



INSTRUCTIVE CASE

Child with new onset nephrotic syndrome as the sole manifestation of SARS-CoV-2 infection

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As the COVID-19 pandemic is moving on and additional data are accumulating, SARS-CoV-2 seems to be associated with acute kidney injury (AKI) in severely infected and critically ill adults among other manifestations. Kidney involvement has been described in studies including mainly adult COVID-19 patients either in ICU or amongst immunocompromised ones. Based on biopsy results, variable forms of glomerulopathy including collapsing type, minimal change disease, membranous glomerulopathy, crescentic transformation of lupus nephritis, anti-GBM nephritis and few cases of acute tubular injury have been described.¹ The novel coronavirus acts through angiotensin-converting enzyme 2 (ACE2) on body cells and since ACE2 is also expressed in tubular epithelial cells and renal podocytes, renal involvement is explained. However, data in children are variable, with a reported rate of AKI in COVID-19 hospitalised critically ill children between 1.2% and 44%.^{2,3} On the other hand, nephrotic syndrome in children following SARS-CoV-2 infection has only been described as relapse of a preceding condition, as commonly seen with other viruses.⁴ Only two case reports with new onset nephrotic syndrome and concurrent gastrointestinal or respiratory symptoms due to SARS-CoV-2 have been described in literature.^{5,6}

Key Points

- 1 SARS-CoV-2 is mainly a respiratory pathogen, acting through binding of the virus to angiotensin-converting enzyme 2 (ACE2) of respiratory epithelial cells.
- 2 ACE2 is also expressed in renal cells, so kidney involvement can occur in SARS-Cov-2 infection, described so far as acute kidney injury, almost exclusively in severely infected or immunocompromised adults.
- 3 COVID-19-nephrotic syndrome in children is extremely rare and is mostly described as relapse of a previous condition.
- 4 Awareness should be raised for SARS-CoV-2 infection-associated paediatric nephrotic syndrome, either new onset or relapse.

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Hereby we describe the first paediatric case with new-onset nephrotic syndrome as the only presenting symptom in the course of COVID-19 infection.

Case Report

A 7-year-old girl of Afghan origin was admitted to our hospital due to swollen eye lids and edema of her lower extremities. Her mother reported a 3-day history of fever up to 39°C and intermittent abdominal pain. However, no other symptoms or signs were reported. Her past history was unremarkable apart from a UTI a few months ago. On admission, apart from her facial edema and a distended abdomen, she was feverless, with blood pressure 100/65 mmHg, heart rate 90 bpm and SatO₂ 97%. RT-PCR from nasopharyngeal swab was positive for SARS-CoV-2. The urine spot was positive for protein (3+) and blood (3+) and her blood tests showed mild leucopenia (WBC 4170/ml, N 58%, L 36.4%), total protein 3.8 g/dl, albumin 1.7 g/dl, creatinine 0.2 mg/dl, cholesterol 422 mg/dl and triglycerides 131 mg/dl. Inflammation markers such as ferritin, CRP and IL-6 were within normal limits, while fibrinogen and D-dimers were increased (642 mg/dl and 1842 ng/ml respectively). Her blood and urine cultures were sterile. Her blood gas was unremarkable while her chest X-ray showed no lung involvement, and her abdominal US showed a small accumulation of ascitic fluid. In the context of the nephrotic syndrome, a spot biochemical urine analysis was as follows: microalbumin 1255 mg/dl, protein 1567 mg/dl, creatinine 154 mg/dl, protein/creatinine = 10,19, while investigation for autoimmunity or post streptococcal glomerulonephritis (ASOT, ANA, C3, C4) was unremarkable. Patient was seronegative for HAV, HCV, HIV and HBV, excluding these viruses from pathogenesis. Given the rare COVID-19 manifestation as new-onset nephrotic syndrome and in the context of probable viraemia, we also performed RT-PCR for SARS-CoV-2 in blood, which returned negative. Due to lack of knowledge about the exact impact of SARS-CoV2 on the renal function of immunocompetent children apart from PICU patients with AKI, we wanted to have additional information in regard to direct versus indirect viral injury to the kidneys. For this reason, we also performed RT-PCR for SARS-CoV-2 in urine, which returned negative as well.

The girl was treated with prednisone (2 mg/kg/day) and due to significant hypoalbuminemia with repeated doses of human albumin and furosemide IV. Due to the high risk of thromboembolic events, she received low dose heparin SC in prophylactic dose for a total of 12 days. We did not treat her with remdesivir since she had no respiratory involvement, was afebrile for more than 12 h when admitted and remained so, and in addition

current guidelines for the management of COVID-19 in hospitalised children did not support antiviral treatment. Her clinical picture and lab tests gradually improved and she was discharged from hospital after 16 days, with oral prednisone for at least 3 months from diagnosis. She was still SARS-CoV-2 positive on the day of her discharge. One month after discharge, she is in excellent condition with no proteinuria and with normal blood pressure. The most probable diagnosis, based on her age, response to corticosteroids and normal renal function and absence of hypertension, is minimal change disease.

Discussion

Renal involvement during COVID-19 infection is not at all common within paediatric population. Among 295 children hospitalised with COVID-19 in a recent study, proteinuria and gross hematuria were seen in 4.76% and 1.9% of cases, respectively.⁷ Current literature is referring mainly to hospitalised children with severe COVID-19 pneumonia and AKI. It seems that the need for ventilation, sepsis and nephrotic syndrome are independent risk factors for AKI in the course of COVID-19 infection.⁷ SARS-CoV-2 may also act as a trigger for NS relapse as most respiratory infections do. It seems that at least 50% of relapses are triggered by a viral upper respiratory tract infection.⁴ A paediatric case report of NS relapse following SARS-CoV-2 infection has already been described.⁸

Our child did have the full picture of new onset nephrotic syndrome with no impairment of renal function and responded to corticosteroid administration. Only two children with new onset nephrotic syndrome in the context of COVID-19 infection are described so far. The first one was an 8-year-old boy from the USA presenting with diarrhoea and the second one a 15-year-old boy from Spain presenting with mild respiratory symptoms.^{5,6} In our case, nephrotic syndrome was the presenting symptom of COVID-19 infection. We did not demonstrate SARS-CoV-2 RNA in her urine. However, it is known that the pathogenesis of renal damage can be multi-factorial; direct cytopathic effects of the virus, immune complex-mediated damage or secondary to systemic effects on kidney tissue of cytokine inflammatory response to the virus. We did not perform a renal biopsy since our patient responded well to treatment and thus renal biopsy was not justifiable. Recent finding from studies in adults with nephrotic range proteinuria with or without AKI during COVID-19 infections is a connection of *APOL1* genotype with COVID-19 collapsing glomerulopathy.⁹

Nephrotic syndrome and COVID-19 are two independent risk factors for thromboembolic events. Venous thromboembolism occurs in roughly 3% of children with nephrotic syndrome, though incidence approaches 25% in high-risk groups.¹⁰ A case of pulmonary embolism in a child with nephrotic syndrome diagnosed 2 months before COVID-19 infection has also been reported.¹¹ Taking into account this risk, anticoagulation prophylaxis was started.

In conclusion, this is the first paediatric case with new onset nephrotic syndrome as the main manifestation of COVID-19 infection in a febrile child with no respiratory or gastrointestinal symptoms. Although references are rare so far, paediatricians should be aware of SARS-CoV-2-associated nephrotic syndrome either new onset or relapse.

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