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IMPAIRED RENAL FUNCTION AND CYTOKINE PROFILE IN COVID-19-ASSOCIATED ACUTE RENAL PATHOLOGY IN CHILDREN


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БОЛАЛАРДА COVID-19 ФОНИДА ЎТКИР БУЙРАК ПАТОЛОГИЯСИДА ЦИТОКИНЛАР КЎРСАТКИЧИ ВА БУЙРАКЛАР ФУНКЦИЯСИНИНГ БУЗИЛИШИ

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НАРУШЕНИЕ ФУНКЦИОНАЛЬНОЙ СПОСОБНОСТИ ПОЧКИ И ПОКАЗАТЕЛИ ЦИТОКИНОВОГО ПРОФИЛЯ ПРИ ОСТРОЙ РЕНАЛЬНОЙ ПАТОЛОГИИ НА ФОНЕ COVID-19 У ДЕТЕЙ

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Резюме. *Ўткир буйрак шикастланиши (ЎБШ) COVID-19 нинг асорати бўлиб, COVID-19 даги ЎБШ патофизиологияси кўп омиллар билан боғ`лиқ. COVID-19 билан оғриган бемор болаларда буйрак дисфункциясининг патофизиологияси цитокин бўрони, органларнинг ўзаро боғ`лиқлиги, тизимли таъсирлар ва тўғридан-тўғри тубулогломеруляр шикастланишга иккиламчи сифатида қаралади. Найча ҳужайраларининг шикастланиши тубулоинтерстициал бузилишларнинг шаклланишидаги асосий омили сифатида бу ҳужайралар томонидан яллиғланиш цитокинлари ва ўсиш омилларининг экскрециясини кучайиши ва уларнинг маҳаллий воситачилар сифатида муҳим ролини кўрсатади.*

Калит сўзлар*: Ўткир буйрак шикастланиши, цитокинлар, COVID-19 ,буйрак дисфункцияси, болалар.*

Abstract. *Acute kidney injury (AKI) is a complication of COVID-19, and the pathophysiology of AKI in COVID-19 appears to be multifactorial. The pathophysiology of renal dysfunction in patients with COVID-19 has recently been suggested to be secondary to cytokine storm, organ cross-talk, systemic effects and direct tubuloglomerular damage. Damage to tubulointerstitial cells, as a key event in the formation of tubulointerstitial disorders, stimulates the excretion of proinflammatory cytokines and growth factors by these cells and indicates a significant role for the latter as local mediators.*

Keywords: *Acute kidney injury, cytokines, COVID-19, renal dysfunction, children.*

Relevance. Coronavirus disease 2019 (COVID-19) has been declared a pandemic, given its global spread. Children account for 1% of patients and are less likely to be severely ill than adults; although pre-school children and infants may have severe clinical manifestations [5,6].

Urinary system damage in children with Covid-19 disease is progressive and is one of the most pressing medical problems of the present day[1,2]. Renal pathology has a high risk of development in children at different stages of Covid-19 compared to the general population [3,4].

The aim of the study was to determine the features of renal impairment and assess the relationship between partial renal function and cytokine profile in children with acute renal pathology developed in the background of Covid-19.

Subject and object of study. We studied 132 children, including 65 children with AP, of which 30 with AP without history of Covid-19 and 35 with AP in the background of Covid-19, as well as 67 patients with acute TIN, of which 35 with aTIN without history of Covid-19 and 32 with aTIN in the background of Covid-19, aged from 4 to 18 years.

Metod of study. General clinical history, examination, blood and urine tests, instrumental - excretory urography, renal ultrasound, nephroscintigraphy, blood pressure measurement, cytokine profile - IL-4, TNF-a, y-INF in serum and urine, biochemical -

blood and urine creatinine, AT and urine ammonia, PCR.

Results of the study. The concentration of proinflammatory cytokines TNF-a and y-INF in the blood of patients with active AP was reliably increased. The increase of anti-inflammatory IL-4 activity of group 1 children was more than five times (28,92±4,14 pg/ml, whereas for healthy children this index was 5,73±2,48 pg/ml (p≤0,001)) from control values, which was accompanied by increase of TNF-a and y-INF concentration (nearly nine and seven times respectively). Whereas, in group 2 patients serum IL-4 was elevated more than six-fold, TNF-a more than eleven-fold and y-INF eight-fold, respectively.

We determined that the impairment of the serum cytokine profile was more pronounced in patients with a history of Covid-19. The levels of the cytokines studied in the urine of patients with acute pyelonephritis are shown in Table 1.

The table shows that the active process was accompanied by a significant increase in urinary concentrations of IL-4, TNF-a and y- INF. We found that the impairment of the serum cytokine profile was more pronounced in patients with a history of Covid-19. The levels of these cytokines in the urine of patients with acute pyelonephritis are shown in Table 2.

The table shows that the active process was accompanied by a significant increase in urinary concentrations of IL-4, TNF-a and Y - INF. Whereas in children of the 1st group values of TNF-a were nearly fourfold and values of -NNF- were tenfold higher than those of control group, while in children of the 2nd group these values were sevenfold and 15 fold higher, constituting 83.44±6.17 and 225.84±14.23pg/ml (p≤0.001) respectively. Against this background, IL-4 was more than six-fold excess (37.45±7.79pg/ml (p≤0.001)).

The study of serum concentrations of the cytokines studied in patients with aTIN revealed a statistically significant increase in proinflammatory TNF-a and y-INF cytokines (Table 3). The anti-inflammatory IL-4 control values exceeded almost threefold against the background of an almost tenfold increase in TNF-a and fourfold in group 1 children, while in group 2 children these values exceeded those of healthy children by five, fifteen, and sixfold (Table 3).

It should be noted that in comparison with the same parameters of active phase of AP, statistically significant differences were found only for TNF-a (Table 3). The levels of this cytokine in aTIN were characterised by higher values. The concentrations of the studied cytokines in the urine of patients in the active stage of aTIN are presented in Table 4.

As can be seen from the table, active inflammation in aTIN is characterized by increased concentrations of the studied cytokines not only in serum, but also in urine. In group 1 children had values of TNF-a nearly eight times (in OP four times), and y-INF - ten times higher than the control ones, while in group 2 children the levels of TNF-a and y-INF were 12 and 14 times higher correspondently.

Table 1. Serum cytokine concentration of AP patients depending on the presence of Covid-19 (pg/ml)

Indicator	In healthy people	Before treatment	
		1 group (n=30)	2 group (n=35)
IL-4	5,73±2,48	28,92±4,14 p≤0,001	37,45±7,79 p≤0,001
TNF-a	7,26±1,80	66,48±8,92 p≤0,001	83,44±6,17 p≤0,001
y-INF	27,48±2,55	165,72±19,15 p≤0,001	225,84±14,23 p≤0,001

Note: p is the statistical difference between the serum cytokine profile of OP patients before treatment and healthy children.

Table 2. Urinary cytokine concentration of AP patients according to the presence of Covid-19 (pg/ml)

Indicator	In healthy people	Before treatment	
		1 group (n=30)	2 group (n=35)
IL-4	6,35±2,35	32,7±2,54 p≤0,001	38,8±3,23 p≤0,001
TNF-a	11,8±2,50	48,4±1,2 p≤0,001	83,4±1,35 p≤0,001
y-INF	13,35±3,27	137,5±2,47 p≤0,001	205,25±8,98 p≤0,001

Note: p - statistical difference between the urine cytokine profile of AP patients before treatment and healthy children.

Table 3. Serum cytokine concentration of aTIN patients depending on the presence of Covid-19 (pg/ml)

Before treatment	Indicators		
	IL-4	TNF-a	y-INF
1 group (n=35)	18,2±2,8 p≤0,001	73,40±1,28 p≤0,001	110,7±2,8 p≤0,001
2 group (n=32)	28,7±2,9 p≤0,001	109,2±2,5 p≤0,001	165,7±3,2 p≤0,001
In healthy people	5,73±2,48	7,26±1,80	27,48±2,55

Note: p - statistical difference between serum cytokine profile of aTIN patients before treatment and healthy children.

Table 4. Urinary cytokine concentrations in patients with aTIN, depending on the presence of Covid-19 (pg/ml)

Before treatment	Indicators		
	IL-4	TNF-a	y-INF
1 group (n=35)	45,4±2,5; p≤0,001	95,4±3,6;p≤0,001	135,7±11,16;p≤0,001
2 group (n=32)	64,7±2,8; p≤0,001	142,6±2,7; p≤0,001	187,2±10,5;p≤0,001
In healthy people	6,35±2,35	11,8±2,50	13,35±3,27

Note: p - statistical difference between the cytokine profile in the urine of aTIN patients before treatment and healthy children.

Table 5. Renal secretory function in investigated patients with renal pathology according to DNSG in relation to the presence of Covid-19

Diseases	Tmax in the group with symmetrical unchanged curves (in min.)		Tmax in the group with asymmetric curves (in min.)	
	Left kidney	Right kidney	On the side of greater lesion	On the side of less lesion
AP	-	-	7,61±0,99	4,85±0,4
AP in the background Covid-19	-	-	8,52±1,05	6,53±0,95
aTIN	7,2±0,6	7,2±0,6	-	-
aTIN in the background Covid-19	8,2±0,7	8,2±0,7	-	-

Table 6. Renal excretory function in the investigated AP patients as measured by DNSG in relation to the presence of Covid-19

Groups of patients	On the side of greater lesions	On the side of less lesions
AP	9,84±1,55	6,79±1,34
OP in the background Covid-19	11,55±1,45	7,38±1,36
In healthy people	Up to 6 minutes	

Against the background of increased TNF-a activity, IL-4 values were almost three times higher in group 1 patients (in AP almost three times) and ten times higher in group 2 children in comparison with controls.

Thus, in contrast to serum values, urinary concentrations of investigated cytokines had statistically significant predominance not only of TNF-a, but also of IL-4 in comparison with those in AP in children of both subgroups, where more pronounced disorders were characteristic of Group 2 children, which we attribute to pathological effects of coronovirus infection toxins.

The functional state of the kidneys in patients with renal pathology during the Covid-19 pandemic according to dynamic nephroscintigraphy. To estimate functional state of tubular nephron division in 15 patients with aTIN against the background of Covid-19 we carried out dynamic nephroscintigraphy with the use of tubulotropic RFP Tc-MAG-3, which is secreted by proximal tubule epithelium. As a comparison group, 10 patients with aTIN without a history of Covid-19 were examined. During the study period, visual assessment of scintigrams was performed, which revealed a "humped" kidney in 2/2 patients, an increase in the longitudinal size of the kidney in 6/4 patients.

Qualitative analysis of computerized renograms showed that 2/3 of patients (65%) had timely contrasting of renal tissue, delayed contrasting was observed in 1/3 of children (35%), whereas in children with aTIN without the presence of Covid-19 these indices were 75/25%. Uniform distribution of RFP was observed in 60% of patients with aTIN against Covid-19 and diffuse irregular distribution of RFP was observed in the remaining 40%, whereas in patients without a history of Covid-19 this figure was 78/22%. Local retention of RFP in the renal tissue was observed in 40 and 25% of patients, and delayed RFP excretion was observed in 48 and 18% of patients, respectively.

As can be seen from the data presented (Table 5), the characteristic symmetrical QQm functional abnormalities in children with aTIN with tubulotropic RFP Tc-MAG3 were detected in all patients, but were more pronounced in children with aTIN on Covid-19.

As can be seen from the data presented (Table 6), symmetrical impairment of renal secretory function was also detected in all aTIN patients, while a more pronounced impairment was noted in children

with aTIN against Covid-19. No renal excretory dysfunction was noted in patients with a TIN.

We analyzed renal secretory excretory function in patients with AP. Impairments of renal secretory function according to DNSG with Tc99m-MAG-3 in children with AP against the background of Covid-19 were more marked than in patients with AP without Covid-19, Tmax was 9.2±4.67 and 5.84±2.79 minutes on the "more affected kidney" side and 5.66±3.07 and 3.92±0.93 minutes respectively on the "less affected kidney" side.

During the period of our observation, asymmetry of RFP excretion time was observed in the majority of patients with pyelonephritis. In three patients T/4 was not determined during the observation period. The mean T1/2 on the "more affected" side was 9.84+1.55 min, and on the "less affected" side 6.79+1.34 min (p>0.5).

We analysed renal secretory-excretory dysfunction in patients with acute pyelonephritis in an OOm study with Tc-MAG-3. The disturbances of secretory function on the "more affected kidney" side according to DNSG with Tc-MAG-3 in children with AP on the background of Covid-19 was more severe in comparison with patients with AP without Covid-19, Tmax was 7.51±4.17 and 5.4±1.45 minutes respectively. On the 'less affected kidney' side, secretory function was almost identical in both groups of patients (4.9±1.08 and 4.82±2.43 minutes, respectively).

The renal excretory function abnormalities were more pronounced in children with AP against Covid-19 than in patients with AP without Covid-19, T1/2 was 14.23±10.54 and 8.84±6.31 minutes on the "more affected kidney" side and 8.49±8.90 and 6.3±3.56 minutes on the "less affected kidney" side, respectively. In addition, in AP patients without Covid-19, there was unilateral impairment of secretory and excretory function in 8 patients (50%), whereas in children with AP with Covid-19, there was bilateral renal impairment in all patients (100%).

Conclusion. Active inflammation in aTIN and AP is characterised by increased concentrations of the cytokines studied not only in the serum but also in the urine of Covid-19 in children. Our studies have established that in patients with AP, impaired tubular secretion is asymmetrical, while in patients with aTIN there is a symmetrical lesion of the renal tissue. In AP patients with Covid-19, more pronounced changes in the tubular nephron are characteristic, bilaterally. In children with AP along with tubular secretion abnormalities excretory disorders are revealed, asymmetrical in the majority of patients, while in patients with aTIN no excretory abnormalities were noted.

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НАРУШЕНИЕ ФУНКЦИОНАЛЬНОЙ СПОСОБНОСТИ ПОЧКИ И ПОКАЗАТЕЛИ ЦИТОКИНОВОГО ПРОФИЛЯ ПРИ ОСТРОЙ РЕНАЛЬНОЙ ПАТОЛОГИИ НА ФОНЕ COVID-19 У ДЕТЕЙ

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Резюме. *Острое почечное поражение (ОПП) является осложнением COVID-19, и патофизиология ОПП при COVID-19 представляется многофакторной. Патофизиология дисфункции почек у пациентов с COVID-19 недавно была предположена как вторичная по отношению к цитокиновому шторму, перекрестному взаимодействию органов, системным эффектам и прямому тубулогломерулярному повреждению. Поражение канальцевых клеток как ключевое событие в формировании тубулоинтерстициальных нарушений, стимулирует экскрецию этими клетками провоспалительных цитокинов и факторов роста и указывает на значимую роль последних как местных медиаторов.*

Ключевые слова: *ОПП, цитокины, КОВИД-19, почечная дисфункция, дети.*