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THE PATHOGENETIC ROLE OF ENDOGENIC INTOXICATION IN CHRONIC TUBULOINTERSTITUAL NEPHRITIS IN CHILDREN

Summary (abstract). The inflammatory process in the tubular-interstitial tissue (TIT) of the kidneys progresses against the background of specific and nonspecific etiological factors. Interstitial tissue (IT) is a pathological focus in tubular-interstitial kidney damage, subsequently encompassing the blood, lymphatic vessels, and tubules of the renal stroma. The purpose of the study was to assess the role of endogenous intoxication (EI) in the development of chronic tubulointerstitial nephritis (TINN) in children. Patients and methods: examination was conducted on 120 children with CSTIN aged 4 to 15 years. Taking into account the clinical variant of TIN, all patients were divided into 2 groups: 1 group - 52 (43%) children with recurrent forms of chronic tubulointerstitial nephritis (rChTIN) and 2 group - 68 (57%) patients with latent chronic tubulointerstitial nephritis (lChTIN). Of these, 65 (54%) were boys and 55 (46%) were girls. All patients underwent general clinical, laboratory, and instrumental examinations. Results: The conducted studies have shown that in the development of rChTIN and lChTIN, an important mechanism for damage to the renal IT, the development of clinical symptoms, and the course of the disease is both metabolic disorders leading to structural shifts at the level of various elements of the nephron and changes in the functional state of the kidneys, as well as the instability of the cytoembranes of tubular cells. This justifies the need for combined therapy in patients with CTHIN, which will contribute to the elimination of the inflammatory process, the excretion of endotoxins from the kidney tissue, and the stabilization of cell cytomembranes and kidney function.

Keywords: chronic tubulointerstitial nephritis; endogenous intoxication; cytomembrane instability.

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ПАТОГЕНЕТИЧЕСКАЯ РОЛЬ ЭНДОГЕННОЙ ИНТОКСИКАЦИИ ПРИ ХРОНИЧЕСКОМ ТУБУЛОИНТЕРСТИЦИАЛЬНОМ НЕФРИТЕ У ДЕТЕЙ

Аннотация Воспалительный процесс в тубулоинтерстициальной ткани (ТИТ) почек прогрессирует на фоне специфических и неспецифических этиологических факторов. Интерстициальная ткань (ИТ) является патологическим очагом при тубулоинтерстициальном поражении почек, впоследствии охватывающем кровь, лимфатические сосуды и канальцы почечной стромы. Целью исследования было оценить роль эндогенной интоксикации (ЭИ) в развитии хронического тубулоинтерстициального нефрита (ХТИН) у детей. Пациенты и методы: обследование проведено у 120 детей с ХТИН в возрасте от 4 до 15 лет. С учетом клинического варианта ТИН все пациенты были разделены на 2 группы: 1 группа - 52 (43%) ребенка с рецидивирующими формами хронического тубулоинтерстициального нефрита (рХТИН) и 2 группа - 68 (57%) пациентов с латентным хроническим тубулоинтерстициальным нефритом (лХТИН). Из них 65 (54%) были мальчиками и 55 (46%) - девочками. Всем пациентам проводилось общеклиническое, лабораторное и инструментальное обследование. Результаты: проведенные исследования показали, что в развитии рХТИН и лХТИН важным механизмом повреждения почечной ИТ, развития клинических симптомов и течения заболевания являются как метаболические нарушения, приводящие к структурным сдвигам на уровне различных элементов нефрона и изменениям в функциональном состоянии почек, так и нестабильность цитомембран тубулярных клеток. Это обосновывает необходимость комбинированной терапии

у пациентов с ХТИН, которая будет способствовать устранению воспалительного процесса, выведению эндотоксинов из ткани почки и стабилизации цитомембран клеток и функции почек.

Ключевые слова: хронический тубулоинтерстициальный нефрит; эндогенная интоксикация; нестабильность цитомембран.

Relevance. The achievements in the diagnosis and treatment of nephrological diseases in children are colossal, but nevertheless, about 23% of patients have a progressive course of the disease, which significantly affects the formation of quality of life. The inflammatory process in the tubular-interstitial tissue (TIT) of the kidneys progresses against a background of specific and nonspecific etiological factors. The interstitial tissue of the kidneys is a focus of pathology in TIPP, subsequently encompassing the blood, lymphatic vessels, and tubules of the renal stroma.

Microscopic findings of TIN include: infiltration (lymphoid or macrophage) of the interstitial tissue with the transition to loose or coarse-fibered sclerosis, dystrophy, and/or atrophy of the tubular epithelium [3; 5;7].

Studies in recent decades have proven an important role in the origin of TYPES of kidney damage molecules. They can simultaneously participate in many processes of endotoxin formation and their accumulation in the body's internal homeostasis [1;2;6;].

A number of authors have noted that endotoxicosis is a cascade process. Despite the successes achieved in the treatment and prevention of CKD in children, currently there is no accurate algorithm for the diagnosis of this pathology in the literature. The comparative clinical and laboratory diagnosis of the main types of tubulointerstitial nephritis has also not been fully developed. There is no data on the pathogenetic relationship between tubular functions and protein metabolism indicators in blood serum and urine in children with different forms of CTI. Developing a new pathogenetically justified complex treatment for CKIN in children remains a significant research task.

Research objective. Assess the pathogenetic role of endogenous intoxication (EI) in the development of chronic tubulointerstitial nephritis (TINN) in children.

Materials and methods of research. This study presents the results of examination and treatment of 120 children with CSTD, in the active phase of the inflammatory process, who were in the pediatric nephrology department of the Samarkand Regional Children's Multidisciplinary Scientific Center, during the period 2019-2021.

Taking into account the clinical variant of CSTIN, all patients were divided into 2 groups: 1 group - 52 (43%) children with recurrent form (rCSTIN) and 2 group - 68 (57%) patients with latent form (lCSTIN). Of these, 65 (54%) were boys and 55 (46%) were girls. Patients underwent general clinical, laboratory, and instrumental examinations.

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

Renal indicators were assessed during the exacerbation of the disease, during the formation of clinical and laboratory remission, 1 year, 2 and 3 years after the exacerbation period. During the study, no children with CTHIN against a background of severe congenital pathology combined with impaired renal function were found.

The state of renal function was assessed based on the state of renal filtration function (determination of the clearance of endogenous creatinine according to the Van Slyk formula and cystatin C using immunotubidimetry on a Cobas Integra 400 plus device (Roche, Switzerland)).

Zimnitsky's test was used to determine the kidney's concentration capacity. In addition, the magnitude of ammonioacidogenesis was determined (in daily urine, titrated acids and ammonia were determined).

In all examined patients, protein metabolism indicators (protein fractions, total serum protein, total and effective albumin concentration, serum toxicity index, albumin binding capacity) were determined. The level of urea and creatinine in the blood serum was also determined.

Results and discussion. The clinical group (1st group: 52 patients) with rChTIN was selected based on the presence of typical symptoms of the disease, such as dysuria

(32.7%), neurogenic bladder (10%), morning pastosity of the soft tissues of the eyelids (46.5%), and back pain (30.8%) against a background of physical exertion (26.9%).

Meanwhile, the clinical group (2nd group: 68 patients) with LCHTIN was isolated based on the more persistent "salting kidney" symptom, which leads to the development of muscle hypotonia - 41.2% (28) and arterial hypotension - 27.9% (19), dysuria - polyuria in 54.4% (37) of patients, the presence of acute renal tissue damage against a background of hyperoxaluria - 100% (68), an abundance of epithelium in 92.6% (63), lympho-monocytic cells - 88.2% (60), brown cylinders - 100% (68). Urine culture is sterile.

Diagnostic criteria for the latent course of CSTD: were identified against the background of respiratory diseases, they were not given due attention due to their brevity, and hereditary history was not taken into account.

We associate the recurrent course of the disease with the presence of a secondary immunodeficiency state, 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 the ongoing antibacterial therapy, multiple foci of chronic infectious pathology, susceptibility to ARVI.

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

In all examined patients, protein metabolism parameters were determined (total serum protein, total albumin concentration (TCA), effective albumin concentration (EFC), albumin binding capacity (ABC), altered albumin concentration and toxicity index (TCI), renal damage molecules (RM) in blood and urine, globulin fractions, cystatin C concentration, albumin functional status indicators, urea levels, and creatinine).

Currently, it has been established that in the development of multiple organ and polysystem failure, metabolic waste products - endotoxins - accumulate in the body. Endotoxins include natural metabolic products that accumulate in the body in high

concentrations, MPPs - intermediate products of proteolysis, variable products, heterogeneous ingredients of non-viable tissues that accumulate in the body when natural detoxification mechanisms are suppressed and metabolism is disrupted [10]. There is a direct relationship between the degree of EI and the volume of urinary GPP, depending on the severity of CTH [11;12].

Research on kidney function and EI indicators is necessary for predicting the course of CTI. The degree of damage to the membrane structures of kidney cells was assessed by the level of MPP and OKA in urine, and in blood by the total concentration of albumin, ECA, CCA, IT, and KIA.

The obtained data showed that the concentration of PPP in urine in patients with rChTIN in the acute phase was 16.3 times higher than in the control group (Table 1), while in children with lChTIN it was 8 times higher. More pronounced cellular structural disorders were noted in patients with rChTIN compared to patients with lChTIN.

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

Table 1.

Parameters of EI in children with CSTIN upon admission (M±m)

N	Indicators	Healthy	Patients with rHTIN n=52.	LHTIN patients n=68.
		in blood		
1.	STP, units.opt.pl.	0.136±0.021	0.148±0.040 P>0.1	0.107±0.002 P>0.1
		in urine		
1.	STP, units.opt.pl.	0.136±0.021	2.23±0.08 P<0.001	1.12±0.07 P<0.001

Both in the active stage and in remission, the state of protein metabolism in rChTIN 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 not characteristic (67.6±0.25g/l) and OKA (49.23±0.28g/l). The protein-synthetic function of the liver compensated for small protein losses associated with fever.

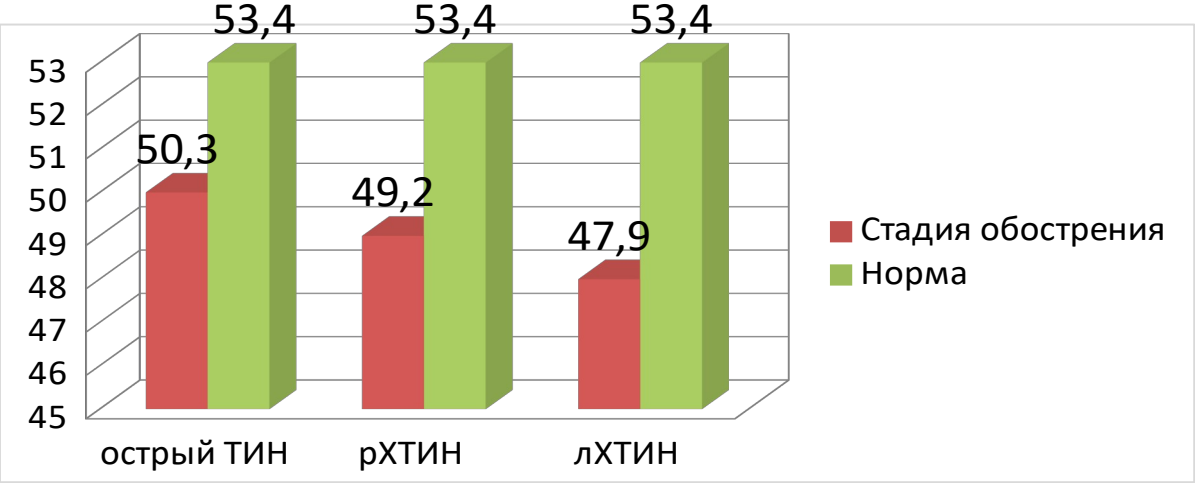

Fig.1. OCA indicator in the exacerbation stage in various forms of the disease in children

In recent years, febrile conditions have rarely been observed in patients, and exacerbations of CTHIN have proceeded in asymptomatic variants. The normal level of protein synthesis was maintained due to the absence of thermal inactivation of liver enzymes.

Table 2.

Parameters of the functional state of albumin before treatment depending on the variants of CSTIN course in children

Indicators	ABOUT (g/l)	OKA (g/l)	ECA (g/l)	CIA (g/l)	SCA (%)	IT cond.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
TIN recurrence	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
LATE	64.7±0.37	47.9±0.24	33.6±0.3	14.3±0.38	69.7±0.72	0.43±0.01

NTINE	P>0.1	P>0.1	P<0.001	P<0.001	P<0.001	P<0.001

Note: P-significance of difference between indicators in healthy individuals and children with chronic TIN

The active phase of CTI was characterized by a decrease in ECA, as in the acute process, but to a greater extent (32.04±0.26 g/l). ECA decrease 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 prolonged intoxication, which is the cause of excessive accumulation of toxic substances contributing to the formation of endotoxicosis and disruption of homeostasis. The nature of intoxication, its severity in a particular form of the disease, affects the rate of breakdown of protein structures.

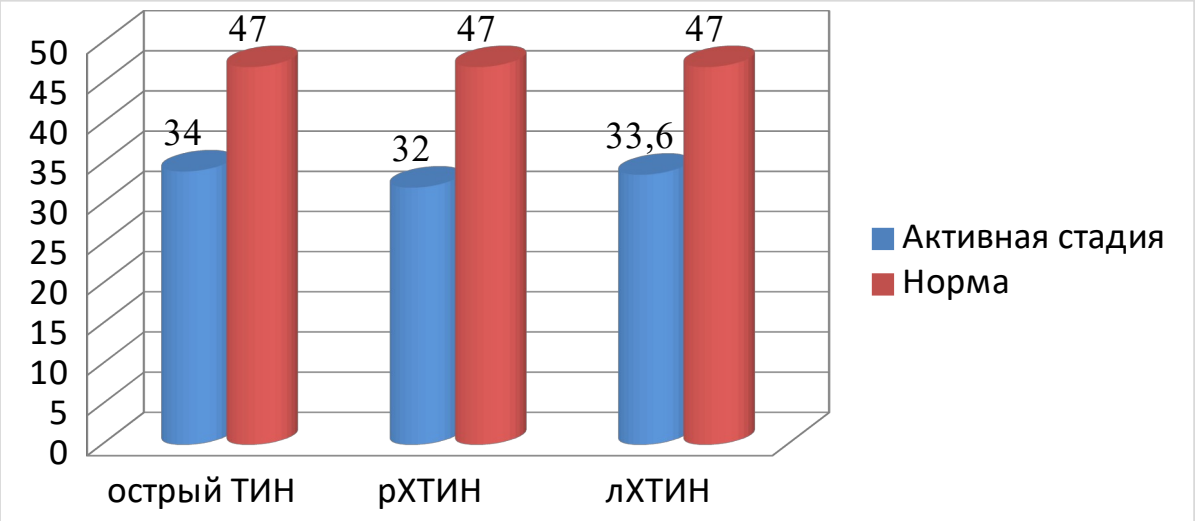

Fig.2. ECA indicator in the active stage in various forms of CSTIN in children

A high level of the toxicity index indicates the presence of intoxication, which is determined in all periods of the disease (Figure 2).

Less pronounced, but persistent changes in protein metabolism are characteristic of the latent course of CHIN. Children are characterized by a decrease not only in ECA but also in general. We found disorders in the protein-synthetic function of the liver in patients with a sluggish kidney process.

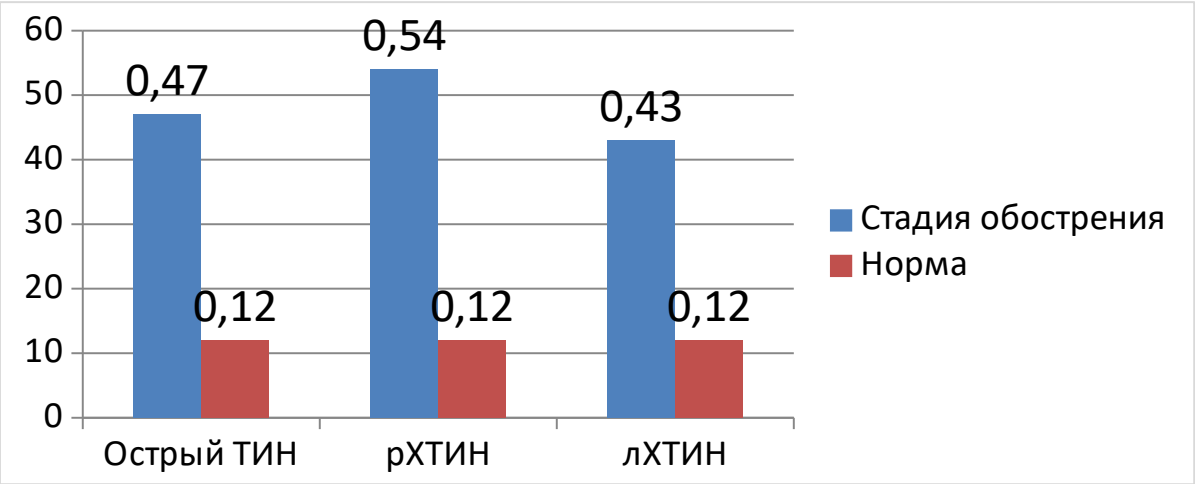

Fig.3. BMI indicator in the active stage in various forms of the disease in children

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

An adaptive reaction against the background of a prolonged pathological process is that albumin is synthesized in smaller quantities, but more fully.

A high CSA contributes to a decrease in the level of intoxication, unlike other variants of TIN, which indicates such an indicator as IT (Fig. 3). Similar changes in albumin lead to the formation of TIN chronicity, indicating that the body's non-specific effector system is functioning [4;7].

In CHTIN, despiralization of the protein molecule is observed. Conformational disorders lead to the formation of discrete forms of albumin, as indicated by a decrease in the level of albumin binding capacity. Limited ability of albumin to bind drugs, this applies to antibiotics, which significantly affects the formation of chronicity of the process.

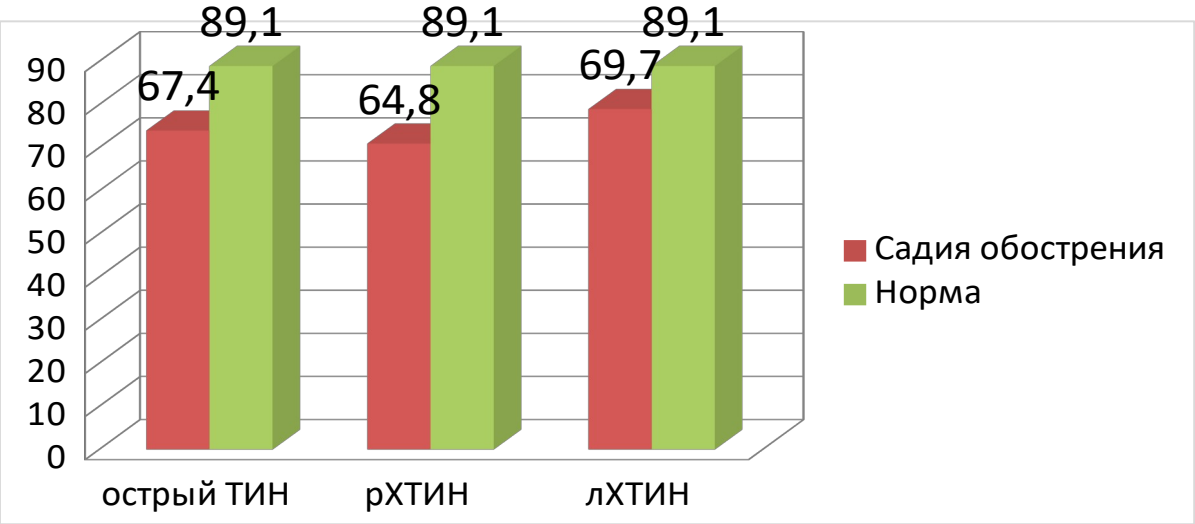

Fig. 4. CSA indicators in the active stage in various forms of CSTIN in children

Conclusions. Thus, the conducted studies have shown that in the development of rChTIN and lChTIN, an important mechanism for damage to the interstitial tissue of the kidneys, the development of clinical symptoms, and the course of the disease is both metabolic disorders leading to structural shifts at the level of various elements of the nephron and changes in the functional state of the kidneys, as well as the instability of the cytoembranes of tubular cells. This justifies the need for combined therapy in patients with CTHIN, which will contribute to the elimination of the inflammatory process, the excretion of endotoxins from the kidney tissue, and the stabilization of cellular cytomembranes and kidney function.

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