ORIGINAL ARTICLE

Is the COVID-19 disease associated with de novo nephritic syndrome?

Hamad Dheir[1]
Savas Sipahi[1]
Selcuk Yaylaci[2]
Ahmed Cihad Genc[2]
Fevziye Turkoglu Genc[2]
Ahmed Bilal Genc[2]
Ertugrul Guçlu[3]
Gurkan Muratdagi[4]
Hande Toptan[5]
Oguz Karabay[3]

1. Sakarya University Faculty of Medicine, Division of Nephrology, Sakarya, Turkey
2. Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya, Turkey
3. Sakarya University Faculty of Medicine, Department of Infection Diseases, Sakarya, Turkey
4. Sakarya University Faculty of Medicine, Department of Family Medicine, Sakarya, Turkey
5. Sakarya University Faculty of Medicine, Department of Microbiology, Sakarya, Turkey

http://dx.doi.org/10.1590/1806-9282.66.9.1258

SUMMARY

INTRODUCTION: *This study aims to determine the incidence of de novo nephritic syndrome (NS) in COVID-19 patients and identify its associated factors.*

METHODS: *All ward patients with COVID-19 pneumonia were investigated. After determining the inclusion and exclusion criteria, the study population was identified. The urine dipstick test and urine protein creatinine ratio (UPCR) measurements were performed. Patients with de novo NS findings, nasopharyngeal swab, and urine RT-PCR tests were performed simultaneously*

RESULTS: *This descriptive cross-sectional study was conducted with 21 patients with COVID-19. The mean age of the patients was 42.2±8.8 years, and 71.4% of them were male. The mean duration of follow-up was 28.4±9.3 days. The urine RT-PCR test was positive in one patient (4.8%). Improvements were observed in hematuria by 71.4%, and proteinuria by 85.7% at the end of the follow-up. A significant decrease in the measured UPCR was found in comparison to the baseline(P=0.000). Also, improvements were recorded in the complete blood counts, inflammatory parameters, ferritin, and coagulation tests, compared to the baseline. There was a positive correlation between baseline UPCR and ferritin, and a negative correlation between baseline UPCR and sodium values*

CONCLUSION: *COVID-19-induced de novo nephritic syndrome may occur mainly due to tubulointerstitial involvement and often results in spontaneous remission. However, why these findings were not present in all patients who had no comorbidities is not clear.*

KEYWORDS: *Coronavirus Infections. Hematuria. Proteinuria. Acute kidney injury. Nephritis.*

INTRODUCTION

The Coronavirus (COVID-19) outbreak was recognized as a pandemic in March 2020 by the World Health Organization (WHO). Fever, cough, and shortness of breath are the most common complaints in these patients[1]. According to our knowledge, the respiratory, immune, and coagulation systems are

DATE OF SUBMISSION: 05-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Hamad Dheir
Sakarya University Faculty of Medicine, Division of Nephrology - Adnan Menderes Cad. Sağlık Sok. No. 1, Adapazarı, Sakarya, Turkey - Tel: +905325293390
E-mail: hamaddheir@sakarya.edu.tr

among the major targets of the virus[2]. In terms of organ involvement, acute respiratory distress syndrome (ARDS) due to pneumonic infiltration of the lung is the first organ to be affected[3]. Subsequent clinical and autopsy studies showed damage in several extrapulmonary organs, including acute heart and kidney damage, in addition to ARDS[4,5]. The mechanisms of kidney damage in COVID-19 patients and whether the kidney is a hidden viral nest are still unclear. COVID-19 virus has been shown to cause injury in tubulointerstitial areas rather than in the glomeruli of the kidney[6]. In an autopsy study on COVID-19-induced kidney injury, acute proximal tubular and endothelial damage was found. Acute kidney injury (AKI) and proteinuria were shown to develop due to the presence of particles of the virus in the proximal tubule epithelium and podocytes[5]. In the normal population, active urinary sediments may occur due to AKI, sepsis, and multiorgan failure[7]. Proteinuria and hematuria were found to be associated with the risk of AKI and mortality in critically ill patients without COVID-19 disease[8,9]. Microscopic hematuria and proteinuria are common, especially in severe COVID-19 patients in intensive care units (ICU)[8]. The presence of these renal involvements (AKI, hematuria, proteinuria) was shown to increase the risk of COVID-19-induced mortality, compared to patients without renal involvement[7,8]. Conflicting results on COVID-19-induced microscopic hematuria and proteinuria were reported. The symptoms of proteinuria and hematuria detected in the studies may be due to underlying comorbidities, such as hypertension and diabetes mellitus. In addition, due to the low viremia potential of COVID-19, the microscopic hematuria and proteinuria found in particularly severe patients in ICU may develop secondary to AKI, cytokine storm, and sepsis. However, symptoms of de novo nephritic urine, developed in stable patients with no comorbid disease and no AKI or sepsis condition may be associated with COVID-19 disease.

This study aims to determine the incidence of de novo nephritic syndrome in patients with pneumonia due to COVID-19, and to investigate whether urinary findings were associated with COVID-19.

METHODS

All ward but not ICU patients with COVID-19 reverse transcription-polymerase chain reaction (RT-PCR) positivity were detected. Patients >18 and <60 years of age, with proteinuria and/or hematuria detected in their urine, without any chronic disease, such as hypertension, diabetes mellitus, chronic renal failure, glomerular disease, patients who did not receive any antihypertensive medication, and patients without a history of previous microscopic hematuria and/or proteinuria were included in the study. Patients who received a therapeutic or herbal medicine that may cause nephritic syndrome, patients with viral hepatitis, AKI, renal transplant, kidney stones, urinary tract infection, and ICU patients, patients with a urinary catheter, with a history of malignancy, and female patients with menstrual bleeding were excluded from the study. The urine dipstick test positivity detected on the first day of hospitalization was repeated on the first morning using the dipstick test, and urine protein creatinine ratio (UPCR) was measured. Patients' biochemical parameters were recorded at admission and after discharge. The study was carried out upon receiving approval by the Ethics Committee of the Sakarya University Faculty of Medicine (No:71522473/050.01.04/248).

Statistical analysis: Quantitative data were expressed as mean values ± SD, medians, and ranges. Qualitative data were expressed as numbers and percentages. The assumption of normality was tested by the Shapiro-Wilk test. Paired Samples T-test and Wilcoxon Signed Rank tests were used when appropriate. The Spearman correlation coefficient was used to evaluate the degree of correlation between the parameters. P-values <0.05 were considered statistically significant. Analyses were performed by using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Statistics; Armonk, NY, USA).

RESULTS

A. General characteristics

A total of 1669 COVID-19 patients were investigated in this descriptive cross-sectional study between March 15th and April 20th, 2020. The study was conducted with 21 patients (1.26%) who met the criteria for inclusion in the study and had de novo microscopic hematuria and nephritic proteinuria, according to urine tests and a history of comorbidities. The mean age of the patients was 42.2±8.8 years, and 15 (71.4%) were male. The mean body mass index and duration of the follow-up period were 23.6±5.0 kg/m2 and 28.4±9.3 days, respectively.

B- Urine analysis and laboratory outcomes

Two consecutive results of more than trace or 1+ of protein on the dipstick test were considered as positive proteinuria (1+ in 8 patients, 2+ in 5 patients, 3+ in 8 patients). Two consecutive results of more than trace or 1+ of blood on the dipstick test were considered as positive hematuria (1+ in 9 patients, 2+ in 7 patients, 3+ in 5 patients). Two consecutive results of random UPCR were measured and >300 mg/g creatinine was considered as abnormal proteinuria.

Just one patient (4.8%) had positive urine COVID-19 RT-PCR test results. Hematuria and proteinuria were found to be improved by 71.4% and 85.7%, respectively. In addition, there was a significant decrease in the measured UPCR compared to the baseline (409.1±218.6 vs 109.1±218.6 mg/g creatinine, P=0.000) (Table 2). The complement, antinuclear antibody, anti-neutrophil cytoplasmic antibody, and Anti-ds-DNA antibodies were negative at admission. As the treatment for COVID-19, 21 (100%) of the patients received hydroxychloroquine, 10 (47.6%) received oseltamivir, 8 (38%) received azithromycin, and 5 (23.8%) received favipiravir. At the end of the follow-up, complete blood counts, CRP, procalcitonin, serum albumin, eGFR, ferritin, and coagulation parameters were found to be significantly improved compared to the baseline values (P<0.05) (Table 3). There was no significant correlation between baseline hematuria and proteinuria and other parameters. However, there was a moderately positive correlation between basal UPCR and baseline ferritin (r=.0.47 p=0.037), and a moderately negative correlation between baseline UPCR and baseline Na (r=-0.45 p=0.042).

TABLE 1. BASELINE CHARACTERISTICS OF COVID-19 PATIENTS

Items	Outcome
Age (years)	42.2 y 1l ± 8.8
Sex M/F (no) (%)	15/6 (71.4/28.6)
BMI (kg/m2)	23.6 ± 5.0
Duration of follow up (days) mean values ± SD (min.-max.)	 28.4 +/- 9.3 (17- 24- 44)
Complaints (no) (%) Fever Cough Shortness of Breath Myalgia Diarrhea Sore throat Anosmia	 16 (76.2) 16 (76.2) 8 (38.1) 6 (28.5) 3 (14.2)2 2 (9.5) 1 (4.8)
Radiologic findings No involvement (no) (%) Unilateral involvement (no) (%) Bilateral involvement (no) (%)	 2 (9.5) 2 (9.5) 17 (80.9)
Urine RT-PCR (no) (%)	1 (4.8)

M: male, F: female, BMI: Body mass index, RT-PCR: reverse transcription-polymerase chain reaction.

DISCUSSION

In this study, we investigated 1669 COVID-19 patients with de novo nephritic syndrome. Spontaneous remission was found in 85.7% and 71.4% of the patients' proteinuria and hematuria findings, respectively. In addition, there was a statistically significant remission in random UPCR. Recently, the incidence of proteinuria and hematuria in COVID-19 patients were found to be 65.8% and 41.7%, respectively. By using dipstick tests, the reduction ratio of proteinuria and microscopic hematuria were 68.5% and 43.1%, respectively. Moreover, a greater incidence of proteinuria (81.2% and 85.7%, respectively, versus 43.8%) and hematuria (39.1% and 69.6%, respectively, versus 33.3%) were demonstrated in severe or critically ill COVID-19 patients. The prevalence of hypertension and diabetes mellitus was 32.2% and 22.9%, respectively. In our study, however, the random UPCR was also measured in addition to the urine dipstick test. As our patients did not have any chronic illness, this suggests that the COVID-19 virus itself directly causes renal involvement. To our knowledge, for the first time, we demonstrated de novo nephritic syndrome in COVID-19 patients. The reversibility of most of the findings in patients suggests that it may be due to tubulointerstitial nephritis (TIN) caused by the virus. However, eosinophilia and eosinophiluria are expected in addition to microscopic hematuria

TABLE 2. CHARACTERISTICS OF URINE FINDINGS AND COVID-19 TESTS

Variable	Baseline value	End of follow up value	P
Hematuria frequency (no) (%)	21/21 (100.0 %)	6/21 (28.6 %)	*
Proteinuria frequency (no) (%)	21/21 (100.0 %)	3/21 (14.3 %)	*
UPCR (mg/g creatinine) mean values ± SD (min.-max.)	409.1 ± 218.6 (77.7 – 935.0)	109.1 ± 218.6 (47.7 – 311.0)	0.000**
NP swab RT-PCR positivity (n) (%)	21/21 (100.0 %)	--	--
Urine RT-PCR positivity (n) (%)	1/21 (4.8 %)	--	--

* McNemar Test was not calculated. ** Wilcoxon Signed Rank Test was used.

UPCR: Urine protein creatinine ratio, NP: Nasopharyngeal, RT-PCR: reverse transcription-polymerase chain reaction

TABLE 3. DEMOGRAPHIC LABORATORY PARAMETERS OF PATIENTS AT BASELINE AND END OF FOLLOW-UP

Variable	Baseline value mean values ± SD (min.-med.-max.)	End of follow up value mean values ± SD (min. med. max.)	P
White Cell Count NV: 5.6-10.2 (K/uL)	6.97 ± 3.14 (2.95 – 16.20)	6.05 ± 1.62 (3.14 – 10.80)	0.205*
Lymphocyte Count NV: 0.6-3.4 (K/uL)	1.41 ± 0.43 (1.40 – 12.40)	2.03 ± 0.47 (1.40 – 3.62)	0.000**
Eosinophil NV: 0.0-0.7 (K/uL)	0.066 ± 0.110 (0.000 – 0.390)	0.151 ± 0.100 (0.010 – 0.400)	0.000*
Neutrophil/ Lymphocyte ratio	3.79 ± 2.48 (1.03 –10.71)	1.56 ± 0.49 (0.65 – 2.81)	0.000*
Eosinophil/Lymphocyte ratio	0.039 ± 0.110 (0.000 – 0.200)	0.074 ± 0.100 (0.000 – 0.180)	0.001*
Platelet Count NV: 142-424 (K/uL)	190.7 ± 58.3 (103.0 – 340.0)	252.4 ± 52.7 (182.0 – 364.0)	0.000**
INR NV: 0.8-1.3	1.10 ± 0.12 (0.94 – 1.31)	1.02 ± 0.12 (0.80 – 1.33)	0.020*
Serum Creatinine NV: 0.67-1.17 (mg/ml)	0.73 ± 0.19 (0.27 – 1.10)	0.67 ± 0.14 (0.39 – 0.90)	0.175**
e-GFR NV: 90-120 (ml/dk/1.73m2)	107.0 ± 11.7 (89.0 – 138.0)	113.3 ± 10.4 (99.0 – 135.0)	0.003**
Uric acid NV: 3.5-7.2 (mg/ml)	4.8 ± 1.2 (3.3 – 8.3)	5.1 ± 1.1 (3.8 – 7.2)	0.254*
Sodium NV:136-146 (mmol/L)	137.4 ± 2.9 (132.0 – 142.0)	139.5 ± 2.1 (135.0 –– 142.0)	0.005*
C-Reactive Protein NV: 0-5 (mg/L)	74.5 ± 69.1 (2.5 – 260.0)	5.2 ± 6.9 (2.0 – 34.8)	0.000*
Procalcitonin NV: 0.5 (ng/ml)	0.61 ± 0.78 (0.01 – 2.10)	0.04 ± 0.01 (0.02 – 0.06)	0.000*
D-Dimer NV: 0-500 (ug/L)	1045.0 ± 1383.4 (22.0- 4620.0)	225.6 ± 168.8 (32.0 – 630.0)	0.002*
Ferritin NV: 21.81-274.66 (mcg/L)	432.3 ± 417.5 (15.0 – 1292.0)	99.8 ± 98.6 (10.0 – 442.0)	0.000*
Fibrinogen NV: 200-400 (mg/ml)	463.1 ± 117.8 (290.0 – 720.0)	278.1 ± 52.3 (183.0 – 409.0)	0.000**
Serum Albumin NV: 3.2-4.6 (gr/dl)	37.0 ± 4.6 (30.2 – 46.0)	39.9 ± 8.6 (4.0 – 48.8)	0.006*
Lactate Dehydrogenase (LDH) NV: 0-248 (U/L)	340.7 ± 149.3 (179.0 – 653.0)	180.5 ± 37.7 (118.0 – 271.0)	0.000**

* Wilcoxon Signed Rank Test was used. ** Paired Samples T-Test was used. INR: İnternational normalized ratio

and nephritic proteinuria as TIN due to certain viral infections and drugs[10,11]. In contrast, there have been studies reporting eosinopenia during the active period of the COVID-19 disease[12]. In our study, a significant improvement in the median eosinophil count and ENR was recorded at baseline. Although the pathophysiology of the detected eosinopenia is not fully understood, eosinopoesis inhibition in the bone marrow during the active period of the disease may develop due to eosinophil apoptosis and decreased expression of chemokine receptor/adhesion factors[13,14]. The postmortem autopsy results of 26 recent COVID-19 cases showed virus particles in the proximal tubule epithelium and podocytes, rather than the glomeruli of the kidney. Also, hemosiderin granules were detected in the tubular epithelium of four patients with hematuria detected by the dipstick test. Some patients have been shown to have erythrocyte plugs in their microvascular structures, followed by endothelial damage[4]. All of these patients had high cytokine storm and multi-organ failure. For these reasons, we believe that COVID-19 plays a significant role in the emergence of severe renal findings in postmortem results. However, due to the low viremia potential of COVID-19, renal involvement in mild-moderate patients may result in mild or transient symptoms.

The results of our study showed significant improvement in complete blood counts, kidney function tests, hypoalbuminemia, ferritin levels, infection, and coagulation parameters at the end of the follow-up period ($P<0.05$). According to the evaluations performed using the Spearman correlation coefficient, there was a positive correlation between baseline UPCR and basal ferritin ($r=.0.47$ $p=0.037$), and negative correlation between baseline UPCR and baseline Na ($r=0.45$ $p=0.042$). Under normal conditions, it is known that the majority of sodium and iron filtered from the glomeruli are absorbed from the proximal tubule of the kidney[15]. High expression of ferritin in the proximal epithelial cells was shown in mice study models related to renal iron metabolism[16]. Particularly the iron regulator protein-1 and iron regulator protein-2 (IRP1, IRP2) were shown to be expressed in high amounts in the proximal tubule[17,18]. These proteins regulate the expression of both the heavy (H) and light (L) chains of ferritin, transferrin receptor-1 (TfR1), and multiple other iron proteins. IRPs are cytosolic proteins that sense cytosolic iron levels and bind to RNA stem-loop motifs, which are found in the mRNA transcripts of iron metabolism genes. The IRP1 dysregulation causes hypoxia in the proximal tubule, while the IRP2 dysregulation causes tissue iron metabolism degradation and ferritin elevation[16,19]. COVID-19 may have caused more damage to the proximal tubule, thus causing deterioration in the reabsorption mechanisms of sodium and ferritin. As a result, excessively high acute-phase reactants during the active phase

of the disease decrease in sodium and eGFR values, and subsequent spontaneous remission may be due to reversible damage of the proximal tubule caused by the viral load (Table-3).

The main limitation of our study was the small sample size of participants. Moreover, we were unable to assess eosinophiluria as it could not be measured at the beginning. The histopathological examination could not be performed because of the lack of indications of kidney biopsy. We did not perform a renal biopsy in our patients, nor did we demonstrate the virus directly within the renal tubule cells in the renal tissue, nor were we able to show the immune response-related damage due to the virus.

In conclusion, the incidence of nephritic urine findings due to COVID-19 is low. Perhaps, the proteinuria and hematuria detected may be related to fever and systemic inflammatory associated with COVID-19 in the early stages. The recovery of symptoms and of renal involvement can confirm these results. We believe that renal involvement from COVID-19 needs to be verified with advanced biomarker and immunohistochemical studies.

Author's Contribuitions

Dheir H. and Karabay O. conceived the presented idea. Dheir H. Yaylaci S., Genc A.C., and Genc Turkoglu F. developed the theory and conducted the computations. Genc A.B., Guclu E., Muratdagi G., and Toptan H. verified the analytical methods. Dheir H and Sipahi S supervised the findings of this work. All authors discussed the results and contributed to the final manuscript

RESUMO

INTRODUÇÃO: *Este estudo tem como objetivo determinar a incidência da síndrome nefrítica de novo (SN) em pacientes com COVID-19 e identificar os fatores associados.*

MÉTODOS: *Todos os pacientes da enfermaria com pneumonia por COVID-19 foram investigados. Após a determinação dos critérios de inclusão e exclusão, a população do estudo foi identificada. Foram realizadas medições do teste da vareta da urina e da razão da creatinina das proteínas na urina (UPCR).*

RESULTADOS: *Este estudo transversal descritivo foi realizado com 21 pacientes com COVID-19. A idade média dos pacientes foi de 42,2±8,8 anos e 71,4% dos pacientes eram do sexo masculino. A duração média do seguimento foi de 28,4±9,3 dias. O teste de RT-PCR na urina foi positivo em um paciente (4,8%). Houve melhorias observadas na hematúria em 71,4% e na proteinúria em 85,7% no final do acompanhamento. E uma diminuição significativa na UPCR medida em comparação à linha de base (p=0,000). Além disso, foram registradas melhorias nas contagens sanguíneas completas, nos parâmetros inflamatórios, nos testes de ferritina e de coagulação, comparados aos valores basais. Houve correlação positiva entre UPCR basal e ferritina, e correlação negativa entre os valores basais de UPCR e sódio.*

CONCLUSÃO: *A síndrome nefrítica de novo induzida por COVID-19 pode ocorrer principalmente devido ao envolvimento túbulo-intersticial e frequentemente resulta em remissão espontânea. No entanto, a questão de por que esses achados não se apresentaram em todos os pacientes que não apresentavam condição comórbida não é clara.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Hematúria. Proteinúria. Lesão renal aguda. Nefrite.*

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