the problem of chronic glomerulonephritis is explained not by the prevalence of the disease, but by the course of the disease and the development of renal failure [19, 6].

At the beginning, the disease is immune-inflammatory, with damage to the glomeruli, tubules and interstitial tissue, but in the future, non-immune factors of progression are quickly turned on, which lead to systemic damage to organs, including the cardiovascular system. The extracellular matrix is present in all tissues of the body, therefore, disruptions in its functioning lead to the development of connective tissue diseases, premature aging and cell death. The most obvious incentive for the study of ECM is the need to treat diseases associated with disorders of the connective tissue structure [15]. There are many such diseases, they can be difficult and significantly worsen the quality of life of patients. The unifying pathogenetic mechanisms of chronic glomerulonephritis can be considered the activation of the systemic inflammatory reaction with the formation of an excess of oxidative stress products and imbalance in the "proteolysis-antiproteolysis" system, which can enhance the processes of tissue remodeling [16].

THE MAIN FINDINGS AND RESULTS

Matrix metalloproteinases (MMPs) are considered key effectors of tissue remodeling for a variety of reasons. These are proteins, the expression of which are present in all tissues at various stages of ontogenesis and is finely regulated and activated under conditions of intensive tissue rearrangement. They are secreted both on the cell surface and in the intercellular space and function under physiological and pathological conditions [20, 17]. As poly-functional proteins, MMPs are involved in the mechanisms of angiogenesis and apoptosis. MMPs can independently affect the main components of the connective tissue matrix, as well as affect intercellular interactions, various signal transduction pathways in the cell, and also promote the production of certain biologically active molecules. The activity of MMPs in tissues depends on the level of expression of their genes and on the presence of activators and specific tissue inhibitors - STI [9, 4]. TIMPs are produced simultaneously and together with MMPs. One of the main reasons for the development of pathology is the imbalance between the synthesis and degradation of the components of the extracellular matrix, which in turn depends on the balance between the activity of MMP and STI. Under pathological conditions, there is a change in the expression, production and activity of MMPs, which are regulated by the transcriptional activity of the corresponding genes, which can lead to an increase in the inflammatory response and tissue destruction [11].

The relevance of studying the role of matrix metalloproteinases (MMPs) and their tissue inhibitors (STIs) in the pathology of the urinary system is determined by its significant prevalence, the tendency to recurrent kidney disease in children [4,1,25,8]. It is known that MMP-1 has an anti-inflammatory effect, while MMP-2 and MMP-9 prevent inflammation. STI-1 and STI-2 limit the breakdown of collagen. Imbalance between MMP and TIMP is accompanied by the accumulation of extracellular matrix, increasing the risk of complications of chronic glomerulonephritis. The involvement of MMPs in the pathogenesis of diseases makes them an attractive target for drugs [4,2].

Scientists from the University of Manchester (UK) have identified 35 genes that are associated with chronic kidney disease. The

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authors believe that the discovery will take a long-awaited step forward in the study of genetically determined diseases that, if left untreated, lead to organ loss, according to the university's website. The researchers used the latest generation of RNA sequencing, which helped to analyze the genetic characteristics of the kidneys in one of the largest samples. The team is confident that the identified genes will become attractive targets for the development of new methods for early diagnosis and treatment. Many kidney diseases currently have morphological, immunological and clinical classifications, which often do not explain the underlying pathophysiological mechanisms. Despite its strengths, morphological assessment is limited in the interpretation of renal lesions with nonspecific etiological associations. These limitations jeopardize the ability to establish an accurate diagnosis and prescribe effective treatment [3,5].

In modern medicine, fundamental scientific attitudes have been formed, the need for the active development of methods for molecular diagnostics of kidney diseases, which not only complement traditional methods, but also provide an understanding from the point of view of molecular pathophysiology. The active development of methods for molecular diagnostics of kidney diseases opens a large branch of medicine, which can be called "molecular nephropathology". Further study of kidney diseases from the point of view of molecular biology will allow us to take a fresh look at the pathogenesis of many diseases and solve a number of problems from the point of view of personalized therapy that takes into account the genetic characteristics of the patient. The development of molecular diagnostics methods increasingly opens up the prospects for a personalized approach to the study of pathology at various levels of interaction; these achievements provide a qualitative assessment of DNA, RNA, proteins and their metabolites, which makes it possible to determine new biomarkers [12,3].

Thus, the need for molecular diagnostics is gradually moving into the daily clinical practice of examining nephrological patients. Numerous studies in recent years have thoroughly studied the mechanisms of development and progression of chronic glomerulonephritis. Most diseases are genetically determined, but progress in developing new tests has been very slow to date. The modern strategy of fighting for increasing life expectancy is aimed at finding significant and reproducible biological markers that allow early and accurate diagnosis of risk and prognosis of complications. Nevertheless, the number of works devoted to the study of molecular biology in the pathogenesis of chronic glomerulonephritis in sick children is still small, and their results are contradictory [16].

The results of experimental and clinical studies obtained so far confirm the role of the MMP / STI system in the pathogenesis of diseases. Six representatives of MMP-1,2,3,9,13,14 were identified in the kidneys. Tissue inhibitors regulate MMP and are in a 1: 1 ratio. STI-2 is a universal inhibitor [11]. The MMP-9 genes, like many other genes, are characterized by polymorphism. Polymorphic genetic loci may not cause any changes in the phenotype, but may have a functional effect, influencing the level of gene expression and the amount of protein product. According to numerous studies, single-nucleotide substitutions in gene regions significantly affect the change in the structure of the protein, leading to a disruption of the encoded protein, which may accompany the development of the disease. If a mutation occurs with a frequency of more than 1.5-3% and does not lead to obvious phenotypic manifestations of the disease, it is

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considered as polymorphism. Genetic polymorphism in the human genome in 95% of cases is associated with single nucleotide substitutions - SNP (from the English Single nucleotide-polymorphism - polymorphism of one nucleotide) [7, 21, 17, 24]. To date, more than 10 million single nucleotide substitutions are known.

MMP-1 has the following polymorphic variants: rs5854, rs4707474, rs470221, rs11799750, rs484915.

MMP-2 has the following polymorphic variants: rs2285053, rs243865

MMP-9 has the following polymorphic variants: Rs2274755, rs2664538, rs2236416, rs2274756, rs13925.

Mutations in the nephrin family of proteins - NEPH1, NEPH2, and NEPH3 - lead to the development of congenital nephrotic syndrome, accompanied by resistance to steroid therapy. Also, an important role in the development of nephrotic syndrome is played by the integral membrane protein podocin, which is part of the slit membrane, closing nephrin in podocytes. This protein is encoded by the NPHS2 gene located on chromosome 1, in the 1q25 – q31 region. Histological analysis of renal biopsies in patients with nephrotic syndrome caused by a mutation of the podocin gene, as a rule, was noted with focal segmental glomerulosclerosis [18]

Nephrine was the first podocyte gene (NPHS1) discovered in patients with congenital nephrotic syndrome and its discovery was a revolutionary discovery in understanding the pathogenesis of kidney disease.

Podocin is a member of the family of stomatin proteins, encoded by the NPHS2 gene located on chromosome 1q25-q31. NPHS2 mutations were first described in children with familial steroid-resistant idiopathic nephrotic syndrome. CD2-associated protein (CD2AP) is a molecule originally identified as a ligand for a T-cell adhesion protein that is expressed in all tissues except the brain. Plays a key role in the kidneys, where it is required for the functioning of the slit diaphragm to ensure filtration functions [1].

Polymorphism of genes IL-4 in the promoter region (C-590T) and IL-13 in the 4th exon (G4257A), NPHS1 in the 3rd exon (G349A) and NPHS2 in the 5th exon (G755A) in patients with nephrotic syndrome. The polymorphic marker 4G / 5G of the PAL-1 gene was studied in children with chronic glomerulonephritis and it was concluded that the 4G allele affects the development of proliferative nephritis and the progression of the disease [23].

Numerous molecular genetic studies are devoted to the study of polymorphism of genes involved in the processes associated with the development of chronic disease. The most studied MMP polymorphic genes, which play a role in the pathogenesis of these diseases:

MMP1 polymorphic locus-rs1799750, in the development of chronic pancreatitis, endometriosis, periapical granuloma, glaucoma, idiopathic pulmonary fibrosis, acute lymphoblastic leukemia, lung cancer, renal carcinoma, stomach cancer, and bladder cancer.

MMP-2 polymorphic locus-rs2285053 is important in reducing the risk of developing squamous cell carcinoma of the esophagus, breast cancer and cancer of the nasopharynx.

MMP-9 polymorphic locus-rs3918242 is involved in pathological conditions in renal fibrosis, pulmonary emphysema, myocardial

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infarction, ischemic stroke, chronic pulmonary obstruction, coronary heart disease, and diabetes mellitus. At the present stage, the polymorphism of candidate genes is being actively studied as one of the potential risk factors for the development of a pathological process [23, 24].

Thus, the study of the association of genetic polymorphisms in the pathogenesis of the development of chronic glomerulonephritis in children seems to be the most urgent. Taking into account the proven participation of the matrix metalloproteinase system in the development of chronic hepatitis, we considered it important in our work to collect the latest literature data on polymorphic variants of the MMP-9 genes and their tissue inhibitors STI-2.

In acute inflammatory processes in the renal tissue, STI -1 is an inhibitor of MMP-9; it binds to the active catalytic center of the enzyme and blocks its activity and the ratio between them changes. When the process is chronized, STI -2 is included in the process, because it is a universal inhibitor. STI -2 - prevent the breakdown of extracellular matrix proteins. An imbalance between the activity of MMPs and their inhibitors leads to the accumulation of extracellular matrix and glomerular obliteration, which contributes to the development of fibrosis and sclerosis of the renal vessels. These disorders can affect the processes of filtration and reabsorption [22, 5].

Renal tissue remodeling is the result of an imbalance in the synthesis and decomposition of the components of the extracellular matrix with the ratio of MMP and STI [21]. In the kidney, MMP-2, MMP-3, and MMP-9 are expressed predominantly by mesangial cells, glomerular podocytes, and tubular cells. The studies carried out prove the pathogenetic role of MMPs in acute and chronic kidney diseases. It is noted that the podocyte is associated with the glomerular membrane by integrins. An increase in the values of integrin bound kinase induced by MMP-9 causes podocyte detachment from the basement membrane and podocyturia in vivo. Overexpression of MMP-2 promotes nephrosclerosis and optimizes all pathological and functional changes in chronic kidney disease. Given that MMPs are relatively large in size, which negates filtration and urinary excretion, their circulating levels may reflect the content of these proteinases in the affected kidney. In children with chronic kidney disease, dysfunction and imbalance of the MMP / STI system is determined, aggravated by the progression of renal failure [10].

In children with pyelonephritis, there is an increase in urinary excretion of MMP and their tissue inhibitors. Thus, in acute pyelonephritis, a sharp overproduction of MMP-9 and STI -1 was revealed. With exacerbation of chronic pyelonephritis, the level of MMP-9 was below the reference level, requiring renoprotective therapy. The detection of higher STI-1 values in urine compared to MMP-9 means significantly significant changes in acute pyelonephritis, which indicates the highest degree of acute kidney destruction and the development of nephrosclerosis [25]. MMP-2 is also important in the processes of inflammation and fibrogenesis, in particular, inhibition of MMP-2 at an early "prefibrotic" stage of the disease can slow down or stop the progression of nephrosclerosis [13].

CONCLUSION

It was noted that in children with exacerbation of pyelonephritis, there is an increase in urinary excretion of MMP-9 with a simultaneous decrease in the MMP-9 / STI-2

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index, and in patients with a chronic process in the kidneys, the level of metaloproteinase decreases, reaching normal values. As a result, the ratio of MMP-9 / STI -2 increases, which indicates a slowdown in the formation of STI in nephrosclerosis? Therefore, the higher the activity of inflammation, the higher the level of MMP-9, and the more pronounced tubulointerstitial fibrosis and glomerulosclerosis, the lower it becomes with an increase in the MMP-9 / STI -2 index [8].

It was noticed that in acute and chronic course of glomerulonephritis, the level of MMP-1 in the blood increases, the content of MMP-2 does not change significantly, and the value of MMP-9 decreases, which indicates an active inflammatory process. An increase in the content of STI-1 in acute and STI -2 in chronic glomerulonephritis is also recorded [14, 8].

Thus, the imbalance of proteinases and their inhibitors thus serves as a reflection of the activity of inflammation and a marker of the progression of nephrosclerosis. The studies carried out show a significant role of MMP and their inhibitors both in the processes of tissue proliferation and in the progression of nephropathy. MMP and TIMP control the proteolytic activity of enzymes and are involved in the remodeling of the extracellular matrix and basement membranes. The obtained data will contribute to the understanding of new ideas about the mechanisms of progression of kidney disease in children with the improvement of the screening and prevention mechanisms of renal pathology in the early stages.

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