PROTEIN METABOLISM AND CHRONIC TUBULOINTERSTITIAL NEPHRITIS IN CHILDREN

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Annotation. Today, the following scientific research is being carried out in the world to establish the state of protein metabolism.

Purpose of the study. To identify features of protein metabolism indicators in chronic tubulointerstitial nephritis in children (taking into account the form of the disease).

Material and research methods. Depending on the clinical form of renal pathology, all patients (120 children) were divided into 2 groups: group 1 - 52 children (43.3%) with recurrent CTIN, group 2 - 68 sick children (56.7%) with latent CTIN. The duration of the chronic form of the disease ranged from 1 year to 9 years.

Research results. We assessed the degree of damage to the membrane structures of kidney cells by the level of KDM in the urine, as well as by the level of protein metabolism indicators - TAC, EAC, ABC, TI in the blood.

Discussion. Thus, the studies have shown that in the development of CTIN, an important mechanism of damage to the interstitial tissue of the kidneys and the development of clinical symptoms are toxic KDMs, which lead to disruption of the functional state of the kidneys.

Conclusion. In patients with CTIN, pronounced changes in indicators of endogenous intoxication are observed, which is reflected in a decrease in EAC, ABC and a stable increase in TI content due to an increase in toxic KDMs in the urine, which determines the importance of this diagnostic for the early detection of aseptic inflammation in the kidney tissue.

***Key words**: chronic kidney pathology, protein metabolism*

Relevance. Today, the following scientific research is being carried out in the world to establish the state of protein metabolism, the functional state of the kidneys during chronicity of the aseptic inflammatory process in the renal tissue, including in the following priority areas: substantiation of the mechanisms of influence of endogenous and exogenous risk factors influencing the development of pathology in the urinary tract system; determination of changes in biochemical parameters during chronicity of the aseptic inflammatory process of renal tissue in connection with changes in indicators of the functional state of the kidneys; development of methods for early diagnosis and treatment of chronic tubulointerstitial nephritis; comparative

diagnosis of the course of chronic aseptic inflammatory diseases of the urinary system; improving the treatment and rehabilitation of diseases of the urinary system [1, 2].

The identification of the leading role of endogenous intoxication in typical pathological processes as biologically active compounds determined the goal of studying the status of these messengers in the mechanisms of damage to the tubules and interstitium of the kidneys in the development and progression of fibrotic processes in interstitial tissue [3, 4]. Further studies have proven the significant role of renal damage molecules (KDMs) in the genesis of CTIN [5, 6].

Tubular cells acquire the ability to express chemokines that act as local mediators produced directly in the renal tissue. An imbalance of KDM determines the severity of inflammatory processes in the renal tissue, which allows us to consider them as markers of dysfunction of the body's regulatory mechanisms [7].

The task set in our work was to determine the importance of a method for determining indicators of endogenous intoxication in CTIN in children, aimed at preventing their progression and development of chronic renal failure [8].

Purpose of the study. To identify features of protein metabolism indicators in chronic tubulointerstitial nephritis in children (taking into account the form of the disease).

Material and research methods. Depending on the clinical form of renal pathology, all patients (120 children) were divided into 2 groups: group 1 - 52 children (43.3%) with recurrent CTIN, group 2 - 68 sick children (56.7%) with latent CTIN. The duration of the chronic form of the disease ranged from 1 year to 9 years. The average duration of CTIN was 4.2±0.5 years. In children with latent CTIN, it was determined from the moment of detection of urinary syndrome according to form No. 112. The frequency of relapses was 2-3 times a year. At the beginning of the study, at the Department of 2-Pediatrics of SamMU (head of the department - Doctor of Medical Sciences, Associate Professor N.I. Akhmedzhanova), an individual observation card for the patient was compiled, including data on the patient's life history and illness, genealogical and medical data. biological history, results of clinical, paraclinical, instrumental examination of the child.

The clinical diagnosis of CTIN was made according to the diagnostic criteria proposed in the classification by N.A. Korovina, I.N. Zakharova (2003), where special attention was paid to the characteristics of the pedigree history: determination of IMS, TIN, ICD, metabolic disorders at an early age, which were symptoms of exudative-catarrhal diathesis, dysuric disorders against the background of crystalluria.

All patients with CTIN were characterized by the absence of complaints and the occasional detection of urinary syndrome during clinical examination or examination in connection with the disease of one of the family members. Features of the clinical characteristics of the latent variant of CTIN (85.2% (58/68)) - random determination

of isolated urinary syndrome, in 88.2% (60/68) cases in combination with signs of endogenous intoxication, a tendency to hypotension in 58, 8% of cases (40/68). The constant persistence of urinary syndrome in these patients did not allow us to clearly distinguish between the stages of CTIN.

With the undulating course of CTIN, in 100% of cases the symptoms of endogenous intoxication predominated, as well as weight loss, anorexia, fatigue, and arterial hypotension. Dysuric symptoms occurred in 40.0% (20/52), pain in the abdomen and lumbar region - 78.8% (41/52), skin rashes in 5/52 patients, low-grade fever - in 38.4% (20/52) .

We noted the following variants of TIN with a chronic course: circulatory TIN often occurred against the background of anomalies of the renal vessels (7 (13.4%)), kidney rotation, and nephroptosis. Dysmetabolic TIN was characteristic of patients with secondary oxalate crystalluria (29 (55.7%)); against the background of dysembryogenesis (anomalies of the urinary system with impaired urodynamics) - 6 (11.5%). One child (1.9%) had an autoimmune nature of the disease. The manifest onset of the disease, established in 52 children (43%), subsequently took on a wave-like character. The latent variant of the chronic course occurred in 68 patients (57%). Among them there were 65 boys (54%), 55 girls (46%).

Noteworthy is the family history of kidney disease and metabolic disorders (urolithiasis, cholelithiasis), amounting to 82% of cases. The parents of 4 patients (3.3%) reported occupational hazards (chemical factors).

Unfavorable antenatal history was one of the development factors in 57 cases (47.5%). Pathological course of pregnancy with a predominance of early gestosis in mothers of observed children (19), acute perinatal gestosis (3) and intrauterine infection (1). Perinatal encephalopathy was observed in 4.1% of cases (5 children). A short period of breastfeeding was noted in 84 (70%) children.

Indicators of protein metabolism were also determined (total serum protein, protein fractions, concentration of total and effective albumin, albumin binding capacity, altered albumin coefficient and toxicity index, and the content of toxic molecules of kidney damage). The value of the total and effective concentration of albumin was determined using the Albumin - UTS kit (manufactured by Eiliton LLC, commissioned by JSC A/O Unimed ") in quartz cuvettes with a cross-section of 1 by 1 cm. The binding capacity of albumin and the toxicity index were calculated using the formulas: ABC = (TAC/ECA) * 100%, TI = (TAC/EAC) - 1, where TAC is the total concentration of albumin in g/l, EAC - effective concentration of albumin, equivalent to "healthy" albumin, measured by the luminescence method with a K-35 probe, in g/l.

The content of toxic KDM (KDM 254) in urine was determined using the Kalkar formula.

Methods of statistical processing. The statistical significance of the obtained results was assessed using parametric Student-Fisher tests with calculation of mean values (M), standard deviation (δ) and error of the arithmetic mean (m). Using the table, Student's t-test was used to determine the probability (p) of a possible error. The result was considered statistically significant at $P<0.05$. The correlation coefficient (r) between data on the functional state of the kidneys and metabolic changes was determined by Brava-Pearson.

Research results. It has now been established that with the development of CTIN, products of impaired metabolism - endotoxins - accumulate in the body. Endotoxins include products of natural metabolism that accumulate in the body in high concentrations, KDMs are intermediate products of proteolysis, variable products, ingredients of non-viable tissues, heterogeneous in composition and accumulate in the body when natural detoxification mechanisms are inhibited and metabolic disorders occur. There is a direct relationship between the degree of EI and the level of KDM in the urine in children with CTIN.

Studies of kidney function and parameters of endogenous intoxication are important for predicting the course of CTIN and assessing the effectiveness of treatment. We assessed the degree of damage to the membrane structures of kidney cells by the level of KDM in the urine, as well as by the level of protein metabolism indicators - TAC, EAC, ABC, TI in the blood.

In 98.4% of patients with CTIN, changes in urine were noted before treatment (decrease in the level of effective albumin concentration (EAC), albumin binding capacity (ABC), increase in the toxicity index (TI) and kidney damage molecules (KDM) in the urine).

Data were assessed using the average values obtained from all 120 patients. There is evidence of the possibility of using these methods for early identification of aseptic damage to renal tissue characteristic of CTIN at the level of processes occurring in cells (Zufarova Sh.), which is important in differential diagnosis and predicting disease outcomes.

The need to determine the level of KDM in urine in patients with CTIN is due to the absence of obvious signs of exacerbation of the inflammatory process in the kidneys in CTIN in children.

In all examined patients, there were no significant differences in the concentration of KDM in the blood plasma, in contrast to their level in the urine.

The results of the study showed that in the urine of patients with recurrent CTIN in the acute phase, the level of KDM was 16.3 times higher than in the control group (Table 1), and in children with latent CTIN it was 8 times higher than the level in healthy children. The identified changes in biochemical parameters in the urine reflect a violation of the state of the cell membranes of the interstitial tissue of the kidneys.

Thus, patients with CTIN had pronounced disturbances in the cellular structures of the renal tissue. We attribute the increase in the level of KDMs in urine in CTIN to the fact that their low molecular weight allows them to freely pass through the membranes of the proximal tubules, where, under the influence of aseptic inflammation, an increase in tubular conductivity occurs (in healthy children, they are reabsorbed by 99.9% in the proximal tubules). During inflammatory-destructive processes of the tubulointerstitial system, the reabsorption of KDM is disrupted and their excretion in the urine is observed. Disruption of the tubulointerstitial tissue of the kidneys in CTIN leads to an increase in KDM in the urine, which leads to tubular atrophy and organic structural changes.

A reliable moderate correlation was established between the level of KDM in the urine and proteinuria, i.e. the higher the proteinuria, the more active the pathological process and the higher the level of KDM in the urine (r=0.50; p=0.03). A direct correlation of a high degree was noted between the level of KDM in the urine and leukocyturia (r=0.70; p=0.02). Daily proteinuria in the pathology under study was in an inverse relationship with leukocytosis (r = - 0.709; p = 0.014), which indicates the aseptic genesis of the disease. But it directly correlated with the duration of the disease (r = 0.781; p = 0.005).

Thus, the higher the level of KDM in the urine, the more active the aseptic inflammatory process in the renal tissue, which indicates the predominant tubular type of renal dysfunction.

Studying the function of albumin in endotoxicosis caused by metabolic disorders in CTIN has not only diagnostic but also prognostic significance for clinical practice.

The following albumin parameters were studied: total albumin concentration, effective albumin concentration, albumin binding capacity, toxicity index in blood plasma.

We did not find a significant decrease in serum total protein (TP) levels (67.6 ± 0.25 g/L) and total albumin concentration (49.23 ± 0.28 g/L). Minor protein losses are compensated by the protein-synthetic function of the liver. Due to the fact that exacerbations of CTIN in modern conditions occur mainly in the form of low-symptomatic variants, febrile conditions were rare in children of this group. Thermal inactivation of liver enzymes did not occur, which allowed maintaining a normal level of protein synthesis.

Table 1.

Indicators of protein metabolism in CTIN in children upon admission (M±m)

№	Indicators	Healthy children (n =30)	Recurrent CTIN (n =52)	Latent CTIN (n =68)
In blood				

1	KDM, units	0,136±0,021	0,148±0,040 p>0,1	0,107±0,002 p>0,1
2	TP, (g/l)	67,5±0,45	66,6±0,25 P>0,1	64,7±0,37 P>0,1
3	TAC, g/l	52,5±0,55	49,23±0,28 p>0,1	44,9±0,24 p=0,01
4	EAC, g/l	40,4±3,7	23,4±0,84 p=0,001	24,3±0,44 p=0,001
5	ABC, (EAC\TAC) %	93±0,9	64,8±0,65 p=0,001	69,7±0,72 p=0,001
6	TI (units)	0,12±0,01	0,29±0,006 p=0,04	0,28±0,007 p=0,03
In urine				
1	KDM, units	0,136±0,021	2,23±0,08 p=0,001	1,12±0,07 p=0,001

Note: p-significance of the difference between the indicators in healthy children and children with CTIN.

The latent course of CTIN is characterized, on the one hand, by less pronounced but persistent changes in protein metabolism. In this group of children, for the first time, we noticed a decrease not only in the effective concentration of albumin, but also in the total concentration (Table 1). The data obtained allow us to indirectly assume the presence of disorders in the protein-synthetic function of the liver in children with a sluggish process in the kidneys.

The exacerbation period is characterized by a decrease in the effective concentration of albumin, but to a greater degree of severity (23.4±0.84 g/l; 24.3±0.44; p=0.001). A moderate negative correlation was revealed between EAC and γ-globulin (p=-0.54; p=-0.50), as well as between the studied indicator and the level of ammonia excretion in the urine (p=-0.61; p=- 0.58).

A decrease in this indicator is accompanied by a decrease in albumin binding capacity (64.8±0.65%; p=0.001; 69.7±0.72% p=0.001).

The identified changes are apparently associated with more pronounced aseptic inflammation that persists for a long time. There is an excessive accumulation of toxic KDMs in the body, causing a state of endotoxemia and disruption of homeostasis. It is known that the nature of intoxication and its intensity in a particular pathology determine the rate of decay of protein structures.

Intoxication of the body is a factor capable of supporting the first phase of the metabolic reaction, accompanied by a catabolic shift in protein metabolism. Possibly, intoxication contributes to sensitization. This increases the permeability of membranes to toxins. The presence of KDM intoxication is confirmed by a high level of toxicity index, determined during all periods of the disease.

Discussion. Consequently, patients with CTIN may experience an exacerbation of the aseptic inflammatory process without visible laboratory manifestations, which may be one of the reasons for late diagnosis and aggravation of the latent course of the disease.

The liver, under conditions of constant inflammation in the body, intoxication, and immune disorders, is not able to provide compensation for catabolic protein metabolism. During the latent course, the effective concentration of albumin remained reduced to a lesser extent than during the recurrent process. This indicates the presence of compensatory processes in the liver, when less albumin is synthesized, but it is qualitatively more complete, which is, apparently, an adaptive reaction in conditions of a constant inflammatory process. The level of "modified", conformationally changed albumin in the blood in this case is lower, which makes it possible to preserve its function to a greater extent than in other variants of the process.

Compensatory processes in the body are also reflected by the dynamics of such an indicator as the binding capacity of albumin. While remaining lower than under normal conditions, its level is higher (with latent CTIN) than with a more active course of aseptic inflammation. The higher binding capacity of albumin ensures the binding reactions of hydrophobic ligands not only due to hydrophobic bonds, hydrogen bridges (weak acids and amines are involved in the interaction), but also electrostatic interactions (they bind organic and inorganic electrolytes). This mechanism apparently makes it possible to maintain a lower level of toxic KDMs, which is reflected in such an indicator as the toxicity index.

Thus, the studies have shown that in the development of CTIN, an important mechanism of damage to the interstitial tissue of the kidneys and the development of clinical symptoms are toxic KDMs, which lead to disruption of the functional state of the kidneys. This justifies the need to determine the studied parameters of endogenous intoxication in patients with CTIN for the purpose of early diagnosis, which will prevent the development of secondary kidney scarring in children.

Conclusion. In patients with CTIN, pronounced changes in indicators of endogenous intoxication are observed, which is reflected in a decrease in EAC, ABC and a stable increase in TI content due to an increase in toxic KDMs in the urine, which determines the importance of this diagnostic for the early detection of aseptic inflammation in the kidney tissue.

Thus, the higher the level of KDM in the urine, the more active the aseptic inflammatory process in the renal tissue, which indicates the predominant tubular type of renal dysfunction.

A correlation has been established between indicators of endogenous intoxication and the functional state of the kidneys in CTIN in children. A high direct correlation was revealed between the amount of KDM excretion in the urine and daily proteinuria

and leukocyturia. Daily proteinuria in the pathology under study had an inverse relationship with leukocytosis (r = - 0.709; p = 0.014), which indicates the aseptic genesis of the disease. But it directly correlated with the duration of the disease (r = 0.781; p = 0.005).

In addition, a moderate negative correlation was found between EAC and γ-globulin (p=-0.54; p=-0.50), as well as between the studied indicator and the level of ammonia excretion in the urine (p=-0.61; p=-0.58), which is associated with severe aseptic inflammation that persists for a long time.

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