



Original Article

Extreme Hypertension Associated with SARS-COVID-19 Infection in Pediatrics with Kidney Disease: A Retrospective Observational Study

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ARTICLE INFO

Article history

Receive: 2022-05-23

Received in revised: 2022-06-12

Accepted: 2022-07-29

Manuscript ID: JMCS-2205-1514

Checked for Plagiarism: Yes

Language Editor:

Dr. Fatimah Ramezani

Editor who approved publication:

Dr. Majid Darroudi

DOI:10.26655/JMCHMSCI.2023.1.10

KEYWORDS

COVID-19

Hypertension

Kidney Failure

Chronic

Nephrotic syndrome

Pediatric

ABSTRACT

Introduction: There are no reports of hypertensive emergency as a manifestation or comorbidity of the COVID-19 infection in pediatric patients.

Method: In this retrospective observational study, we report patients diagnosed with COVID-19 with presentation of acute severe hypertension from March to February, 2021. Confirmed cases were defined by positive reverse transcription-polymerase chain reaction (RT-PCR) of nasopharynx swab, elevated antibody against, or imaging pattern in favor of it on chest CT-scan. Hypertensive crisis was elucidated by the acute rise of blood pressure more than stage 2 cut off with the potential risk of end-organ damage.

Results: Six confirmed SARS-CoV-2 patients with an average age of 4.2 years old were described. Four patients with recently diagnosed nephrotic syndrome and two with chronic kidney disease who were on orderly dialysis were enrolled without clinical signs of liquid accumulation. The lowest and highest systolic and diastolic blood pressures all along hospitalization was 160-200 mmHg and 100-155 mmHg, respectively. All children had poorly controlled hypertension, managed with Labetalol infusion titrated to maximum dosage, extended for at most seven days, and their blood pressure had been regulated with four or five antihypertensive drugs.

Conclusion: It is crucial to consider the COVID-19 diagnosis in a patient displaying a hypertension crisis, even in the absence of classic signs of the virus. We recommend that medical practitioners consider the probability of COVID-19 infection in cases presenting to the hospital with acute severe hypertension.

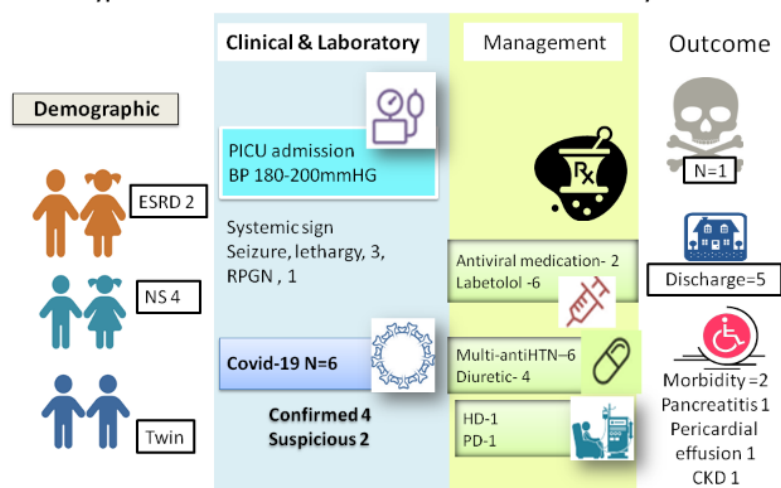
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GRAPHICAL ABSTRACT

Hypertension crisis in COVID-19-infected children with kidney disease



Conclusion: It is crucial to consider the diagnosis of COVID-19 in a patient presenting with a hypertension crisis, even in the absence of classic signs of the virus.

Introduction

At the beginning of the pandemic of Severe Acute Respiratory Syndrome Coronavirus 19 (SARS-COVID19), there was very limited information on the clinical features and the disease course in infants. Children aged less than 10 years old consists less than 1% of novel COVID-19, while 16% were asymptomatic, none of the symptomatic cases revealed kidney manifestation [1]. In a recent systematic review and meta-analysis of 42 studies, Tsankov *et al.* addressed that youngsters' indexes with underlying disease and obesity are at a larger harm for more severe infection and mortality with 1.79 and 2.8 relative risk ratio, respectively. Severe COVID-19 was detected in 5% of children with comorbidity and 0.2% without comorbidity [2]. As one of the comorbid conditions, chronic kidney disease (CKD) is associated with a greater danger for disease severity [3]. Since patients with chronic kidney conditions, especially those on hemodialysis, require more hospital visits, they tend to be at a greater risk for acquiring the virus through contacts with infected people. It was reported that pre-existing hypertension as a comorbid condition for older patients with COVID-19 infection [4]. A study of COVID-19 patients admitted during outbreaks in a city of Iran, hypertension was a comorbidity that had no impact on hospitalization course [5]. Even hypertensive cases presented with GI symptoms

of COVID-19 had a similar course of hospitalization and the outcome [6]. Recently, it was reported a single kidney adult patients who had COVID-19 had a normal renal function after a team working in his management [7]. However, based on our information, there is no record of *hypertension crisis* as comorbidity or a presentation sign of COVID-19 infection. Here, we reported six pediatric patients with renal diseases presenting with hypertension crisis that had tested positive for COVID-19 or had the infection evidence on Chest Computed Tomography (CT) imaging.

Materials and Methods

In a retrospective observational study, the pediatric cases with 2019 Novel Coronavirus infection and severe hypertension admitted to a pediatric intensive care unit from March 2020 to February 2021 were enrolled in this case series. Verified subjects were characterized by one or more of the following: a positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test from nasopharynx daub sample, serological examinations by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, and chest CT scan findings in favor of the infection. In doubt individuals were diagnosed by impersonal clues (pyrexia, dysentery, and hack) and diagnostic techniques (leukocytopenia, lymphopenia, elevated C-reactive protein, d-

dimer, lactate dehydrogenase, cardiac markers, Ferritin, or alanine transaminase, with no growth of any bacteria) and an intimate exposure with a contaminated person [8,9]. Hypertensive crisis was annotated by a sudden upsurge of blood pressure (BP) higher than stage 2 stoppage with the capacity hazard of end-organ damage [10].

For dichotomous and continuous variables, frequency and mean (standard deviation) were calculated by using IBM SPSS software.

Results

Six patients with definite diagnosis of SARS-CoV-2, were enrolled who referred with hypertensive

crisis. The age of patients was 4.1 years old in average (in the rage of 1-12). Table 1 indicates the clinical features of the study subjects. Recently diagnosed nephrotic children who were on prednisolone (2 mg/kg/day), experienced a brisk rise in blood pressure. The remaining two sufferers were endured from stage 5 chronic kidney diseases (CKD-5) that were on consistent hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) with no edema or signs of fluid overload.

Table 1: Pathological conditions, signs, and symptoms

Clinical features, patients ID	1	2	3	4	5	6
Age (y)	3	3	12	1	3	3
Sex	Female	Male	Male	Female	Male	Male
Underlying condition	Carnitine palmitoyltransferase 2 (CPT2) deficiency and End-stage renal disease	Nephrotic Syndrome	End-stage renal disease	Nephrotic Syndrome	Nephrotic Syndrome IDENTICAL TWINS patient 6	Nephrotic Syndrome
Max BP on admission (mmHg)	200/120	170/100	200/155	200/115	200/130	200/110
History of close-contact with COVID-19 patients	+ (three weeks prior to admission)	+ (two weeks prior to admission)	-	+ (roommate in local hospital))	+ (two week prior to admission)	+ (two week prior to admission)
Presentation signs and symptoms	Tonic-colonic Seizure Need Mechanical Ventilation	Generalized edema, Fever, Gross hematuria	Fever, Respiratory distress, Dyspnea	-	Fever, Diarrhea Apnea Need Mechanical Ventilation	Tonic-colonic seizure Apnea Need Mechanical Ventilation
Imaging studies (Figure 2)	Brain MRI: Normal Chest X-ray: Evidence of pulmonary edema	Chest CT scan: small subpleural ground-glass patches supportive of SARS-COVID-19	Chest CT scan : patchy peripheral consolidations agreeable to COVID-19	Chest CT scan: mild ground-glass opacities possible COVID-19	Chest CT scan: Ground-glass opacifications in favor of COVID-19	Brain MRI: in favor of PRES syndrome Chest CT scan: Ground glass opacifications in favor of COVID-19
COVID-19 confirmatory tests PCR Anti-SARS-CoV-2 IgM /IgG (EIA) IL6	Neg 5.2 / Neg 10	Neg 1.32/Neg UA	Positive UA 200	Neg 1.36 / 3.44 UA	Neg NI/NI UA_	Neg 0.94/NI UA
Extra-pulmonary Complications	Fluctuations in Consciousness, Multi-organ dysfunction	AGN with low C3 Renal biopsy FSGS	Pericardial effusion, Pancreatitis, and chronic Diarrhea	Chronic kidney Disease	None	None
Outcome	Death	Discharge	Discharge	Discharge	Discharge	Discharge

Initially, the lowest and highest systolic BP during hospitalization was 160 mmHg and 200 mmHg,

respectively. The diastolic BPs were between 100-155 mmHg. Five out of six patients had close-

contacts with COVID-19 cases. The BPs of all patients were normal or being in control prior to entrance. Three patients presented with fever, two out of whom experienced other COVID-19 symptoms, such as respiratory distress and diarrhea. The remaining three cases presented

with acute severe hypertension without any fever, respiratory, or gastrointestinal symptoms. Table 2 depicts laboratory data and Figure 1 represented the abnormal CT scan of the lung of the index cases in favor of COVID-19.

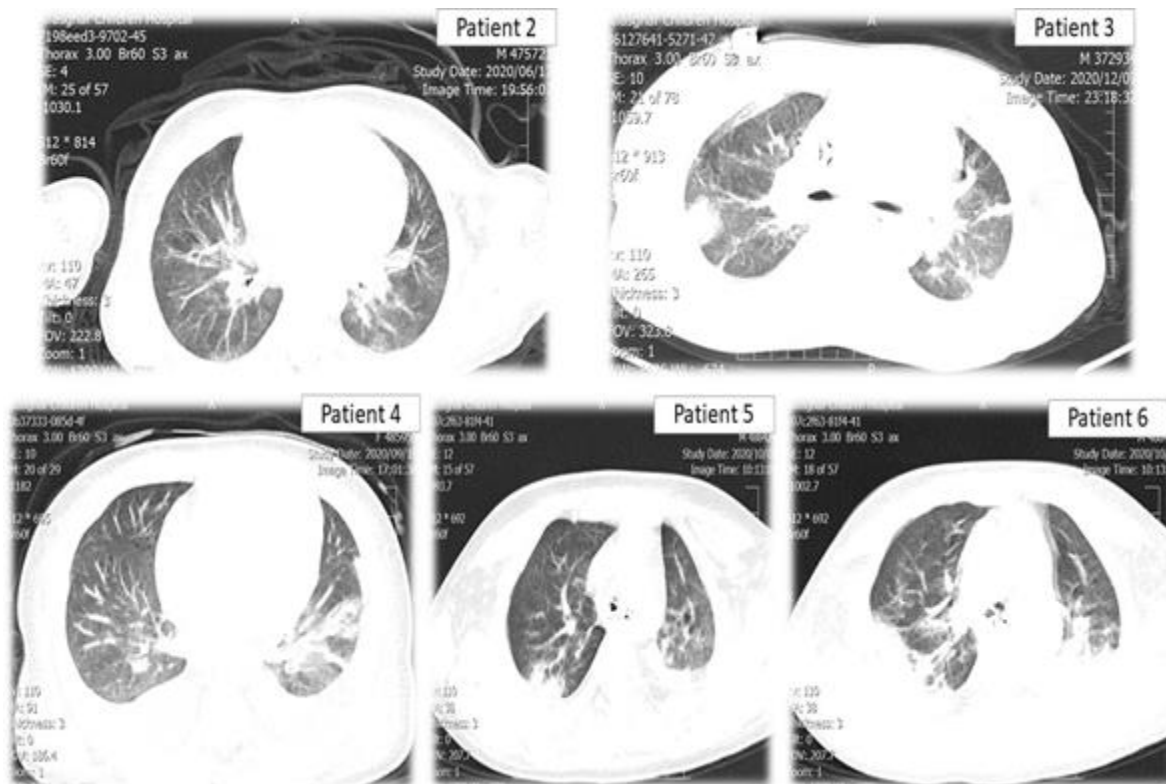


Figure 1: Abnormal Pulmonary CT scan of the patients in favor of SARS-COV19 (details are available in Table 1)

Table 2: Summary of the lab tests of the cases during hospitalization

Laboratory tests	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
White blood cell count, $\times 10^9/L$	18.1	22.1	22.8	8.1	13.3	16.0
Lymphocyte, %	8	22	35	30	28	22
Hemoglobin, g/dl	9.1	8.3	9.0	7.5	13.6	12.3
Platelet, $\times 10^9/L$	254	898	90	509	641 > 110	671 > 102
C-reactive protein, mg/L	108	5	115	7	12	31
Ferritin ng/ml (nl:140)	3064	442	1050	40	151	68
D-dimer $\mu g/ml (<2)$	4.5	2	2.55	1.5	2.5	6
Alanine aminotransferase, U/L	18	20	25	10	27	30
Max Creatinine, mg/dl	4.6	5	2.6	1.8	0.4	0.5
LDH(IU)	1605	1076	727	UA	900	917

Infusion of labetalol was started for all admitted cases. The dosage was adjusted to approximately maximum while continued for not less than one week as required. Subsequently due to inadequate clinical response, oral anti-hypertensive drugs of various categories were added (Table 3). Furthermore, one of them, being on CAPD, expired following loss of consciousness and multi-organ

dysfunction. The other was HD patient intricate with pericardial effusion, pancreatitis, and chronic dysentery. All nephrotic syndrome patients, being resistant to steroid, went on renal biopsy, and eventually treated with calcineurin inhibitor for massive proteinuria. All reported cases had resistant hypertension, required more than four antihypertensive medications to reduce BP-level.

Table 3: Administered anti-hypertensive and antiviral medications during hospitalization

Patients ID	1	2	3	4	5	6
Labetalol infusion Maximum dosage	+ 3 mg/kg/h	+ 2.5 mg/kg/h	+ 2.5 mg/kg/h	+ 3 mg/kg/h	+ 2.5 mg/kg/h	+ 2.5 mg/kg/h
Antihypertensive, oral	Enalapril Losartan Metoprolol Amlodipin Hydralazin Terazocin	Enalapril Amlodipin Hydralazin Terazocin	Losartan Metoprolol Amlodipin Terazocin Clonidin	Enalapril Losartan Metoprolol Amlodipin Prazocin	Enalapril Losartan Amlodipin	Enalapril Metoprolol Amlodipin
Diuretic	-	Furosemide hydrochlorot hiazide	-	Furosemide	Furosemide	Furosemide
Anti-microbial and COVID-19 treatment	Ceftriaxone, Vancomycin IVIG x3days Lopinavir/Rito navirx 5days	None	Meropenem, piperacillin- Tazobactam, Teicoplanin, Remdesivir x5days	Hydroxychlor oquine	Meropenem, Teicoplanin	Ceftriaxone

Discussion

In this study, we have reported six pediatric cases, presented to the hospital with hypertension crisis, without signs of fluid overload and mostly without any classic symptoms of COVID-19, who tested positive for the virus or had evidence of the infection on chest CT imaging. Based on published articles in adult-related study, hypertension has been recognized as one of the paramount prevalent comorbidities in Coronavirus Disease-19 [4,10]. However to this date, there is by no means detailed of *hypertension crisis* as a presenting sign, or comorbid condition of the infection, and it is crucial to consider this diagnosis in a patient presenting with a *severe* rise in blood pressure even in the absence of classic signs of the virus. The importance of this consideration is the initiation of the proper isolation of the patient in the hospital so that other patients who have been admitted for non-

infectious causes are kept safe from catching the virus.

Sahraei *et al.* reported that the frequency of comorbidity of hypertension were similar (about 26-28 %) among COVID-19 patients regardless of gastrointestinal symptoms (n=56), 1694 with GI symptoms (n=1694), of GI with other symptoms (n=766) [6]. Raofi *et al.* presented a 43- years old case with single kidney admitted for COVID-19 who had acute kidney injury stage one and mild hypertension (BP=145/85mmHG) the first day of hospitalization that normalized the following days of management [7].

In a review by Pousa *et al.* [11], renal and cardiovascular complications were the second and the third most prevalent manifestations of 2019-nCoV Infection in infants, respectively. From renal manifestations, acute kidney injury, uremia, and hematuria were the most frequent drawbacks of this infection in youngsters. Hypotension, shock, and tachycardia were a number of the

cardiovascular features of the disease. Three of our cases presented with hypertension crisis without any other symptoms of viral infection and surprisingly diagnosed with COVID-19 during the laboratory workup or CT scan. Sardu *et al.* found that there might be a cause and effect correlation between hypertension and COVID-19 infection [12]. However, regardless the virus as-it-is can give rise to aggravate hypertension or not, is unknown so far, and more comprehensive studies are needed to identify this correlation. An adult study by Wei *et al.* showed a more severe COVID-19 disease course in patients with hypertension. However, hypertension on admission did not increase the risk for severe disease independently [4]. None of the studies of adult setting with first or recurrent of COVID-19 infection in Iran had a hypertensive crisis presentation and that make our study unique and novel [13,14]. Most of our patients had not developed severe COVID-19 symptoms, and the reason for their admission was hypertension crisis, and after controlling the blood pressure, they were discharged from the hospital, except for one patient who developed encephalopathy and multi-organ dysfunction and unfortunately passed away.

Conclusion

In conclusion, we recommend the medical practitioners to consider the probability of COVID-19 infection in cases presenting to the hospital with hypertension crisis, especially those with controlled blood pressure followed by this acute presentation, and to maintain proper testing and isolation to protect other patients from the disease.

Acknowledgment

The abstract of this article has been presented as poster in 53rd ESPN annual meeting held in Amsterdam, the Netherlands on September 2021.

Funding

This research did not receive any specific grant from fundig agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

Authors declared that none of them has any conflicts of interest related to this submission.

Declaration

Ethics Approval and Consent to Participate

The ID of all participants remained anonymous, while the consents were obtained from the parents. Meanwhile, this study was adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Hospital (IR.IUMS.AACH2022.20303).

Data Availability

The datasets used in the current study are presented in details and showed in tables 1-3.

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HOW TO CITE THIS ARTICLE

Masoud Hashemzadeh Esfahani, Behzad Haghghi Aski, Ali Manafi Anari, Golnaz Gharehbaghi, Maryam Sakhaei, Eslam Shorafa, Nakysa Hooman, Extreme Hypertension Associated with SARS-COVID-19 Infection in Pediatrics with Kidney Disease: A Retrospective Observational Study. *J. Med. Chem. Sci.*, 2023, 6(1) 79-85

<https://doi.org/10.26655/JMCHEMSCI.2023.1.10>

URL: http://www.jmchemsci.com/article_154288.html