CASE REPORT

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A Rare Cause of Transient Proximal Tubule Dysfunction: COVID-19

Kenan DOĞAN[a], Fatih KİLCİ[b], Mehmet Baha AYTAÇ[a]

[a]Division of Pediatric Nephrology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye
[b]Division of Pediatric Endocrinology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye

ABSTRACT Coronavirus disease-2019 (COVID-19), the plague of our time, affects many systems. Kidney involvement may cause acute kidney injury by affecting proximal tubules along with other probable sites. Although renal effects of COVID-19 have been reported in adults, pediatric data are limited. A five-year-old, previously healthy boy hospitalized for COVID-19 infection, developed polyuria on the 3rd day of his admittance. Laboratory workup was compatible with proximal renal tubulopathy and normal clinical and laboratory status was achieved within 5 days with only conservative therapy. Laboratory findings were normal at the first month out-patient visit. We hypothesize that the transient proximal tubulopathy experienced in our case is related to COVID-19 infection. Clinicians should keep in mind the potential tubular involvement in children with COVID-19 infection.

Keywords: COVID-19; kidney; polyuria; proteinuria; proximal tubulopathy

The novel type of coronavirus disease-2019 (COVID-19) is a pandemic disease that started in China's Wuhan province in December 2019 and continued to affect the whole world. Although the disease mainly involves the respiratory system, it can also affect the cardiac, hematological, hepatic and renal systems.[1]

While there is no clear data on the incidence of kidney involvement due to COVID-19 in childhood, it has been reported that renal involvement is observed in 40% of the cases followed in the hospital with the diagnosis of COVID-19 in all age groups.[2] Renal involvement may present with proteinuria and/or hematuria and acute kidney injury may occur because of disturbed tubule functions.[3]

Here, we present a 5-year-old male patient who developed proximal tubule dysfunction while being followed-up with the diagnosis of COVID-19 infection.

CASE REPORT

A 5-year-old, previously healthy boy presented with complaints of fever, poor general condition and seizures. He had no history of metabolic disease and drug use. On examination, his body temperature was 38.4 °C, respiratory rate was 22/minute, oxygen saturation in room air was 98% and blood pressure was 102/61 mmHg which is within normal limits for his age. His weight was 17 kilograms (-0.6 SDS) and height was 107 cm (-0.7 SDS). He had no dysmorphic features. Initial laboratory tests showed leukocytosis ($17.4\times10^3/\mu L$), lymphopenia ($0.6\times10^3/\mu L$) and elevated C-reactive protein levels (90 mg/L). His biochemical parameters were normal. His reverse transcription polymerase chain reaction of nasal swab was positive for COVID-19. He was followed-up in the pediatric intensive care unit. Levetiracetam was started as anticonvulsant therapy. He did not receive any antibacterial or antiviral treatment. On the 3rd day

Correspondence: Kenan DOĞAN
Division of Pediatric Nephrology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye
E-mail: drdogankenan@gmail.com

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of hospitalization, he developed polyuria (11 mL/kg/hour), which he did not have before. A serum profile revealed a glucose of 87 mg/dL; creatinine 0.37 mg/dL; sodium 132 mg/dL; potassium: 2.9 mg/dL; chloride: 108 mg/dL; uric acid: 2.4 mg/dL; albumin: 3.2 g/dL; phosphorus: 2.3 mg/dL; calcium: 9.8 mg/dL; parathyroid hormone: 6 ng/mL; 25-hydroxyvitamin D: 38 ng/mL. Venous blood registered a pH of 7.12, PCO_2: 30 mmHg, $cHCO_3$: 9.7 mmol/L and anion gap, 14.3 mmol/L. Simultaneous urine analysis showed glycosuria (+2) and proteinuria (+3). The urine pH was 5.0. Spot urinary protein/creatinine ratio was 1.2 mg/mg, fractionated sodium excretion was 8.7% and tubular phosphorus reabsorption was 74%, indicating proximal tubular dysfunction (Table 1).

Sodium bicarbonate and potassium replacements were initiated while levetiracetam was continued. On the fourth day of treatment, his clinical picture improved, the need for bicarbonate and potassium replacements decreased and he was discharged from the pediatric intensive care unit. He did not need mechanical ventilation during hospitalization. Subsequently, he was followed-up in the pediatric service.

On the 5th day of the treatment, the polyuria subsided (2.2 mL/kg/hour), and there was no proteinuria and glucosuria in the spot urine analysis. He had normal serum glucose, creatinine, sodium, potassium, phosphorus and uric acid levels. Also, venous blood gas pH, PCO_2 and $cHCO_3$ levels were within normal limits. Then bicarbonate and potassium replacements were discontinued.

During the follow-up period in the pediatric service, the patient did not have any deterioration in kidney functions and daily urine output was within normal limits. After the treatment of the primary disease, the patient was discharged with full recovery. It was observed that laboratory values were normal at the 1st month visit.

Informed consent form was taken from the patient's family.

DISCUSSION

Proximal tubule dysfunction may manifest as tubular proteinuria, glycosuria, hypouricemia, and characteristic electrolyte and acid-base balance disorders.[4] The most common causes of proximal tubule dysfunction in childhood are hereditary metabolic diseases and drug use.[5]

However, since clear data on proximal tubule dysfunction, which is thought to be related to COVID-19, have not yet been revealed, it has not

TABLE 1: Laboratory variables during the follow-up of the patient.

Parameter	On admission	3rd day	8th day	1st month	Normal range
Serum glucose	81	87	84	92	70-100 mg/dL
Serum creatinine	0.46	0.37	0.39	0.41	0.3-0.6 mg/dL
Serum sodium	141	132	137	140	136-145 mg/dL
Serum potassium	4.1	2.9	3.8	4.3	3.5-5.1 mg/dL
Serum chloride	101	108	99	102	98-107 mg/dL
Serum phosphorus	4	2.3	3.9	4.1	3.7-5.6 mg/dL
Serum uric acid	5.2	2.4	4.8	4.2	3.4-7 mg/dL
pH	7.39	7.12	7.4	7.38	7.35-7.45
PCO_2	34	30	32	40	35-45 mm/Hg
Bicarbonate	24.7	9.7	25.1	23.2	22-26 mmol/L
Urine glucose (Dipstick)	Negative	++	Negative	Negative	Negative
Urine protein (Dipstick)	Negative	+++	Negative	Negative	Negative
Spot urine protein/creatinine ratio	0.09	1.2	0.07	0.1	<0.2 mg/mg
Tubular phosphate reabsorption	ND	74%	93%	91%	>85%

ND: Not done.

been fully clarified how the disease will manifest itself or what the prognosis will be.

The present case displayed features of renal proximal tubulopathy; hypophosphatemia, hypokalemia, hypouricemia, polyuria, proteinuria and glycosuria with normal serum glucose levels in the course of COVID-19 infection. We could not perform urine electrophoresis for tubular proteinuria but his spot urinalysis and high phosphorus output along with polyuria were suggesting proximal tubular damage. He was discharged without developing acute kidney injury with appropriate treatment.

We consider that the transient proximal tubule dysfunction experienced in our case, who had no metabolic disease and no history of drug intake, and normal laboratory and clinical findings in the follow-up, was due to COVID-19 infection. Tubulopathy of our case, whose levetiracetam treatment was continued without interruption, improved. Therefore, we thought that levetiracetam could not be the cause of the tubulopathy.

The main receptor for severe acute respiratory syndrome-CoV-2 (SARS-CoV-2) is angiotensin converting enzyme 2 (ACE2), a metallopeptidase found in the membranes of target cells. This enzyme is expressed in arterial and venous endothelial cells of many organs, including the kidneys.[6] Renal proximal tubules express ACE2 and may be potential targets for SARS-CoV-2 during COVID-19.[7]

Electrolyte disturbances, most commonly hyponatremia and hypokalemia, can be seen during COVID-19 infection. Syndrome of inappropriate antidiuretic hormone secretion is mostly blamed in the pathogenesis of hyponatremia.[8] In addition, SARS-CoV-2 may affect sodium and potassium transport via Na+/K+ ATPase in renal tubular epithelium through ACE2-related renin-angiotensin system activation.[9]

Post-mortem studies in patients who died due to COVID-19 revealed the presence of significant acute tubular injury in light microscopy, while the presence of viral particles in both tubular epithelium and podocytes was shown in electron microscopy, which has been attributed to direct infection of the kidneys by COVID-19.[10,11]

In a study conducted in France, it was suggested that the findings of proteinuria, hypophosphatemia, hypouricemia, and glycosuria are common in patients who developed proximal tubule damage due to COVID-19 and that these findings can be used as markers of proximal tubule damage.[12] In the same study, the authors reported that 88% of patients with Stage 2 and 3 acute kidney injury developed proximal tubule damage before acute kidney injury. They also described cases with isolated renal tubular involvement associated with COVID-19, as well as cases with tubulopathy with glomerular involvement. Although tubular findings are prominent in our case, it cannot be said that the glomeruli are preserved or not affected at all. Although we did not discriminate the type of proteinuria, its amount suggests that there may have been some glomerular involvement as well. Improvement of tubular or glomerular renal findings after COVID-19 in our case can be interpreted as indirect evidence showing their relationship with COVID-19. However, it is not possible to report which parts of the kidney are most affected by the COVID-19 infection with a single case.

In a study conducted in China in 2020 including all age groups, it was shown that the level of proteinuria is associated with the degree of proximal tubule damage.[7] Although there is no study specific to children on this subject, Sengupta et al. reported a 5-year-old girl who experienced proximal renal tubular acidosis during the course of COVID-19.[13] They stated that the COVID-19 infection played a role in the proximal tubulopathy experienced in the case that reached normal parameters in the follow-up, and the disease was self-limited with the resolution of the derangements on recovery.

In a study conducted in Saudi Arabia, it was revealed that the course of COVID-19 cases with at least one of the indicators of renal involvement, including hematuria, proteinuria, tubulopathy, and acute kidney injury, was more severe.[14] Therefore, it may be suggested that there is a linear relationship between the duration of intensive care follow-up of our patient and the course of tubulopathy.

We think that our case, which overlaps clinically and biochemically with the cases with tubular involvement due to COVID-19 described in the literature, may contribute to the data on the small number of pediatric case definitions and the prognosis of the disease. Further studies are needed to reveal the incidence, symptoms, and long-term effects of tubular involvement in children with COVID-19.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kenan Doğan, Fatih Kilci;* ***Design:*** *Fatih Kilci;* ***Control/Supervision:*** *Mehmet Baha Aytaç;* ***Data Collection and/or Processing:*** *Kenan Doğan, Fatih Kilci;* ***Analysis and/or Interpretation:*** *Kenan Doğan;* ***Literature Review:*** *Kenan Doğan;* ***Writing the Article:*** *Kenan Doğan, Fatih Kilci;* ***Critical Review:*** *Mehmet Baha Aytaç;* ***References and Fundings:*** *Fatih Kilci;* ***Materials:*** *Kenan Doğan.*

REFERENCES

1. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, et al. Clinical characteristics of 82 cases of death from COVID-19. PLoS One. 2020;15(7):e0235458. [Crossref] [PubMed] [PMC]
2. Braun F, Huber TB, Puelles VG. Proximal tubular dysfunction in patients with COVID-19: what have we learnt so far? Kidney Int. 2020;98(5):1092-4. [Crossref] [PubMed] [PMC]
3. Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol. 2020;16(12):747-64. Erratum in: Nat Rev Nephrol. 2020. [PubMed] [PMC]
4. Bagga A, Bajpai A, Menon S. Approach to renal tubular disorders. Indian J Pediatr. 2005;72(9):771-6. [Crossref] [PubMed]
5. Foreman JW. Fanconi syndrome. Pediatr Clin North Am. 2019;66(1):159-67. [Crossref] [PubMed]
6. Maksimowski N, Williams VR, Scholey JW. Kidney ACE2 expression: implications for chronic kidney disease. PLoS One. 2020;15(10):e0241534. [Crossref] [PubMed] [PMC]
7. Liu L, He F, Cai SS, Hu KL, Yu C, Huang Y, et al. Clinical characteristics of hospitalized patients with 2019 novel coronavirus disease indicate potential proximal tubular dysfunction. Chin Med J (Engl). 2020;133(16):1983-5. [Crossref] [PubMed] [PMC]
8. De Carvalho H, Richard MC, Chouihed T, Goffinet N, Le Bastard Q, Freund Y, et al. Electrolyte imbalance in COVID-19 patients admitted to the Emergency Department: a case-control study. Intern Emerg Med. 2021;16(7):1945-50. [Crossref] [PubMed] [PMC]
9. Pani A, Inglese E, Puoti M, Cento V, Alteri C, Romandini A, et al. Sex differences in electrolyte imbalances caused by SARS-CoV-2: a cross-sectional study. Int J Clin Pract. 2021;75(12):e14882. [Crossref] [PubMed] [PMC]
10. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-27. [Crossref] [PubMed] [PMC]
11. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol. 2020;31(8):1683-7. Erratum in: J Am Soc Nephrol. 2020;31(10):2494. [Crossref] [PubMed] [PMC]
12. Kormann R, Jacquot A, Alla A, Corbel A, Koszutski M, Voirin P, et al. Coronavirus disease 2019: acute Fanconi syndrome precedes acute kidney injury. Clin Kidney J. 2020;13(3):362-70. [Crossref] [PubMed] [PMC]
13. Sengupta A, Krishnamurthy N, Khosla I, Udani S. Transient Fanconi syndrome in a child with acute COVID-19 infection. Indian J Pediatr. 2021;88(12):1260. [Crossref] [PubMed] [PMC]
14. Allemailem KS, Almatroudi A, Khan AA, Rahmani AH, Almarshad IS, Alekezem FS, et al. Manifestations of renal system involvement in hospitalized patients with COVID-19 in Saudi Arabia. PLoS One. 2021;16(7):e0253036. [Crossref] [PubMed] [PMC]