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KALLIKREIN-KININ SYSTEM, PROTEASE INHIBITORS FOR CHRONIC GLOMERULONEPHRITIS

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Abstract
Objective: to determine the state of the kallikrein-kinin system and protease inhibitors in various clinical forms of glomerulonephritis in children. Materials and methods of the study. To solve the set tasks, 85 children with glomerulonephritis aged 3 to 15 years will be examined.
Results and discussion. Patients of the first group showed significant activation of the KKS. The activity of K exceeded the norm by 1.7 times ($p<0.001$). The level of PC was reduced by 1.1 times ($p<0.01$). Conclusions: the state of the KKS has certain features in various clinical forms of CGN: mild CGN is characterized by pronounced activation of the KKS controlled by the protease system, probably caused by immune inflammation.

Keywords: Kallikrein-kinin system, glomerulonephritis, children.

Introduction

Glomerulonephritis (GN) occupies a central place in modern nephrology. The medical and social significance of this pathology is due to its prevalence among children, as well as the steady progression of the disease and the inevitable outcome in renal failure (1,2).The incidence of primary urinary tract diseases in children has increased 2.5-3 times over the last decade (Shtulko B.I., 2002). According to M.S. Ignatova (2000), children with various forms of glomerulonephritis account for more than 20% of all nephrological patients.The unfavorable course of GN in some cases leads to the development of renal failure already in childhood, early disability and often to death, which determines the relevance of studying the pathogenetic mechanisms of the development of this disease and targeted therapy.

At the same time, the state of the pituitary-adrenal system (PAS) plays a significant role in the formation of the main syndromes (primarily hypertensive) of glomerulonephritis (3,4,5,6). A significant number of studies have been devoted to the state of the RAAS and KKS of the kidneys in chronic glomerulonephritis in adults, while plasma RAAS and KKS in the pediatric population remains poorly studied (Madeddy P., 2021).Clinical interest in it is due to the high biochemical activity of kinins and, above all, their ability to dilate blood vessels, reduce blood pressure, and increase vascular permeability (7,8), in contrast to angiotensin (9,10). However, their relationship, joint role in the pathogenesis of glomerulonephritis, and influence on the development of the chronic process in the kidneys remains insufficiently studied.Also, the role of RAAS, HNS, KKS and the hemocoagulation system in the regulation of central and organ hemodynamics in various forms of glomerulonephritis in children is clear today.

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The aim of the study is to determine the state of the kallikrein-kinin system and protease inhibitors in various clinical forms of glomerulonephritis in children, and also to assess the degree of participation of some indicators of the kallikrein-kinin systems in the formation of hemodynamic disorders in patients with glomerulonephritis to determine the severity of the disease.

Materials and Methods of the Study

To solve the set tasks, 85 children with glomerulonephritis aged from 3 to 15 years will be examined. The content of kallikrein, prekallikrein, protease inhibitors in the blood of 85 patients with chronic glomerulonephritis was studied, of which 69 were studied in dynamics. The control group consisted of 20 practically healthy individuals (Table 1).

Results and Discussion

Significant activation of the KKS was revealed in patients of the first group. The K activity exceeded the norm by 1.7 times ($p<0.001$). The PC level was reduced by 1.1 times ($p<0.01$). The activity of protease inhibitors was significantly increased (PI by 1.18 times, $p<0.01$; ag-MG by 1.4 times, $p<0.01$). In dynamics, all KKS indices normalized.When analyzing the correlations between the parameters of the KKS in the latent form of CGN, a direct dependence of the K activity on the content of protease inhibitors was revealed (correlation coefficient with U-IP +0.44, $p<0.05$; with CC2-MG +0.54, $p<0.01$). An inverse correlation was also noted between K and PC ($r=-0.56$, $p<0.01$).This ratio of the components of the KKS is typical for its normal activation caused by an inflammatory process, including an immune one. Restoration of the normal level of KKS indicators in dynamics indicates sufficient compensatory capabilities available in the latent course of CGN.

In the mixed form of CGN, the state of the KKS underwent more serious changes. The PC level did not differ from the control, and the activity of K was reduced (by 1.4 times, $p < 0.05$). The inhibitory potential of plasma increased during the exacerbation period (IP by 1.18 times, $p < 0.01$; (X2-MG by 1.7 times, $p < 0.01$). During the remission period, the balance in the KKS was not restored, but protease inhibitors reached a normal level. Correlation analysis revealed a significant imbalance in the KKS. A complete lack of connections between K and PC was revealed. The activity of IP and MG weakly correlated with K ($r=-0.37$, $p<0.05$ and $r=-0.4$, $p<0.05$ respectively).Such changes reflect the disruption of connections in the biochemical structure of the KKS, its depletion. Signs of disorganization of this depressor system persisted in dynamics: the level of PC had a very weak effect on the activity of K ($r=-0.37$, $p<0.05$), the main proteinase inhibitor MG correlated slightly with the activity of K ($r=-0.41$, $p<0.05$), and there was no dependence between IP and K.

The next (third) clinical group, which included patients with the nephrotic form of CGN, was characterized by profound disturbances in the KKS. During the period of pronounced clinical manifestations of the disease, the PC level increased significantly (by 1.28 times, $p<0.001$), while the K activity also increased by 1.8 times ($p<0.001$). Antiproteases reacted in different directions:IP activity decreased (by 2.25 times, $p<0.001$), the level of ag-MG increased (by 1.93 times, $p<0.001$).Apparently, with this clinical form of CGN, there is an unregulated activation of the KKS, as evidenced by significant kininemia, with a weak direct relationship between K and

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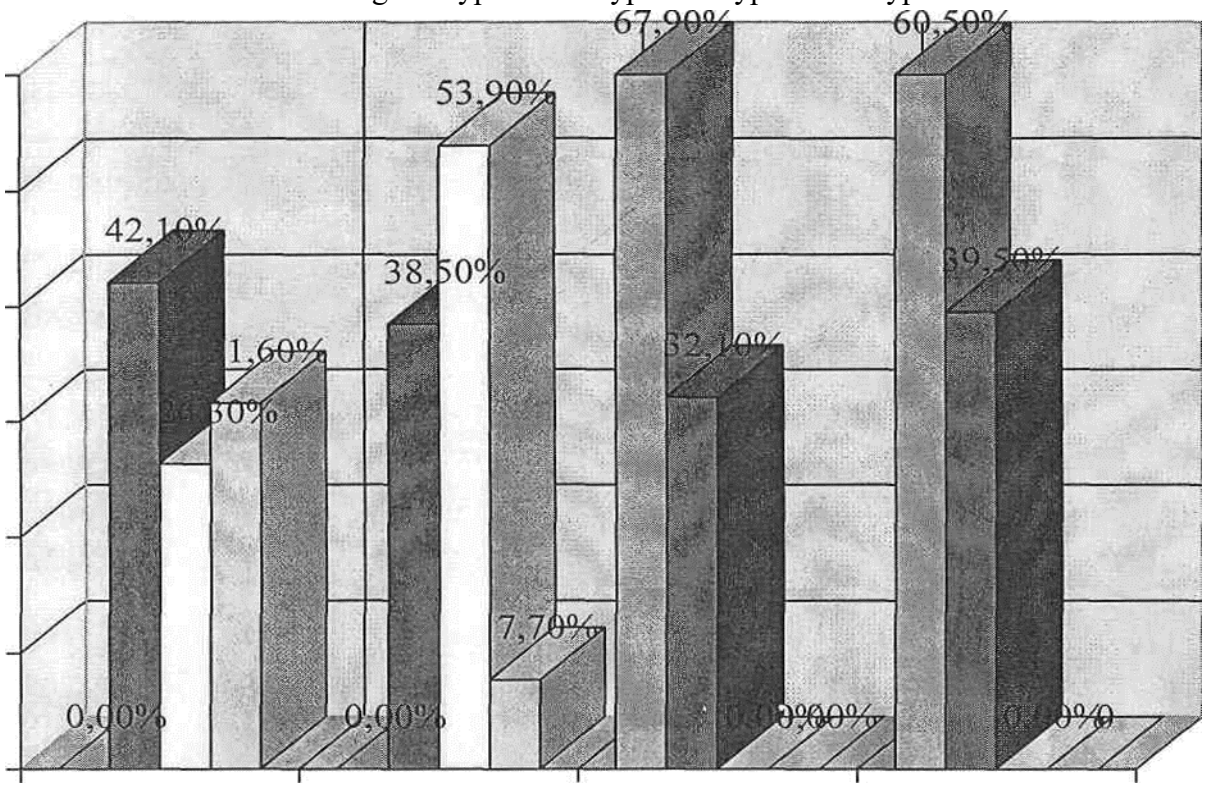
MG (r = +0.55, p <0.05) and a complete absence of such with IP. With the disappearance of signs of exacerbation, the balance between the KKS and protease inhibitors was restored, and the functioning of the depressor system became controlled (correlation relationships between K and IP +0.6, p <0.05, K and OC2-MG +0.71, p <0.01).

Table 1 Parameters of the kallikrein-kinin system and the level of proteinase inhibitors in patients with chronic glomerulonephritis (M+t)

Indicators	Latent form	Hypertensive form	Nephrotic form	Mixed form
	exacerbation n=23	exacerbation n=31	exacerbation n=13 remission n=10	exacerbation n=19 remissionn=12
PK,nmol/min/ml 360.03+7.2	330,14+5,18 p<0,05 356,05+4,70	335,76+11,40 340,50+12,70	461,30+10,20 p<0,00: 370,01+11,20	1 339,50+6,80 p<0,05 350,90+10,70
K,nmol/min/ml 30.6+3.1	52,02+2,70 p<0,001 34,2+4,01	21,50+1,03 p<0,01 23,70+1,03 p<0,05	56,13+2,30 p<0,001 32,70+3,80	39,78+3,20 p<0,05 23,53±1,04p<0,05
a1-IP,IE/ml 34.95+2.13	41,14+1,05 p<0,01 35,71+3,04	41,25+1,90 p<0,01 39,87+2,60	15,49+2,50 p<0,001 30,39+1,20	18,30+1,95 p<0,01 31,80+3,80
a2-MG,IE/ml 2.00+0.19	2,83+0,50 p<0,05 2,30+0,41	3,40+0,30 p<0,01 2,32+0,25	3,86+0,27 p<0,001 2,21+0,21	2,40+0,20 p<0,05 2,39+0,11 p<0,05

Pathological hypokinetic type and hypokinetic type



In patients with a mixed form of CGN, activation of the KKS was also observed, which was less pronounced than in the third clinical group. A moderate decrease in PC (by 1.06 times, p < 0.05)

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was accompanied by an increase in K activity (by 1.3 times, $p < 0.05$). At the same time, the level of IP was reduced by 1.9 times ($p < 0.01$), and MG was increased by 1.2 times ($p < 0.05$). Analysis of correlations showed that a moderate increase in K occurs due to insufficient activity of the protease system, when the increased level of ag-MG did not provide sufficient inhibitory potential of blood plasma (correlations between K and MG $r = -0.17$, $p < 0.05$). In dynamics, the PC level did not differ from the norm, K was 1.3 times lower compared to the control ($p < 0.05$). Normalization of IP in combination with increased activity of Ag-MG led to a decrease in K (correlation between K and IP $r=-0.58$, $p<0.05$; between K and MG $r=-0.62$, $p<0.05$).

Conclusion. Thus, the state of the KKS has certain features in various clinical forms of CGN: mild CGN is characterized by pronounced activation of the KKS controlled by the protease system, probably caused by immune inflammation; with pronounced depletion of this depressor system, the hypertensive form of the disease develops; imbalance in the protease system and, as a consequence, uncontrolled activation of the KKS are characteristic of the nephrotic variant of CGN; with the mixed form of CGN, kininemia is possible due to dysfunction in the protease system. The content of proteinase inhibitors and PC in the blood plasma reflects the state of the protein-synthetic function of the liver. A persistently elevated level of MG in all forms of CGN and an increase in PC synthesis against the background of pronounced disturbances in the hepatic blood flow in patients with the nephrotic form of CGN suggests long-term compensation of the liver function.

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