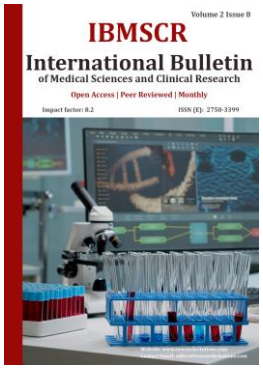

CHARACTER OF THE ETIOPATOGENESIS OF ACUTE RENAL PATHOLOGY IN CHILDREN ON THE BACKGROUND OF COVID -19

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Summary. 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 become seriously ill than adults; although preschool children and infants may have severe clinical manifestations. For two years, the damage to the organs of the urinary system in children with Covid-19 disease has been progressive in nature and today is one of the colossally urgent problems of medicine. Kidney pathology has a high risk of developing in children at different stages of Covid-19 compared to the general population .
Keywords: COVID-19 infection, etiology, pathogenesis, pathological anatomy , kidney function , kidney failure, polycystic, renal hypoplasia.

Резюме. Короновирусная болезнь 2019 года (COVID-19) была объявлена пандемией, учитывая ее глобальное распространение. На детей приходится 1% пациентов, и вероятность тяжелого заболевания у них меньше, чем у взрослых; хотя у детей дошкольного возраста и младенцев могут быть тяжелые клинические проявления. В течение двух лет поражение органов мочевыделительной системы у детей при заболевании Covid-19 имеет прогрессирующий характер и на сегодняшний день является одной из колоссально актуальных проблем медицины. Почечная патология имеет высокий риск развития у детей на разных стадиях Covid-19 по сравнению с общей популяцией.
Ключевые слова: инфекция COVID-19, этиология, патогенез, патологическая анатомия, функции почек, почечная недостаточность, поликистоз, гипоплазия почек.

Annotasiya. Koronavirus kasalligi 2019 (COVID-19) global tarqalishini hisobga olgan holda pandemiya deb e'lon qilindi. Bolalar bemorlarning 1% ni tashkil qiladi va kattalarnikiga qaraganda jiddiy kasal bo'lish ehtimoli kamroq; maktabgacha yoshdagi bolalar va chaqaloqlar og'ir klinik ko'rinishga ega bo'lishi mumkin. Ikki yil davomida Covid-19 kasalligi bilan og'rigan bolalarda siydik tizimi organlarining shikastlanishi tabiatda progressiv bo'lib, bugungi kunda tibbiyotning ulkan dolzarb muammolaridan biri hisoblanadi. Buyrak patologiyasi umumiy aholiga nisbatan Covid-19 ning turli bosqichlarida bolalarda rivojlanish xavfi yuqori.
Kalit so'zlar: COVID-19 infektsiyasi, etiologiyasi, patogenezi, patologik anatomiyasi, buyrak funktsiyasi buzulishi, buyrak etishmovchiligi, polikistikistoz, buyrak gipoplaziyasi.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an emerging global health problem, potentially affecting all organs, including the kidneys. Most reports of renal manifestations have been done primarily in the adult and elderly populations, with limited numbers in children.

There are now increasing efforts to elucidate the specific mechanisms of intrinsic renal pathophysiology following acute COVID -19 infection. Determining these mechanisms can be challenging due to the ethical constraints associated with performing routine kidney biopsy in children, as well as the current lack of an accurate non-invasive diagnostic test [1,2].

Since the onset of the COVID -19 pandemic, describing new or recurrent cases of podocytopathy , glomerular disease, and other intrarenal pathologies in children following acute COVID -19 infection. Some of these cases are confirmed by kidney biopsy, while others are empirical diagnoses based on a history of kidney disease, non-invasive testing, and response to treatment.

While data regarding the epidemiology, pathophysiology, risk factors, and prognosis in adults with renal histopathology after acute COVID -19 infection are becoming more well known, a significant gap remains in our understanding of intrinsic pathological renal manifestations in children after acute COVID -19 infection [3].

Renal manifestations are life-threatening conditions such as end-stage kidney disease (ESRD), especially when associated with viral infections . The analyzes used data from the 2019 Coronavirus Disease -Related Hospitalization Surveillance Network (COVID-NET) to describe hospitalizations, associated with COVID-19 among US children and adolescents aged 0-17 years.

To enter cells, the SARS-CoV-2 virus binds to the ACE2 receptor and the cellular serine protease TMPRSS2. ACE2 is a membrane protein expressed in various tissues, including the lungs and kidneys. Various authors have shown that circulating levels of ACE2 were higher in men than in women with kidney disease.

However, other factors found in such diseases have been described, including hypovolemia, heart failure (both right and left), sepsis, and dehydration. Some COVID-19 patients with AKI present to the hospital complaining of vomiting and diarrhea. In these cases, it has been suggested that this is due to a prerenal problem. The viral spike protein binds to angiotensin-converting enzyme 2 (ACE2) attached to the outer surface of cells in the lungs, vascular endothelium, kidneys, heart, and intestines. It also activates angiotensin II. The transmembrane protease serine 2 (TMPRSS2) cleaves and primes the S protein, allowing the release of viral fusion peptides, thereby promoting membrane fusion. Therefore, co-expression of ACE2 and TMPRSS2 is thought to play an important role in mediating entry of SARS-CoV-2 into host cells.

Transcriptome analysis showed high co-expression of ACE2 and TMPRSS2 in podocytes and cells of the direct tubules. As a result of viral invasion, SARS-CoV-2 can have a direct cytopathic effect on these types of kidney cells. Autopsy tissue quantification of SARS-CoV-2 viral load in patients who have died from COVID-19 shows renal tissue tropism, especially in those with more than two organ systems affected, and is not associated with chronic kidney disease. Viral load is found in all parts of the kidney with an obvious affinity for the glomeruli.In addition to these reasons, it was also assumed that the disease was caused by a concomitant comorbidity or direct invasion of viral material into the renal parenchyma.

Interestingly, some post-mortem histopathology findings indicated interference or damage to the renal tissue of COVID-19 patients that had not previously been detected on routine examination (elevated urea or creatinine), suggesting the possibility of subclinical AKI.

Also revealed a significant increase in C-reactive protein (CRP) and a decrease in the number of platelets in the group. This condition likely correlates with the development of a cytokine storm process that involves an increase in pro-inflammatory mediators such as interleukin-6 (IL- 6), transforming growth factor-β (TGF-β), tumor necrotizing factor -α (TNF-α), vascular endothelial growth factor (VEGF), platelet growth factor (PDGF), IL-10, and soluble plasminogen activator receptor urokinase (suPAR).

This release of pro-inflammatory and anti-inflammatory mediators resulted in a disruption in the coagulation cascades, while thrombus occurred in the later stages and plasminogen stimulation with activation of antithrombin-III occurred in the fibrinolytic system.

Therefore, fibrinolytic factors and fibrinogen were depleted, and thrombus formation and bleeding associated with disseminated intravascular coagulation (DIC) occurred simultaneously.

During the predominance of omicron, 63% of hospitalized infants and children had no comorbidities; Infants <6 months of age accounted for 44% of hospital admissions, although there was no difference in severity by age.

Babies were more susceptible to COVID-19 infection, according to some studies. Therefore, they had symptoms of a severe course of the disease, especially with concomitant diseases accompanied by a decrease in kidney function, as evidenced by an increase in serum creatinine. SARS-CoV-2 infection tends to affect the kidneys, which is manifested by a decrease in glomerular filtration rate (GFR), where it was lower in severe patients (49.59 ml/min/1.73 m2) compared to non-severe (113 ml / min / 1.73 m^2), but statistically insignificant ($p = 0.521$). In this pathology of SARS-CoV-2, significant high levels of CRP and low levels of platelets were found ($p < 0.05$). There are already some reports of COVID -19 infection in children in connection with the epidemic in China. A recent review of 45 scientific papers found that children accounted for 1-5% of diagnosed COVID -19 cases to date , with a minority asymptomatic, the remaining 10% usually having milder disease than adults, and fatalities rare. [4].

The diagnosis, clinical course, and treatment of these patients were similar to those in adults, although only 0.6% of children were critically ill [5].

A high prevalence of severe disease (about 50%) has been observed in infants. Decreased resistance to this pathology in children is explained by less immune dysfunction and immaturity of angiotensin-converting enzyme 2 (ACE2) receptors, which are SARS - CoV - 2 binding sites [6, 7].

Taking into account the data available to date, it can be assumed that ventilation in children under the conditions of this pathological process is less impaired, with less systemic involvement and renal dysfunction compared with adults.

The new syndrome, currently referred to as multisystem inflammatory syndrome in children (MIS - C), has been recognized by clinicians in the UK since April 2020. He describes early healthy children with severe systemic inflammatory syndrome after testing positive for concurrent or recent COVID -19 infection [8]. MIS - C is significantly associated with manifestations of acute kidney injury in children, with an incidence of up to 60% reported in observational studies [8,9].

CKD requiring maintenance dialysis is associated with poor outcomes and mortality in patients with COVID-19.

Key and colleagues described the characteristics of 36 hospitalized children (aged 0 –16 years) with COVID-19 in China, and none of them had reports of renal dysfunction as defined by serum creatinine above 110 μmol/L or serum urea. above 7 mmol / l. Recent data has shown that, in the setting of COVID-19, AP and ATIN occurred in about one fifth of our hospitalized children and in more than a third of children requiring admission to the intensive care unit.

Renal pathology was more common in young children and in those with comorbidities. A small proportion of children with renal pathology developed on the background of COVID -19 may develop acute renal failure by the time of discharge. However, it is milder than in adults, with less need for RRT.

A recent report from a multicentre epidemiological study of critically ill children (the CAKE study) [9] showed that AKI occurred in 18% of enrolled patients, even though little information was provided on classification and severity. The pathophysiology of kidney dysfunction in patients with COVID-19 has recently been suggested as secondary to cytokine storm, organ cross-talk, systemic effects [10] and direct tubuloglomerular damage [11, 12].

Although these assumptions are generally speculative, the evidence regarding these aspects is growing. Potential mechanisms of kidney injury in these patients can be considered under 5 main categories:

1. Dehydration: secondary to decreased fluid intake, vomiting, diarrhea, and excessive use of diuretics to keep the lungs dry. All this predisposes the patient to the development of AKI.
2. Cytokine storm syndrome : In particular, high concentrations of interleukin-6 have been described in patients with COVID-19, especially when lung disease reaches criteria for acute respiratory illness syndrome (ARVI). In patients with a cytokine storm, AKI may occur due to inflammation of the kidneys, increased vascular permeability, fluid loss, intra-abdominal hypertension, hypovolemia, and subsequent shock.
3. Inter-organ interactions: The intensive ventilation of patients with severe hypoxemia is well known to be associated with altered renal function as a component of organ cross-talk [11]. Hemodynamic instability (in addition to ventilation problems may include cardiomyopathy or myocarditis) exacerbated by aggressive volume replacement, positive fluid balance, and co-infection with bacterial pathogens followed by septic shock.
4. Systemic side effects of the virus: Recent first reports have shown the possibility, supported by histopathological findings, that the SARS-COV-2 virus can directly infect the proximal tubules [12, 13].
5. The use of nephrotoxic drugs (namely antiviral drugs and hydroxychloroquine), resulting in increased nephrotoxicity caused by specific COVID-19 treatment, may contribute. As with non-COVID-19 AKI, close attention should be paid to the use of nephrotoxic drugs, their levels monitored, and their use reduced. Their use should be reduced in high-risk patients, especially in conditions of fluid overload and cumulative effects.

Conclusion: Active research is currently underway to differentiate the manifestations of AKI in children from MIS - C after infection with COVID -19, and AKI from direct internal kidney injury as a result of primary infection with COVID -19, while the clinical features of these two cases coincide [1] .

Various kidney lesions in children suffering from this disease can be either mild, manifested by proteinuria or asymptomatic hematuria, or severe, such as acute renal failure.

It can also be assumed that children with comorbidities such as congenital heart disease and congenital kidney disease, as well as kidney transplant patients, have a higher risk of developing acute renal inflammation. Transplant patients have a higher risk of kidney complications with symptomatic COVID -19.

Finally, children requiring intensive fluid resuscitation are at risk of volume overload and may lead to the development of renal complications [14].

Acute renal failure (ARF) is a complication of COVID-19, and the pathophysiology of AKI in COVID-19 appears to be multifactorial.

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