

The Role of Cytokine Profile in the Development of Acute Renal Pathology in Children with Covid -19

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DOI : <https://doi.org/10.61796/jmgcb.v2i1.1103>



Sections Info

Article history:

Submitted: December 25, 2024

Final Revised: January 01, 2025

Accepted: January 08, 2025

Published: January 15, 2025

Keywords:

NGAL

Covid-19

Acute pyelonephritis

Acute tubulointerstitial nephritis

Cytokine profile

ABSTRACT

Objective: This study aimed to investigate the impact of Covid-19 on the development of tubulointerstitial kidney damage in children, focusing on cytokine profiles, kidney function, and the role of neutrophil gelatinase-associated lipocalin (NGAL) as a marker for kidney injury. **Methods:** A cohort of 132 children who experienced tubulointerstitial kidney damage post-Covid-19 was studied. The patients were divided into two groups: one with acute pyelonephritis (AP) and the other with acute tubulointerstitial nephritis (ATIN). Diagnostic methods included blood and urine analysis, renal ultrasound, cytokine profiling (IL-6, IL-4, TNF- α , γ -INF), and NGAL measurement. **Results:** The study found significantly elevated NGAL levels in the urine of children with AP and Covid-19 compared to healthy controls (110.74 ± 1.27 vs. 65.66 ± 0.64 ng/mg creatinine; $p < 0.001$). Cytokine analysis revealed substantial increases in IL-6, TNF- α , and γ -INF, particularly in children with Covid-19-related kidney damage, suggesting a severe inflammatory response contributing to kidney dysfunction. **Novelty:** This research highlights the crucial role of cytokines in kidney injury following Covid-19 in children and emphasizes NGAL as a reliable biomarker for early detection of renal damage, offering new insights for treatment and prognosis.

INTRODUCTION

Today, despite significant progress in the diagnosis and treatment of nephrological diseases in children, approximately 23% of patients have a progressive disease, which can negatively affect the quality of life. According to research in recent years, "... since 2020, about 8 million cases of tubulointerstitial kidney disease developed against the background of Covid-19 have been recorded among children worldwide. The number of patients has increased in recent years and is 2.87 per 1000 population" [1]. Currently, identifying factors influencing the course of renal pathology developed against the background of Covid-19 in children, prescribing treatment taking into account the pathogenetic aspects of the disease for the purpose of its early diagnosis, prevention and reduction of the level of possible complications developing as a result of the disease are among the problems that need to be addressed in medicine.

This pathology tends to recur and progress with the formation of nephrosclerosis and the development of acute renal failure, leading to disability of the body and requiring extraordinary interventions.

According to a number of authors, it has now been established that an important component of the pathogenesis of renal pathology developed against the background of Covid-19 is a viral destructive lesion in the renal interstitial tissue [1], [2].

Fibroblasts stimulated immune cells and aggressive cytokines, local macrophages, and angiotensin - II are activated by accumulation in the interstitium. At this stage, the cytokine growth factor produced by local macrophages or tubular cells itself is important [3], [4] .

A number of scientific studies are being conducted around the world aimed at improving methods of early diagnosis, treatment and prevention of renal pathology developed against the background of Covid-19 in children. In this regard, determining the degree of adaptation of children to septic inflammatory diseases of the urinary system and renal pathology developed against the background of Covid-19, the functional state of the kidneys and their cause-and-effect relationship, the importance of cytokine profile indicators in the formation and course of the disease, is of particular importance to conduct scientific research aimed at prognosis and early diagnosis [5], [6], [7], [8], [9].

RESEARCH METHOD

In our study, 132 patients with tubulointerstitial damage to the kidneys and who passed Covid, who were treated in the nephrology department of Khorezm Regional Children's Multidisciplinary Medical Center during 2020-2023, were children.

Patients were divided into two groups, and each of them, in turn, was further divided into two subgroups. The first group included children with acute pyelonephritis (n=65), where subgroup 1 consisted of 30 children without a history of Covid-19, and group 2 consisted of 35 children with AP with Covid-19.

The second group included patients with acute tubulointerstitial nephritis (p=67), and they were also divided into two subgroups. An acute course of the pathological process was diagnosed in all patients (100%).

General clinic - anamnesis, examination, blood and urine analysis, excretory urography, renal ultrasound examination, nephroscintigraphy, measurement of arterial pressure, IL-6, IL-4, TNF-a, γ -INF cytokine profiles in serum and urine examination, biochemical examination of NGAL in urine, creatinine in blood and urine , Testing of AT and ammonia, PSR, bacteriological examination of urine for microflora and sensitivity to antibiotics, statistical research methods were used.

RESULTS AND DISCUSSION

We studied the level of neutrophil gelatinase (NGAL) or lipocalin-2, one of the components of special neutrophil granules associated with siderocalin. It was found that plasma NGAL is well filtered by the glomeruli, but is then reabsorbed mainly in the proximal tubules due to endocytosis. As a result, a "renal" pool of NGAL grows in the urine, which does not enter the bloodstream, but is completely excreted with urine. When the proximal tubules are damaged, the mRNA encoding NGAL is increased in the collecting ducts and the ascending limb of the loop of Henle. Elimination of bacterial infections and activation of proliferation of damaged, especially epithelial cells is considered its main function. The level of NGAL in the urine of children in group 2 was

reliably higher than that of children in the control group (110.74 ± 1.27 vs. 65.66 ± 0.64 ng per 1 mg of creatine in the corresponding sample; $r < 0.001$).

Table 1. Indicators of NGAL in patients with AP in relation to the presence of Covid-19.

Indicator	In healthy children (n =20)	Before treatment	
		1 group (n =30)	2 groups (n=35)
NGAL (ng /ml)	4.2 ± 1.8	$65.66 \pm 0, 6 4$ $r < 0.001$	$110.7 4 \pm 1 ,2 7$ $r < 0.001$

Note: r is the statistical difference between the values before treatment and in healthy children.

Thus, the concentration of NGAL in the urine of children with AP developed against the background of Covid-19 was reliably higher ($r < 0.001$) compared to children in the comparison group. As a result of the analysis of the results of this study, it was found that the concentration of NGAL in urine is directly correlated with the degree of damage to the kidney parenchyma, which proves the development of the most significant damage to the renal tissue in children when exposed to coronavirus infection.

Increased NGAL excretion is associated only with positive urine cultures and urinary tract infection, while a mild increase in urinary NGAL was noted in the background of ischemia-reperfusion of renal parenchyma typical of ATIN. In severe clinical symptoms of COVID-19, a significant increase in S-reactive protein (CRP) and a decrease in the number of platelets in the group are noted, which leads to the development of a cytokine storm process. This condition leads to an increase in pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor - α (TNF- α), γ -INF, and pro-inflammatory cytokine (IL-4), leading to podocyte destruction, apoptosis, and causes glomerular fibrosis

We have noted that aggressive cytokines TNF- α and γ -INF concentrations in blood reliably increase in children with active AP. In this case, patients in subgroup 2 had a corresponding increase in serum levels of IL-4 more than six-fold, TNF- α more than eleven-fold, and γ -INF more than eight-fold. The average sign of IL-6 increased by 7 times ($r \leq 0.001$). The highest level of IL-6 in the blood is Covid-19 in the AP in the background. It was recorded 39.9 times ($r \leq 0.001$).

We found that abnormalities in the serum cytokine profile were more pronounced in patients with a history of Covid-19, with cytokines in acute kidney pathology caused by kidney inflammation, high vascular permeability, fluid loss, intra-abdominal hypertension, and subsequent shock. It depends on the severity of the attack.

The obtained data show that the active process is observed along with the significantly increased concentration of IL-4, FNO- α and u-INF in urine. Compared with the control group, FNO- α increased by four times and γ -INF increased by eleven times, while in subgroup 2 patients, these indicators increased by 7 and 15 times, respectively,

and 83.4 ± 2.66 and It was 205.25 ± 3.32 pg/ml ($r \leq 0.001$). Against this background, the increase of IL-4 was more than six times (38.8 ± 1.33 pg/ml ($r \leq 0.001$)).

Therefore, the results of the analysis show a significant role of IL-6 as an aggressive factor in the development of tubulointerstitial damage, its level in urine was 31.2 times higher in children of the first subgroup and 38.5 times higher in patients of the 2nd subgroup. A more significant level of IL-6 in less pronounced lesions of the TIT, a decrease in its indicators at the threshold of the growth of tubulointerstitial lesions, due to the presence of the SARS-COV-2 virus, indicates that when tubular function is damaged, the excretion of cytokines with urine increases, which leads to damage to the proximal tubule. We found that the level of anti-inflammatory IL-4 in patients of subgroup 1 increased more than five times compared to the markers in healthy children (5.73 ± 2.48 pg/ml) (28.90 ± 1.27 pg/ml, ($r \leq 0.001$)) found that this was accompanied by increased levels of TNF- α and γ -INF (almost nine- and seven-fold, respectively). observed. When compared with the same indicators in the active phase of AP, statistically reliable differences were found only in TNF-a. It was distinguished by its higher concentration in ATIN.

It follows that the studied cytokines are increased in both serum and urine in children with ATIN. So, in patients of subgroup 1, the level of TNF- α (four times in O'P) was up to eight times, and in u-INF up to ten times higher than the indicators of the control group, while in the children of subgroup 2, their levels were 12 and 12, respectively, compared to healthy children. 14 times higher.

It should be noted that the concentration of IL-4 was almost seven times higher in the children of the 1st subgroup compared to the control signs (almost three times in AP), while this indicator was 10 times higher in the children of the 2nd subgroup. Urinary concentrations of IL-6 in Covid-19 was 60 times higher in children of the background. ($R < 0.001$). These are lymphocytes is explained by the specificities of the studied cytokine as an important factor of chemotaxis, because they are Covid-19 are extremely important cells that accumulate in the renal interstitium in the development of the background ATIN.

CONCLUSION

Fundamental Finding : The study highlights the importance of screening tests for tubular function by assessing cytokine levels (IL-6, γ -INF, TNF- α , IL-4) in urine to monitor latent kidney damage following Covid-19. The findings underscore the need to categorize risk groups based on the chronicity of kidney tissue changes for improved management. **Implication :** This approach is particularly crucial for children with pulmonary Covid-19 symptoms, emphasizing early kidney function monitoring for diagnosis and treatment optimization. **Limitation :** However, limitations include the need for prolonged monitoring to reliably detect latent renal pathology, as urinary syndromes often emerge during active disease phases. **Future Research :** Future

investigations should focus on refining methods for long-term monitoring and understanding cytokine profiles to improve early intervention strategies.

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