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The State of Protein Metabolism in Chronic Tubulointerstitial Nephritis in Children

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Abstract The achievements in the diagnosis and therapy of neurological diseases in children are enormous, but nevertheless, in about 23% of patients, the disease has a progressive course, which significantly affects the formation of the quality of life. A survey of 120 children with CTIN, aged from 4 to 15 years, was conducted. Considering the clinical variant of CTIN, all patients were divided into 2 groups: group 1 – 52 (43%) children with recurrent form of CTIN and group 2 - 68 (57%) patients with latent CTIN. Among them, there were 65 boys (54%), 55 girls (46%). The conducted studies have shown that with the development of rCTIN and lCTIN, an important mechanism of damage to interstitial kidney tissue, the development of clinical symptoms and the course of the disease is both a metabolic disorder leading to structural shifts at the level of various elements of the nephron and changes in the functional state of the kidneys, and instability of the cytomembranes of tubular cells.

Keywords Protein metabolism, Chronic tubulointerstitial nephritis, Endogenous intoxication, Instability of cytomembranes

1. Introduction

The achievements in the diagnosis and therapy of neurological diseases in children are enormous, but nevertheless, in about 23% of patients, the disease has a progressive course, which significantly affects the formation of the quality of life. The inflammatory process in the tubulointerstitial tissue (TIT) of the kidneys progresses against the background of specific and nonspecific etiological factors. Interstitial kidney tissue is a focus of pathology in the TKD that further covers the blood, lymphatic vessels and tubules of the renal stroma [5,7,9].

Renal glycosuria is defined as the excretion of glucose in urine in a normoglycemic state. It results from renal tubular dysfunction or immaturity of tubular function in the newborn. Etiologically, renal glycosuria is of 3 types-benign renal glycosuria, glycosuria with diabetes mellitus (including gestational diabetes) and tubular defects (Fanconi syndrome). Prognosis of benign renal glycosuria is excellent and reversible. Acute interstitial nephritis (AIN) is one of the main causes of acute renal failure and may often result in tubular dysfunction. In this study, the authors report the occurrence of AIN with acute renal failure that contributed to reversible renal glycosuria. The glycosuria observed in the patient of this study was an isolated tubular defect, with no phosphaturia, aminoaciduria or bicarbonaturia. Such a presentation is very rare in adults and has not been previously reported. These findings confirm that AIN with acute renal failure can cause an isolated tubular defect with benign reversible glycosuria in an adult [5].

Microscopic data of TIN are: infiltration (lymphoid or macrophage) of interstitial tissue with transition to loose - or coarse-fibrous sclerosis, dystrophy and/or atrophy of the tubule epithelium [4,10].

Studies of recent decades have proven an important role in the origin of the TKD of molecules of kidney damage. They can participate simultaneously in many processes of endotoxin formation and their accumulation in the internal homeostasis of the body [1,2,6,13]. A number of authors have noted that endotoxicosis is a cascade process [8,9,12].

Despite the successes achieved in the treatment and prevention of CTIN in children, there is currently no exact algorithm for the diagnosis of this pathology in the literature. Comparative clinical and laboratory diagnostics of the main types of tubulointerstitial nephritis is also not fully developed. There is no data on the pathogenetic relationship between tubular functions and indicators of protein metabolism of blood serum and urine in children with different forms of CTIN. The development of a new pathogenetically based complex treatment of CTIN in children remains a significant research task.

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2. Aim

To develop a method for the complex correction of CTIN in children, considering the identified pathogenetic significance of the parameters of endogenous intoxication and violations of tubular functions.

3. Materials and Methods

This study presents the results of examination and treatment of 120 children with CTIN, in the phase of active inflammatory process, who were in the pediatric nephrology department of the children's regional multidisciplinary scientific Center of Samarkand, in the period from 2019-2021.

Considering the clinical variant of CTIN, all patients were divided into 2 groups: group 1 – 52 (43%) children with recurrent form of CTIN and group 2 - 68 (57%) patients with latent CTIN. Among them, there were 65 boys (54%), 55 girls (46%). The patients underwent general clinical, laboratory and instrumental examinations.

The clinical diagnosis of CTIN was carried out according to the diagnostic criteria proposed in the classification of N.A. Korovina (2003), where special attention was paid to the characteristics of the pedigree anamnesis: the definition of IC, TIN, ICD, metabolic disorders at an early age, which were symptoms of exudative catarrhal diathesis, dysuric disorders against the background of crystalluria.

"Urinary syndrome" was characterized by: abacterialleukocyturia, high osmotic density of urine, microproteinuria, microhematuria, crystalluria.

The control group consisted of 30 practically healthy children who did not suffer from chronic diseases, who had not been ill for the last 6 months, with a favorable nephrological family history at the age of 4 to 15 years.

Renal indicators were assessed during the period of exacerbation of the disease, during the formation of clinical and laboratory remission, 1 year, 2 and 3 years after the period of exacerbation. The study did not detect children with CTIN on the background of severe congenital pathology in combination with impaired functional state of the kidneys.

The state of renal functions was assessed on the basis of two groups of functional techniques:

group I - methods indicating the quantitative state of renal functions of various parts of the nephron.

a) The state of renal filtration function (clearance of endogenous creatinine) was assessed according to the Van Slyke formula:

Using immunoturbidimetry on the Cobas Integra 400 plus apparatus (Roche, Switzerland), cystatin C was determined:

- this is a protein that is formed in the nucleus of cells at a constant rate;
- has the property of free filtration in the glomeruli;
- inversely correlates with GFR and is highly sensitive to its changes compared to its changes in creatinine [9];
- it is metabolized in the proximal tubules during reabsorption;
- it is formed regardless of gender, body weight or tumors of the presence of inflammatory processes;

To determine the concentration capacity of the kidneys, a Zimnitsky sample was used. In addition, the value of ammonioacidogenesis was determined (titrated acids and ammonia were determined in the daily urine).

Protein metabolism parameters (protein fractions, total serum protein, total and effective albumin concentration, serum toxicity index, albumin binding ability) were determined in all examined patients. Serumurea and creatinine levels were also determined.

4. Results and Discussion

The clinical group (group 1: 52 patients) with rCTIN was isolated based on the presence of typical signs of the disease, such as dysuria (32.7%), neurogenic bladder (10%), pasty soft tissues of the eyelids in the morning (46.5%), lower back pain (30.8%) on the background of physical activity (26.9%).

Whereas, the clinical group (group 2: 68 patients) with lCTIN was isolated on the basis of a more permanent symptom of "losing kidney", which leads to the development of muscular hypotension - 41.2% (28) and arterial hypotension – 27.9% (19), dysuria – polyuria in 54.4% (37) patients, the presence of abacterial lesions of renal tissue against hyperoxaluria – 100% (68), an abundance of epithelium in 92.6% (63), lympho– monocytic character - 88.2% (60), brown cylinders – 100% (68). Urine culture is sterile.

Diagnostic criteria for the latent course of CTIN: they were detected against the background of respiratory diseases, they did not receive attention due to their short duration, hereditary history was not considered.

In our studies, a high percentage of the incidence of the continuously recurrent form of CTIN occurred in children aged 10-14 years, which accounted for 43.2% of the total number of patients with the continuously recurrent form of CTIN.

We associate the recurrent course of the disease with the presence of a secondary immunodeficiency condition, the indirect signs of which are: frequent recurrence (more than 2 times a year) and prolonged course (preservation of clinical and laboratory signs for more than 6 months), short-term effect of antibiotic therapy, multiple foci of chronic infectious pathology, susceptibility to acute respiratory viral infections.

In the clinical status of patients with chronic recurrent TIN, the frequency of exacerbation of the disease over the past period was determined and revealed that in 20 (38.7%) children the frequency of exacerbation was 1 time per year, in 19 (36.5%) children 2 times a year and in 12 (23.1%) children more than twice a year.

The parameters of protein metabolism were determined

in all the examined patients (total serum protein, OKA, ECA, protein fractions, CSA, altered albumin concentration and toxicity index, MPP in urine and blood, globulin fractions, cystatin C concentration, albumin functional status indicators, urea, creatinine levels).

Currently, it has been established that with the development of multiple organ and polysystem insufficiency, the products of impaired metabolism – endotoxins - accumulate in the body. Endotoxins include products of natural metabolism that accumulate in the body in high concentrations, MPP - intermediate products of proteolysis, variable products, heterogeneous ingredients of non-viable tissues that accumulate in the body when the natural mechanisms of detoxification and metabolic disorders are suppressed [9]. There is a direct relationship between the degree of EI and the volume of MPP in the urine, depending on the severity of CTIN [6,8].

Studies of kidney function and EI indicators are necessary to predict the course of CTIN. The degree of damage to the membrane structures of kidney cells was assessed by the level of MPP and OCA in the urine, in the blood by the total concentration of albumin, ECA, CSA, IT and KIA.

The data obtained showed that the concentration of MPP in the urine of patients with rCTIN in the acute phase was 16.3 times higher than the control group (Table 1.), whereas in children with lCTIN it was 8 times higher. There were more pronounced violations of cellular structures in patients with rutin compared with patients with lakhtin.

Table 1. Parameters of EI with CTIN in children at admission (M ±m)

№	Indicators	Healthy	Patients with rCTIN (n=52)	Patients with lCTIN (n=68)
in the blood				
1	MPP	0,136± 0,021	0,148±0,040; P>0,1	0,107±0,002; P>0,1
in the urine				
1	MPP	0,136± 0,021	2,23±0,08; P<0,001	1,12±0,07; P<0,001

The increase in the level of MPP in urine with CTIN is apparently due to the fact that during inflammatory and destructive processes of the tubulointerstitial system, the reabsorption of MPP in the proximal tubules is disrupted, since they are reabsorbed there by 99.9%, as a result of which their excretion with urine is observed. The accumulation of MP in the urine is facilitated by a violation of the excretory function of the kidneys, leading to tubular atrophy and organic structural disorders.

Both in the active stage and in remission with rCTIN, the state of protein metabolism was the same as in the acute course of the process. A significant decrease in the concentration of total serum protein in this pathology was uncharacteristic (67.6± 0.25g/l) and OCA (49.23± 0.28g/l). Protein-synthetic liver function compensated for small protein losses associated with fever.

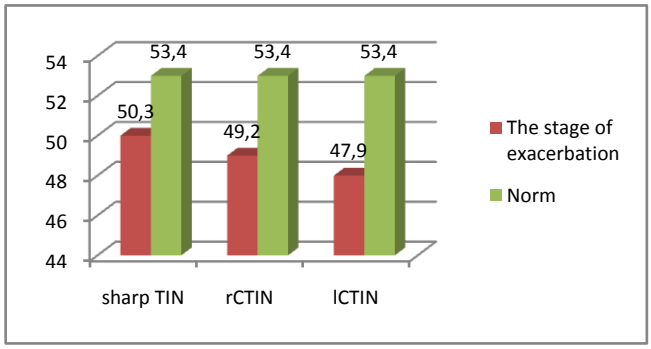

Figure 1. OCA indicator in the acute stage in various forms of the disease in children

In recent years, febrile conditions have been observed rarely in patients, and exacerbations of CTIN have occurred with low-symptomatic variants.

The normal level of protein synthesis was maintained due to the absence of thermal inactivation of liver enzymes.

The active phase of CTIN was characterized by a decrease in ECA, as well as in the acute process, but to a greater extent (32.04 ± 0.26 g/l). The decrease in ECA was combined with a decrease in heart rate to 64.8 = 0.65% (Fig.1.).

In our opinion, the identified changes are associated with more active and persistent intoxication for a long time, which is the cause of excessive accumulation of toxic substances that contribute to the formation of endotoxicosis and homeostasis disorders. The nature of intoxication, its severity in one form or another of the disease affects the rate of breakdown of protein structures.

A high level of the toxicity index indicates the presence of intoxication, which is determined during all periods of the disease (Fig.2.). Less pronounced, but persistent changes in protein metabolism are characteristic of the latent course of CTIN. Children are characterized by a decrease not only in ECA, but also in general. We found in patients with a sluggish process in the kidneys the presence of violations of protein-synthetic liver function.

Table 2. Parameters of the functional state of albumin before treatment, depending on the variants of the course of CTIN in children

Indicators	OB (g/l)	OCA (g/l)	ECA (g/l)	KIA (g/l)	CCA (%)	IT Con.units
Sharp TIN	67,5±0,27 P>0,1	50,3±0,33 P>0,1	34,0±0,18 P<0,001	16,1±0,29 P<0,001	67,4±0,44 P<0,001	0,47±0,09 P<0,001
rTIN	67,6±0,25 P>0,1	49,23±0,3 P>0,1	32,04±0,26 P<0,001	17,1±0,37 P<0,001	64,8±0,65 P<0,001	0,54±0,01 P<0,001
lTIN	64,7±0,37 P>0,1	47,9±0,24 P>0,1	33,6±0,3 P<0,001	14,3±0,38 P<0,001	69,7±0,72 P<0,001	0,43±0,01 P<0,001

Note: P is the reliability of the difference between the indicators of healthy and in children with chronic TIN

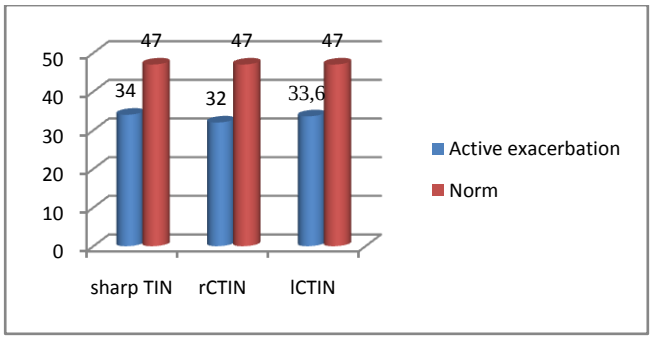

Figure 2. The indicator of ECA in the active stage in various forms of CTIN in children

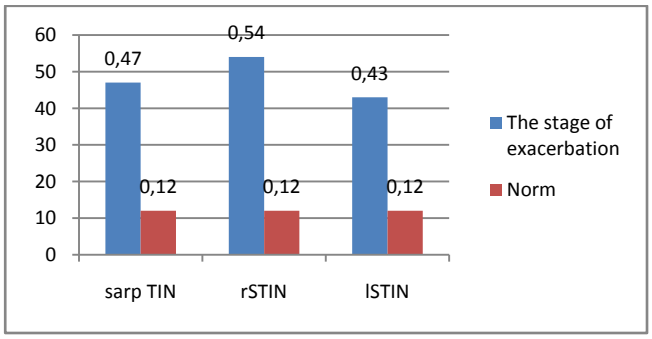

Figure 3. IT indicator in the active stage in various forms of the disease in children

Against the background of intoxication, immune disorders and sluggish inflammation in the body, the liver loses the ability to compensate for protein metabolism disorders. The level of ECA in lCTIN changes to a lesser extent, compared with rCTIN, which is associated with compensatory mechanisms in the liver.

An adaptive reaction against the background of a long pathological process is that albumin is synthesized in a smaller amount, but more complete.

A high CSA helps to reduce the level of intoxication, unlike other variants of TIN, which indicates such an indicator as IT (Fig.3.). Such changes in albumin lead to the formation of chronic TIN, which indicates that the nonspecific effector system of the body is functioning [4,7].

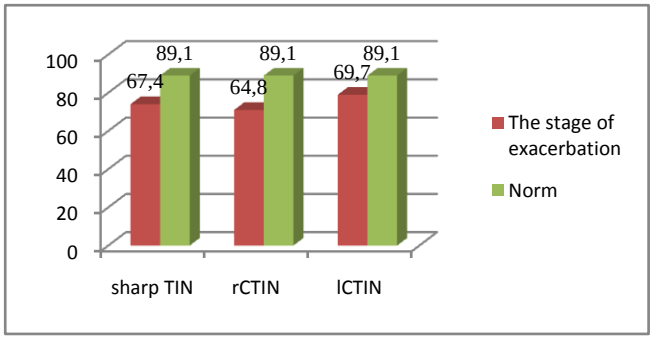

Figure 4. Indicators of CSA in the active stage in various forms of CTIN in children

With CTIN, despiralization of the protein molecule is observed. Conformational disorders lead to the formation of discrete forms of albumin, which is indicated by a decrease in the level of binding capacity of albumin. The limited ability of albumin to bind drugs, this applies to antibiotics, which significantly affects the formation of chronization of the process.

5. Conclusions

Thus, the conducted studies have shown that with the development of rCTIN and lCTIN, an important mechanism for damage to interstitial kidney tissue, the development of clinical symptoms and the course of the disease is both a metabolic disorder leading to structural shifts at the level of various elements of the nephron and changes in the functional state of the kidneys, and instability of the cytomembranes of tubular cells. This justifies the need for combination therapy in patients with CTIN, which will contribute to the elimination of the inflammatory process, the excretion of endotoxins from the renal tissue, stabilization of cellular cytomembranes and kidney functions.

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