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# Pathogenetic Role of Endogenic Intoxication Indicators in Chronic Tubulointerstitial Ephritis in Children

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**Abstract**.

Despite the advances achieved in the diagnosis and treatment of nephropathies, almost 25% of patients continue to progress, which leads to a change in the quality of life.

**Purpose of the study**. To reveal the pathogenetic role of molecules of kidney damage and tubular dysfunctions in chronic tubulointerstitial nephritis (CTIN) in children, taking into account the form of the disease.

**Research material.** Depending on the clinical form of renal pathology, all patients were divided into 2 groups: group 1 - 52 (43%) children with recurrent CTIN (rCTIN) and group 2 - 68 (57%) patients with latent CTIN (lCTIN).

**Results.** It should be noted that patients with rCTIN showed more significant shifts in the osmotic concentration of urine, glomerular filtration rate (GFR), proteinuria, urea, creatinine in the blood and urine than in children with lCTIN, where relatively pronounced hematuria was noted, which confirms the leading role aseptic inflammatory process in the change of tubulointerstitial tissue with impaired re nal function, including glomerular.

**Conclusions**. In patients with rCTIN, in the acute stage, there are more pronounced disorders of the functional state of the kidneys (decreased GFR, urine osmolarity, daily urine output), while the severity of these disorders depends on the form and degree of activity of the pathological process. In patients with rCTIN, more pronounced changes in endogenous intoxication (EI) indices are noted, which are reflected in a decrease in the total concentration of albumin (TCA), the effective concentration of albumin (ECA), the binding capacity of albumin (BCA) and a stable increase in the toxicity index (IT), as well as in the increase of molecules of kidney damage (MPP) and TCA in urine, which determines the importance of

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this diagnosticum.

***Key words:*** chronic tubulointerstitial nephritis, endogenous intoxication, kidney damage molecules.

**Relevance**. Despite the advances achieved in the diagnosis and treatment of nephropathies, their progression continues in almost 25% of patients, which leads to a change in the quality of life [11]. The development of a pathological process in the tubulointerstitial tissue (TIT) of the kidneys is caused by heterogeneous specific and nonspecific etiological factors [1]. The center of inflammatory changes in CTIN is the interstitial tissue of the kidneys with the involvement of the tubules, blood vessels, and lymphatic vessels of the renal stroma in the pathological process [2, 4.19].

Identification of the leading role of endogenous intoxication in typical pathological processes as biologically active compounds determined the feasibility of studying the status of these messengers in the mechanisms of tubular and interstitial damage, in the development and progression of fibrotic processes in the interstitial tissue [5, 6, 9, 18]. Recent studies have shown a significant role in the genesis of CTIN of renal injury molecules (RLM) [8, 10,17].

Tubular cells acquire the ability to express chemokines, which act as local mediators formed directly in the renal TIT. The imbalance of the MPP 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 [12, 13, 14].

Despite numerous studies, in the literature there is no unified approach to the interpretation of the structure of chronic tubulointerstitial nephritis. There are no data on a comparative clinical and laboratory assessment of certain types of tubulointerstitial nephritis; the pathogenetic role of the relationship between violations of tubular functions in patients with different forms of CTIN [3,15]. The task of developing new pathogenetically substantiated methods of early diagnosis of CTIN in children, aimed at preventing their progression and the development of chronic renal failure, remains an urgent task [7,16].

**Purpose of the study.** To reveal the pathogenetic role of molecules of kidney damage and tubular dysfunctions in CTIN in children, taking into account the form of the disease.

**Material and research methods.**

**Material**. Depending on the clinical form of renal pathology, all patients were

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divided into 2 groups: group 1 - 52 (43%) children with rCTIN and group 2 - 68 (57%) patients with lCTIN.

In the study of partial functions of the kidneys, two groups of functional techniques were used:

Group I - methods that allow to characterize the quantitative state of individual kidney functions carried out by different parts of the nephron.

Group II - methods based on the study of some blood parameters, reflecting the result of the total work of both kidneys. Determined urea, creatinine, electrolytes (potassium, sodium).

The indicators of protein metabolism (total serum protein, protein fractions, total and effective concentration of albumin, binding capacity of albumin, coefficient of altered albumin and toxicity index) were determined. The value of the total and effective concentration of albumin was determined using the set "Albumin - UTS" (manufactured by LLC "Eiliton" by order of CJSC "A / o Unimed") in quartz cuvettes with a cross section of 1 by 1 cm. : CCA = (ECA / OKA) * 100%, IT = (OKA / ECA) - 1, where OKA is the total concentration of albumin in g / l, ECA is the effective concentration of albumin, the equivalent of "healthy" albumin, measured by the fluorescence method with a probe K-35, g / l.

The content of toxic MPP (MPP 254) in urine is determined by the Kalkar formula.

The criteria for the inclusion of patients in the study were: the presence of CTIN in the acute phase, at the age of 4-15 years, the presence of informed consent of the patient to participate in the study and compliance with the doctor's instructions regarding the prescribed therapy and clinical and laboratory studies.

CTIN in patients was established by history (burdened heredity through blood relatives) and according to the results of laboratory analysis.

**Results.** Partial renal function was assessed by endogenous creatinine clearance, urine osmolarity, daily urine output, minute urine output, urinary syndrome (leukocyturia, hematuria, proteinuria) before and after treatment in all patients (100%), which depend on the degree of preservation of the functioning renal parenchyma and rCTIN activity. , the duration of the disease and the frequency of relapses.

Almost all children with CTIN with intact glomerular filtration were characterized by hypersthenuria up to 1027.82 ± 4.5 (in the absence of glucosuria) and a significant thick sediment was detected in it.

The results of the study showed that 100% of patients with CTIN were characterized by moderate abacterial leukocyturia in 63 (88%) patients not

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exceeding 18x103 ml, in which 2/3 of urine leukocytes were lymphocytes, while in healthy children leukocyturia did not exceed 5 cells. in p.z.

In children with rCTIN upon admission to the hospital, the GFR indicator was within 73.4 ± 1.23 ml / min, while with lCTIN, this indicator was relatively less than 72.0 ± 0.25 ml / min, compared with patients with rCTIN ( Table 1). In 98.4% of patients with CTIN, changes in urine were noted before treatment. At the same time, selective filtration was noted, mainly of low-molecular-weight proteins with a molecular weight of up to 100 KD (mainly albumin).

Bacteriuria was not observed in children with CTIN. We found microhematuria of 5-6 erythrocytes in the field of view in 90% of patients, while 10% of the examined children had macrohematuria, which was 19-20 cells in group 1 patients. in p.z. In children of group 2, hematuria was less pronounced and amounted to 10-11 cells. in p.z., while in healthy children the number of erythrocytes in the urine is 0-1 cells. in p.z. In children with CTIN, we associate pronounced hematuria with damage to the interstitial tissue, instability of the basement membrane.

The most impaired renal function in CTIN is the osmotic dilution function. Osmoregulation, as a process of maintaining the total concentration of ions and molecules in body fluids, maintaining water and ionic equilibrium, is one of the important aspects of the complex of homeostatic reactions of the body.

**Table 1**

**Indicators of partial renal functions in CTIN in children on admission in the acute phase (M ± m)**

| Indicators | Healthy children (n = 30) | lCTIN (n=52) | rCTIN (n=68) |
|---|---|---|---|
| СКФ, мл/мин.м² | 98,6±7,8 | 73,4±1,23<br>P<0,001 | 72,0±0,25<br>P<0,001 |
| Осмолярность мочи, ммоль/л | 1000±200 | 679,5±17,3<br>P<0,001 | 646,7±9,9<br>P<0,001 |
| Суточный диурез, л/сут. | 1,7±0,036 | 1,14±0,034<br>P<0,05 | 1,06±0,015<br>P<0,05 |
| Минутный диурез, мл/мин | 1,2±0,037 | 0,79±0,02<br>P<0,05 | 0,61±0,010<br>P<0,05 |

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

Osmolarity of urine in children with CTIN was significantly reduced compared to the level in healthy children and amounted to 679.5 ± 17.3 mmol / L (P <0.001),

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while in patients with rCTIN this indicator was even more significantly reduced and amounted to 646, 7 ± 9.9 mmol / L (P <0.001), respectively.

Thus, in all children with CTIN, already in the early stages of the disease, a decrease in renal function by osmotic concentration of urine was revealed.

When analyzing the results of biochemical studies before treatment, it was revealed that in children with CTIN, the protein content in urine exceeded the control values by 10.5% (P <0.05) in 76% of patients, while in children of group 2 by 15, 7% (P <0.05) in 82% of children, characterized by proteinuria from 0.033% to 0.165%.

GFR and urine osmolarity in patients of group 2 were below the control level by 25.6% and 32% (P> 0.1), and in children of group 1, this indicator was even lower and amounted to 27% and 35.4% (P < 0.05), respectively.

At present, it has been established that with the development of multiple organ and polysystemic failure, the body accumulates products of impaired metabolism - endotoxins. Endotoxins include products of natural metabolism that accumulate in the body in high concentrations, MPP are intermediate products of proteolysis, variable products, ingredients of non-viable tissues of heterogeneous composition that accumulate in the body when the natural mechanisms of detoxification are suppressed and metabolic disorders. There is a direct relationship between the degree of EI and the volume of urinary tract infection, depending on the severity of CTIN.

Studies of renal function and EI indices are important for predicting the course of CTIN and assessing the effectiveness of treatment. 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, SSA, IT.

The data were assessed according to the average values obtained in 120 patients. There is information about the possibility of using these methods for early detection of organ damage, at the level of processes occurring in cells, which is important in the course of differential diagnosis and predicting the outcome of the disease.

The need for such a diagnostic test in patients with CTIN is due to the absence of obvious signs of exacerbation of the inflammatory process in the kidneys and, as the analysis of recent literature shows, interest in scientific and practical research.

Since all studied patients had a moderate severity state, no significant differences in the concentration of MPP in blood plasma were found.

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The results of the study showed that in the urine of patients with rCTIN in the exacerbation phase, the level of MPP was 16.3 times higher than in the control group (Table 2), while in children with lCTIN it was 8 times higher than in healthy children. The revealed shifts in biochemical parameters in urine reflect a violation of the state of the cell membranes of the interstitial tissue of the kidneys.

Consequently, in patients with rCTIN, more pronounced disorders of cellular structures were noted in comparison with patients with lCTIN. We associate an increase in the level of MPP in urine with CTIN with the fact that their low molecular weight allows them to freely pass through the glomerular capillaries, but in the proximal tubules they are reabsorbed by 99.9%. In inflammatory and destructive processes of the tubulointerstitial system, reabsorption of MPPs is impaired and their excretion in the urine is observed. Impaired renal excretory function leads to accumulation of MPP in the urine, which leads to tubular atrophy and organic structural changes.

**table 2.**

**Indicators of endogenous intoxication in CTIN in children at admission (M ± m)**

| № | Indicators | Healthy n = 30 | Patients with rCTIN n = 52 | Patients with lCTIN n = 68 |
|---|---|---|---|---|
| | | ***in blood*** | | |
| 1 | MPP, opt.pl. | 0,136±0,021 | 0,148±0,040 P>0,1 | 0,107±0,002 P>0,1 |
| 2 | OKA, g / l | 47,5±0,55 | 30,1±0,3 P<0,001 | 31,2±0,5 P<0,001 |
| 3 | ECA, g / l | 40,4±3,7 | 23,4±0,84 P<0,001 | 24,3±0,44 P<0,001 |
| 4 | SSA, (ECA \ OKA)% | 93±0,9 | 77±0,3 P<0,001 | 77±0,4 P<0,001 |
| 5 | IT for albumin, (Kaka / oka-1) conventional units | 0,170±0,01 | 0,293±0,006 P<0,05 | 0,286±0,007 P<0,05 |
| | | ***in urine*** | | |
| 1 | MPP, opt.pl. | 0,136±0,021 | 2,23±0,08 P<0,001 | 1,12±0,07 P<0,001 |

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| | | | | |
|---|---|---|---|---|
| 2 | OKA, g / l | 0,20±0,01 | 2,34±0,09<br>P<0,001 | 1,81±0,09<br>P<0,001 |

*Note*: P– the reliability of the difference between the indicators in healthy people and in children with CTIN.

The OKA indicator reflects the intensity of all homeostasis processes in the body. The study of the detoxification function of serum ALB in endotoxicosis caused by metabolic disorders in CTIN has not only diagnostic, but also prognostic significance for clinical practice. ALB is one of the links in the detoxification system of the body, it reacts nonspecifically to any "trouble" in the body, accompanied by even minimal metabolic changes and, in particular, the most reactive changes in the process of EI.

We investigated the following albumin parameters - ACA in blood plasma and urine, ECA, SSA, IT for albumin, MPP in blood and urine.

The analyzes of our study show that ACA in the blood plasma of children with lCTIN and rCTIN were significantly reduced and amounted to 31.2 ± 0.5 g / l and 30.1 ± 0.3 g / l (P <0.001), respectively. We associate this with the fact that with CTIN, the reserve capacities of the organism decrease, which reflect the OCA indices.

ECA is an analogue of the amount of full-fledged ALB with normal properties, including normal binding capacity. Normally, ECA is the same as OKA. With CTIN, this value is significantly reduced, even in those cases when the OCA is within the normal range.

We found that the ECA level was significantly lower than the control standards in children with both forms of renal pathology and was 23.4 ± 0.84 g / l with rCTIN and 24.3 ± 0.44 g / l with lCTIN (P <0.001), respectively. A sharp decrease in ECA indicates the development of the inflammatory process before its clinical manifestations in CTIN, the presence of interstitial edema is important, which leads to compression of the nephrons and the microvasculature, with the transition to specific structural elements of the kidneys.

The study made it possible to establish that children with rCTIN showed more significant disorders in the child's body, which were manifested by a decrease in the OCA index in the blood plasma by 43.5%, and with lCTIN by 38% upon admission to the hospital. ECA decreased to a greater extent, respectively, by 50% and 52% (P <0.001).

Analysis of the SSA parameter in sick children upon admission showed that there were no significant differences in the SSA level in both groups. The SSA indicator tended to decrease, both with rCTIN and lCTIN, by 27.3% compared

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with the indicator in healthy children (P <0.001), which was 77 ± 0.3% and 77 ± 0.4% , respectively.

In children with rCTIN, a higher IT level for albumin was 0.293 ± 0.006 conventional units. (P <0.05), while in patients with lCTIN this indicator was 0.286 ± 0.007 conventional units. (P <0.05). We attribute this to the fact that the inflammatory process characteristic of rCTIN aggravates endotoxicosis, which leads to a sharp decrease in ECA, the lower the ECA level, the higher the IT. With rCTIN, a more pronounced endotoxicosis syndrome developed in comparison with lCTIN, which corresponded to the clinical indicators of the severity of the complication. This, apparently, is associated with the development of the inflammatory process and a decrease in the detoxification function of the renal tissue, which is consistent with the literature data.

**Discussion.** It should be noted that patients with rCTIN showed more significant shifts in the osmotic concentration of urine, GFR, proteinuria, urea, creatinine in the blood and urine than in children with lCTIN, which confirms the leading role of the aseptic inflammatory process and changes in tubulointerstitial tissue in renal dysfunction. , including glomerular.

In all children with lCTIN, in the early stages of the disease, relatively less significant pathological changes in the level of GFR, urine osmolarity, proteinuria, urea, blood and urine creatinine were revealed, but, at the same time, relatively pronounced hematuria was noted.

However, the leading role in the decrease in renal function belongs to the frequency of recurrence of the disease, which is confirmed by the presence of significant differences in the average levels of osmotic concentration and GFR in children with CTIN with its frequent recurrence.

In general, the most pronounced functional impairments were characteristic of patients with rCTIN (Table 1), especially in terms of the osmotic concentration function (646.7 ± 9.9 mmol / l, P <0.001 with rCTIN; with lCTIN 679.5 ± 17.3 mmol / L, P <0.001), daily urine output (1.06 ± 0.015 L / day, P <0.05 with rCTIN; 1.14 ± 0.034 L / day, P <0.05 with lCTIN) , minute diuresis (0.61 ± 0.010 ml / min, P <0.05 with rCTIN; 0.79 ± 0.02 ml / min, P <0.05 with lCTIN).

Therefore, in patients with both rCTIN and lCTIN, an exacerbation of the inflammatory process can be observed without its visible laboratory manifestations, which may be one of the reasons for untimely diagnosis and latent course of the disease.

In children with rCTIN and lCTIN, against the background of mild clinical symptoms, there is an increase in urinary toxicity of urinary tract infections, a

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decrease in OCA, ECA, SSA, and an increase in IT for albumin.

All this confirms the fact that in the debut of examination monitoring, an important place should be occupied by the use of these methods of laboratory diagnostics in patients with metabolic disorders of the kidneys. The results of our studies coincide with convincing clinical and experimental data that the degree of MPP accumulation in the urine of patients corresponds to the severity of the clinical condition, in particular, the severity of CTIN recurrence in children.

Thus, the studies have shown that during the development of rCTIN and lCTIN, an important mechanism of damage to the interstitial tissue of the kidneys, the development of clinical symptoms and the course of the disease is both structural changes 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 substantiates the need to determine the studied indicators of EI in patients with CTIN for the purpose of early diagnosis, which will help prevent the development of secondary renal scarring in children.

**Conclusion**. In patients with rCTIN, in the acute stage, there are more pronounced disorders of the functional state of the kidneys (decreased GFR, urine osmolarity, daily urine output), while the severity of these disorders depends on the form and degree of activity of the pathological process.

In patients with rCTIN, more pronounced changes in EI indices are noted, which are reflected in a decrease in OCA, ECA, SSA and a stable increase in the content of IT, as well as in an increase in BMP and OCA in urine, which determines the importance of this diagnosticum.

A correlation was established between the EI indices and the functional state of the kidneys in CTIN in children. A high direct correlation was found between high blood pressure and the amount of MPP excretion in urine, OCA, ECA, IT in blood plasma, and a high direct correlation was also revealed between the amount of MPP excretion in urine and proteinuria, leukocyturia. High inverse correlation was observed between GFR and BMP in urine.

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