Can microalbuminuria be an indicator of renal involvement in pediatric Covid 19 patients?

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Abstract

Background Proteinuria (both tubular and glomerular in origin) and its implications are well-known features of adult patients with COVID19. However, currently, studies addressing proteinuria and its role in the outcome of kidney and patients of pediatric COVID 19 are scarce. We aimed to evaluate the presence of microalbuminuria in order to detect early renal involvement in pediatric COVID 19 patients.

Methods We prospectively evaluated 100 pediatric patients hospitalized with COVID 19 between April and July 2020. Clinical presentations, laboratory findings and outcomes were investigated. Microalbuminuria was compared with the age, gender, disease severity, and hemoglobin, platelet, leukocyte count and serum CRP levels of the patients.

Results Twenty seven out of 100 patients had microalbuminuria. Fourteen patients had mild and fourteen had moderate disease. There was not any significant relation according to age and gender. Microalbuminuria was not related to the severity of the disease. Also, the mean microalbuminuria level did not differ according to the disease course. Hemoglobin, platelet, leukocyte counts and serum CRP levels were also not correlated with microalbuminuria levels.

Conclusion Although there was no difference between the groups with different disease course; microalbuminuria is detected in an important ratio of pediatric patients with COVID 19 in this study. In the highlight of our findings we suggest that urinary findings of pediatric COVID patients should be carefully evaluated.

Keywords PNEP-D-21-00705 children, COVID 19, Kidney involvement · Microalbuminuria

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Introduction

The coronavirus disease of 2019 (COVID 19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first arose in Wuhan, China in December 2019 and soon after became a global pandemic [1]. The primary target of the virus is respiratory system but it also affects other organs and systems. Renal involvement is more commonly being reported in adult patients hospitalized with COVID 19 and the spectrum of the disease may vary from isolated hematuria and proteinuria to severe kidney damage requiring renal replacement therapy [2, 3]. In a systematic review of AKI in COVID 19, the prevalence of acute kidney injury (AKI) was found to be 17%; ranging from 0.5 to 89% [4]. In the first reports from China, hematuria was found to be 26.7% and proteinuria was found to be 43.9% on hospital admission [2]. In the recent report of Chan et al. in which they evaluated 435 patients with AKI, proteinuria was found to be 84%, hematuria was 81% and leukocyturia 60% [5] AKI, hematuria and proteinuria were all related with adverse outcomes in hospitalized adult patients with COVID 19 [1–5].

Although rare when compared to adult counterparts there are studies addressing renal involvement also in children with COVID 19; mainly evaluating the presence of AKI and its relation with prognosis [6–9]. In an early study by Stewart et al. 24 (46%) out of 52 pediatric patients hospitalized with COVID 19, had a serum creatinine level greater than upper limit of reference interval (ULRI) [7]. The reported incidence of AKI ranged from 0 to 70% in different pediatric studies [6]. These discrepancies among studies were attributed to different definitions of AKI and different cohorts [6–10]. Hematuria and proteinuria are well recognized in adult studies but to our knowledge in children there are only anecdotal reports describing new onset hematuria and/or proteinuria or nephrotic syndrome in pediatric patients with COVID 19 [10–14]. In this regard, we aimed to evaluate the presence of microalbuminuria to detect early renal effects in pediatric COVID 19 patients.

Patients and methods

This prospective observational study was carried out with the pediatric patients who were hospitalized with COVID 19 between April 1st and July 1st, 2020. Local institutional committee approved the study and informed consent was obtained from all of the parents to participate.

Children aged 1 month and 18 years were included in the study. Patients with already known diseases as nephrotic syndrome, chronic glomerulonephritis, chronic kidney diseases, recurrent urinary tract infections or patients who had urinary tract infection at the time of study were excluded. Patients with other chronic diseases such as juvenile idiopathic arthritis, systemic lupus erythematosus, inflammatory bowel diseases, familial Mediterranean fever were also excluded from the study. Among the 108 patients hospitalized at the time of study; 5 had urinary tract infection 1 had familial Mediterranean fever, 1 patient had nephrotic syndrome, 1 had juvenile idiopathic arthritis. These patients were not included in the study.

COVID 19 infection was diagnosed by polymerase chain reaction (PCR) from a nasopharyngeal swab specimen. During the study period, all the patients who were positive for SARS-COV-2 test were hospitalized to quarantine and observe the disease course according to national guidelines. Detailed history was obtained from the parents and complete physical examination was performed. Clinical and laboratory findings were obtained from the hospital records at admission. Renal function tests, urine spot microalbumin to creatinine ratio, urine dipstick tests were retrieved. Chest X-ray and computed tomography was performed when indicated. Disease course was described as asymptomatic, mild, moderate and severe. Children with no symptoms were defined as asymptomatic. Children with upper respiratory tract symptoms with or without fever and no evidence of pneumonia or hypoxia were classified to have mild disease. Presence of pneumonia, fever, frequent cough with no obvious hypoxemia is described as moderate disease and presence of pneumonia, dyspnea and an oxygen saturation below 92% on room air were described as severe disease. Children with moderate disease were administered antibiotics according to the national guidelines. The duration of medical treatment changed between 10 and 14 days in these patients. All of the patients including the patients with mild and moderate disease course were discharged with complete recovery.

Microalbuminuria was estimated from spot urine samples test and defined as an albumin-to-creatinine ratio > 10 mg/g [15]. This method has been shown to be superior to urine microalbumin concentrations and detected to be comparable with 24-h urine collections.

Proteinuria was described according to dipstick results and 1+ or higher on dipstick was defined as presence of proteinuria. Microalbuminuria was tested in COVID 19 patients at the time of hospital admission.

Hematuria was defined as presence of five or more erythrocytes on automatized urine microscopy.

Acute kidney injury was defined according to the KDIGO serum creatinine-based criteria [16].

The frequency of microalbuminuria was determined and compared with age, gender and severity of the disease. Also microalbuminuria levels were compared with the mean hemoglobin levels, platelet and leukocyte count, CRP levels.
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Statistical methods

Statistical analysis were performed by IBM SPSS 24 software. Descriptive statistics were given as number and percentage. Normality was assessed by Shapiro Wilk test. Data are expressed as mean ± standard deviation when the distribution was normal. Comparison of two independent groups was performed with Mann-Whitney U test and Chi-square or Fischer’s exact test for continuous and categorical variables, respectively. A p value < 0.05 indicated statistical significance.

Results

A total of 100 patients; 52 girls and 48 boys were included in this study. Mean age of the patients was 11.2 ± 0.3 years (0.11–18 years). The majority of the patients were asymptomatic (72%). Twenty-eight patients had fever and 20 had respiratory symptoms. Among these symptomatic patients only 14 had pneumonia and detected to have moderate disease and received treatment with antibiotics. (Nine patients received monotherapy with either macrolides or ampicillin sulbactam and five of the patients received macrolides and ceftriaxone). Ten patients underwent radiological investigations and only one of them had ground-glass opacities. None of the patients in the study period was diagnosed to have severe disease, none developed acute kidney injury and all of them were discharged with full recovery.

Urine dipstick evaluation of the patients were all normal. Serum creatinine, sodium and potassium levels were also normal in all of the patients. Twenty seven (27%) of the patients had microalbuminuria with elevated microalbumin/creatinine ratio.

No statistically significant difference was observed according to the age and gender (p = 0.494 and p = 0.377, respectively) (Table 1).

When compared according to the disease course; there was no statistically significant difference between the patients who were diagnosed to have moderate disease and received antibiotics with the patients who were diagnosed to have asymptomatic or mild disease and did not receive treatment (p = 0.753). (Table 1) We also compared mean microalbuminuria level between patients who had mild and moderate disease; and there was also no statistically significant difference between the two groups (p = 0.412).

There was also no difference between the groups with and without fever (p = 0.199) and with and without respiratory symptoms (p = 0.143) (Table 1).

The presence of microalbuminuria was also compared with the laboratory parameters at admission. There was no significant correlation between the mean hemoglobin level, leukocyte count, thrombocyte count, and CRP levels and microalbuminuria (p = 0.798, p = 0.291, p = 0.944 and p = 0.764, respectively) (Table 2).

Discussion

One hundred pediatric patients hospitalized with COVID 19 were evaluated in this study to detect microalbuminuria as an early sign of kidney involvement. According to the national guidelines at the time of the study, all patients with a positive test were hospitalized for close observation. Most of the pediatric patients were tested because of household contact with COVID 19. So, the majority of the children in this study population were asymptomatic; 14 had mild and 14 had moderate disease. None of the patients developed severe disease and none developed AKI. Twenty seven of the patients had microalbuminuria. The prevalence of microalbuminuria did not differ according to the severity of COVID 19. The mean microalbumin/creatinine ratio did not differ among the groups in regard of disease severity.

Previous reports have demonstrated that kidney is a vulnerable organ in COVID 19 disease [2–5, 17]. Spectrum of renal involvement ranges from asymptomatic urinary findings as leukocyturia, proteinuria and/or hematuria to acute kidney injury that requires renal replacement therapy [2, 5]. AKI is being increasingly reported among patients hospitalized with COVID 19 both in adult and pediatric studies [2–7]. Major risk factors for AKI in COVID 19 are nephrotoxic medications, hypotension, dehydration and sepsis [18]. Severe inflammation and cytokine storm caused by SARS-CoV-2 are also prominent risk factors for kidney injury [18–20]. As already known SARS-CoV-2 enters cells by
binding angiotensin-converting enzyme II receptors [6, 8, 18, 21, 22]. It is hypothesized that this binding of SARS-CoV-2 to ACE2 receptors gives rise to an inflammatory response which leads to systemic vasculitis like syndrome [19]. ACE2 receptors are highly expressed on proximal tubular epithelial cells and to a lesser extent on podocytes [17, 23]. Together with inflammation and other traditional risk factors as hypotension, nephrotoxic medications, hypoxia; this distribution of the receptors causes kidneys as the target of SARS-CoV-2 [17–20].

As well as AKI, hematuria and proteinuria are also commonly reported in COVID 19 [18, 22]. Proteinuria is not only detected in patients with AKI, but also is observed in patients without AKI [2, 24]. Cheng et al. reported that 1+ dipstick proteinuria was found in 33% of patients without AKI and 40% of patients with AKI and 2+ or 3+ dipstick proteinuria was found 8% of patients without AKI and 30% of patients with AKI [2]. Chaudhri et al. showed that patients with COVID 19 who developed in-hospital proteinuria only 3 out of 23 (13%) had also AKI [18]. Although overt proteinuria is more frequent in patients with AKI, studies suggest that low grade proteinuria can be detected irregardless of AKI [2, 18, 24].

Recent studies demonstrated that kidney involvement; particularly proteinuria is an important and independent predictor of outcome in SARS-CoV-2 infection [21, 22, 25–27]. Ouahmi et al. reported that proteinuria is related with increased length of stay and admission to intensive care unit (ICU) [21]. Chaudhri et al. stated that proteinuria at admission was associated with AKI during hospitalization; and proteinuria during hospitalization was associated with increased risk of death [18]. Karras et al. found that urine protein-creatinine ratio over 1 g/g was strongly associated with unfavorable kidney and patient outcome [22].

The nature of the proteinuria in COVID 19 disease is a subject of debate. Although in most of the studies it was demonstrated to be mainly tubular in origin, there are also studies indicating that glomerular proteinuria may be observed [22, 26, 28]. The reason for this discrepancy may be related with the measurement methods of proteinuria. Some of the studies only evaluated proteinuria by dipstick method that cannot be able to detect non-albumin proteinuria. Some of the studies investigated tubular proteinuria markers while others did not. But the common point of all these studies was that, as mentioned above proteinuria was related with the kidney and patient outcome in COVID 19 disease [18, 22–28].

Nearly all of the studies mentioned here consist of adult COVID 19 patients with moderate to severe disease. To our knowledge, pediatric studies addressing proteinuria in COVID 19 is scarce in English literature. We think that our study is important because it has been carried out in pediatric COVID 19 disease and most of these children had asymptomatic or mild clinical course. Only 14 of them had moderate disease. We did not find any relationship between microalbuminuria and disease course and laboratory parameters of the patients. But we think that a microalbuminuria ratio of 27% cannot be ignored and may suggest that renal involvement may occur even in asymptomatic pediatric patients. In line with these findings, we suggest that patients should be carefully followed up for kidney disease progression.

This study have some limitations. First of all we could not be able to perform follow-up urinary examinations of the patients so we could not be able to determine if the microalbuminuria was transient or not. We also did not perform renal imaging to decrease the risk of exposure among hospital staff but this may cause a limitation for our study. The study population mainly consisted of asymptomatic patients or patients with a mild course so we could not be able to detect the presence of microalbuminuria in severe patients. We could not identify if the microalbuminuria at admission would be an indicator of kidney involvement in severe forms of COVID 19 disease. We could not be able to evaluate the relationship between microalbuminuria and intensive care unit necessity and/or mortality. We did not perform tests to detect tubular proteinuria so we do not know if asymptomatic patients will also have tubular proteinuria or not.

Despite all these limitations, the presence of microalbuminuria in pediatric patients with asymptomatic or mild COVID 19 disease might be an important proof of kidney involvement. Considering these findings and the reported relation with kidney involvement and increased morbidity and mortality in adult COVID 19 patients we want to emphasize that clinicians dealing with pediatric COVID 19 patients should also be aware of urinary findings and kidney involvement of SARS-CoV-2 infection.

Table 2  Comparison of laboratory findings with microalbumin to creatinine ratio

| Laboratory Findings | Mean ± SD | MAC (mean ± SD) | p value |
|--------------------|-----------|-----------------|---------|
| Haemoglobin (g/dl) | 14.43±11.57 | 11.91±4.51 | 0.798 |
| Platelet count/(mm³) | 276,590±83,969.46 | 11.91±4.51 | 0.944 |
| Leukocyte count /(mm³) | 6369±4623.12 | 11.91±4.51 | 0.291 |
| CRP (g/dl) | 8.89±6.71 | 11.91±4.51 | 0.764 |

SD standard deviation, MAC microalbumin to creatinine ratio
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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Research Ethical Committee of Ankara City Hospital approved the study (date:07/05/2020 number: E1-20-547). Patients and their families were informed in detail and written informed consent was obtained.

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