CASE REPORT

Intracerebral Hemorrhage in a Child with Renal Artery Stenosis and COVID-19

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ABSTRACT

Pediatric intracerebral hemorrhage is a rare condition among children. We discuss the case of a 7-year-old Filipino male with generalized tonic seizures and diagnosed to have both SARS-CoV-2 infection and hypertension secondary to renal arterial stenosis. The occurrence of intracerebral hemorrhage in children, though commonly caused by arteriovenous malformations, may be secondary to an acute hypertensive episode. In this case, the presence of COVID-19 in the patient may have been contributory to the development of spontaneous intracerebral hemorrhage due to its direct endothelial effects, as well as its dysregulatory action on the renin-angiotensin-aldosterone system.

Keywords: pediatric intracerebral hemorrhage, COVID-19, hypertensive emergency, renal artery stenosis

INTRODUCTION

Pediatric intracranial hemorrhage (pICH) is a rare condition that occurs primarily in the early neonatal period, manifesting as a parenchymal bleed with or without intraventricular extension.[1] Depending on the patient's age group, pICH will have varying etiologies and predisposing conditions, as well as a predilection for certain anatomic areas of the brain and their resulting symptomatology.[2]

Recently, multiple case reports have associated SARS-CoV-2 infection with cerebrovascular bleed among adult patients.[3] Limited reports have described pediatric COVID-19 patients developing pICH, and a growing interest on the topic has arisen due to the lack of evidence allowing children to be vaccinated against the virus.

This article aims to present a case of intracerebral hemorrhage in a 7-year-old Filipino male who had no cerebrovascular malformation but presented with hypertension and was subsequently diagnosed to have both right renal arterial stenosis and SARS-CoV-2 infection, and to trace the pathophysiology of pICH in relation to this case.

CASE PRESENTATION

This is a report of a 7-year-old Filipino boy who was previously well and developmentally at par. He was admitted to our institution due to generalized tonic seizures.

One week prior to admission, the patient began to complain of severe throbbing frontal headaches, temporarily lysed by oral Paracetamol, but was followed eight hours later by two episodes of generalized tonic convulsions. The tonic convulsions were noted to last less than 30 seconds,

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with one-minute intervals. This episode was followed by generalized malaise, increased sleeping time, and decreased appetite. He was brought to a primary hospital and was advised admission however, due to financial constraints, his parents opted to observe for recurrence at home. The patient continued to have milder headaches, with temporary relief after giving oral Paracetamol.

Five days prior to admission, the patient was noted to have four episodes of seizures, with post-ictal symptoms of moderate throbbing frontoparietal headache, decreased appetite, and increased sleepiness, now accompanied by blurring of vision and irritability. This prompted consultation at a tertiary hospital, where he was found to be tachycardic (pulse rate of 199 beats per minute), tachypneic (respiratory rate of 25 breaths per minute), and hypertensive for age (blood pressure of 130/90 mmHg). He was afebrile (temperature of 37.3 degrees Celsius) and O_2 saturation was 99% at room air. Baseline diagnostics showed a normal blood count, hyponatremia of 127 mmol/L, and hypokalemia of 3.2 mmol/L. Chest radiography showed pneumonia, prompting SARS-CoV-2 nasopharyngeal swab RT-PCR, which turned out positive, and subsequent admission to the hospital's COVID Isolation Unit. Persistent throbbing frontoparietal headache and one episode of generalized tonic convulsions, responsive to IV Diazepam, was noted, but no recurrence of hypertension was recorded. A non-contrast head CT scan was done on the first day of admission, showing intraparenchymal hemorrhage in the right parietal lobe measuring 2.4 x 1.3 x 2.4 cm (3.8 cc) with perilesional edema, and minimal subarachnoid hemorrhage along right parietal lobe (Figure 1). Intravenous Mannitol was started at 1.2 cc/kg every 8 hours, with minimal relief of headache and no recurrence of seizures. Due to the patient's COVID-19 positive status, transfer to a COVID-19 specialty referral center was coordinated, hence his subsequent admission to our institution on his 5th hospital day.

The patient was received at the emergency admitting section still with complaints of on-and-off frontal headache but without recurrence of seizures. Vital signs were significant for elevated blood pressure of 151/116 at the left upper limb, and tachycardia of 117 beats per minute. Neurologic examination was significant for blurring of vision corresponding to visual acuity of counting fingers with no visual field cuts, and left hemiplegia with a grade motor power of 4/5 on the left upper and lower extremities. Fundoscopy revealed bilaterally edematous disc margins with no retinal hemorrhages. He was managed as a case of hypertensive emergency; hence, Mannitol was increased to 5 cc/kg given every 4 hours, and Levetiracetam syrup was started for seizure prophylaxis, delivering 23 mkday. Initial hematology and biochemistry studies showed no significant abnormalities (Table 1).

Cranial CT-Angiography and CT-Venogram showed interval decrease in the amount and attenuation of the previously detected parenchymal hemorrhage in the cortical-subcortical regions of the right high parietal lobe, with normal vasculature. Mannitol was therefore discontinued, and the patient was referred to the Nephrology service. Nicardipine drip was started with good clinical response. Blood pressures were maintained within acceptable range, and then he was started on oral Amlodipine, Enalapril, and Carvedilol as maintenance medications while tapering the intravenous Nicardipine drip in the wards. On renovascular work-up, an abdominal aortogram was done revealing right renal artery stenosis, with a larger left kidney for age, likely compensatory in nature (Figure 2).

With stable blood pressure trends, improvement in the patient's motor strength and vision were recorded. The previously weaker left side was noted to resolve, while vision was gradually corrected. Continuous improvement was noted from then, with no recurrences of fever, seizures, and headache. He was discharged on the 14th day of admission after completing antibiotic therapy for nosocomial sepsis. He was ambulatory, with normal blood pressure of 100/60, and with visual acuity of 20/50 for both eyes with no visual field cuts. He was sent on COVID home quarantine as advised.

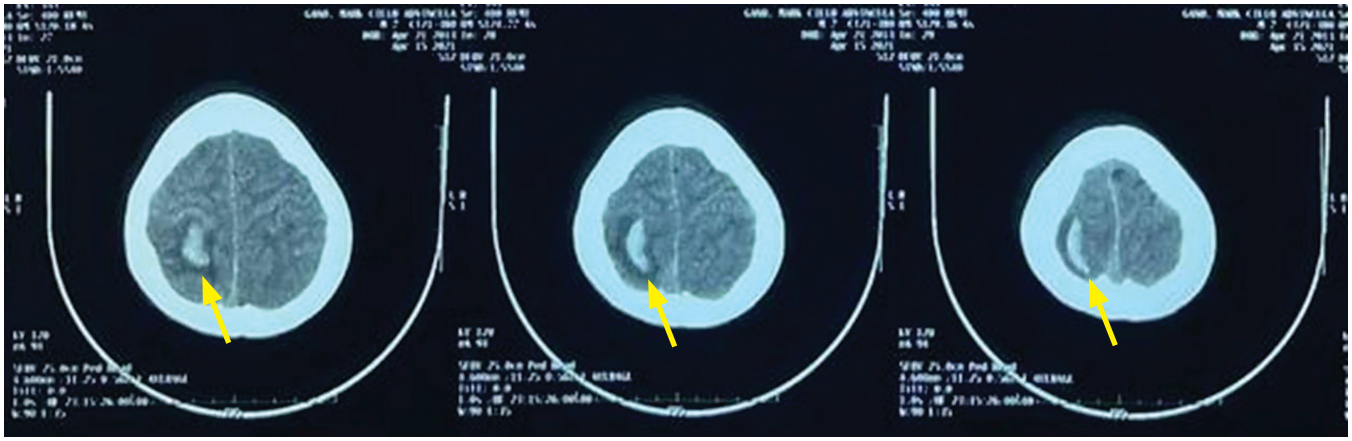

Figure 1. ***Head Computed Tomography (CT scan) of this case.*** Showing intraparenchymal hemorrhage *(arrows)* in the right parietal lobe with perilesional edema, and minimal subarachnoid hemorrhage along the right parietal lobe.

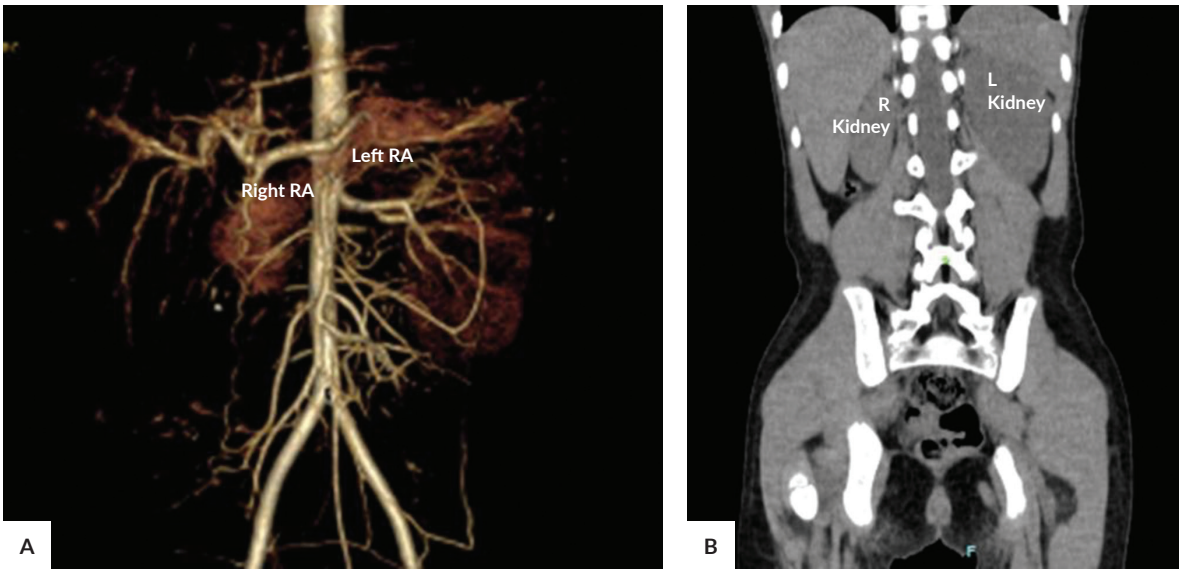

Figure 2. ***Abdominal Computed Tomography (CT scan) of this case.*** **(A)** Showing a generalized decrease in the caliber of the right renal artery relative to the left, most prominent in its ostial and proximal segments. The narrowest diameter of 1.4 mm (left renal artery: 3.1 mm). **(B)** The right kidney is small, measuring approximately 6.08 x 2.55 x 2.35 cm (Normal CC for age: 7.09 - 8.09 cm), while left kidney is large for age, measuring 9.99 x 4.33 x 4.83 cm (Normal CC for age 7.59 - 8.49 cm).

Table 1. Laboratory and Diagnostic Studies

	Reference Range	Result
Hematology		
Hemoglobin	135 – 180 g/L	121
Hematocrit	0.4 – 0.54	0.36
WBC	4.5 – 11 x10^{12}/L	14.2
Neutrophil	0.5 – 0.70	0.85
Platelet	150,000 – 450,000	468,000
Blood Chemistry		
BUN	3.2 – 7.1 mmol/L	4.8
Creatinine	46 – 92 umol/L	37
Serum Sodium	135 – 145 mmol/L	135
Serum Potassium	3.5 – 5 mmol/L	4.3
Serum Calcium	2.1 – 2.55 mmol/L	2.39
Coagulation Tests		
PT	11.4 – 13.9 secs	12.6
APTT	25.8 – 35 secs	29.8
D-Dimer	0 – 0.50 ug/mL	0.29
Protein C	70 – 130 IU/dL	143
Protein S	93 – 126 U/dL	77
Anti-thrombin III	83 – 128%	87.5
Fibrinogen	200 – 400 g/L	383
Acute Phase Reactants		
Procalcitonin	<0.25 ng/mL	0.05
ASO Titer	170 – 330 Todd units/mL	<200
Others		
ABG	Normal acid base balance	
2D Echo	Good LV contractility with an Ejection Fraction of 66%; Normal chamber dimensions. No valvular regurgitations seen. No pericardial effusion seen.	

DISCUSSION

The case presents the clinical picture of a 7-year-old Filipino male who initially presented with seizures and was noted to have elevated blood pressure on admission, subsequently diagnosed to have intracerebral hemorrhage and COVID-19 infection, with findings of right renal arterial stenosis on work-up.

Intracranial hemorrhage in children is a rare condition, with possible sequelae of chronic disability or even death in severe cases.[4] In a study done by Kumar and colleagues, spontaneous pICH was mainly due to arteriovenous malformations, occasionally due to brain tumor bleed, and rarely due to hypertension.[2] Awada et al., on the other hand, noted hypertension in 6.6% of patients with non-traumatic intracranial hemorrhage.[5] This was the same conclusion made by Kupferman et al., who found a prevalence of 3.4% to 10% among the pICH patients he included in this systematic review.[6] Location of pICH was found to be supratentorial in up to 77.5% of cases, with the most common locations noted as lobar in 68.7%, followed by thalamic in 18.1%, and ganglionic in 13.2%.[7] In the case presented, the pICH was lobar, which is consistent with the majority data from literature.

The American Academy of Pediatrics defines hypertension in children between 1 and 13 years old "as a BP equal to or greater than the 90th percentile to less than the 95th percentile or between 120/80 mmHg and less than the 95th percentile.[8] Causes of hypertension in children may be divided into two categories: primary hypertension

where no cause is identified while secondary hypertension is linked to an underlying etiology. Causes of secondary hypertension have been divided into renal, endocrine, neurologic, psychologic, pharmacologic, vascular, and other causes.[9] In the case presented, hypertension was thought to be secondary to the noted right renal arterial stenosis. Hypertension due to renovascular disease has been attributed to the activation of the renin-angiotensin-aldosterone system (RAAS) secondary to decreased renal blood flow from stenosis.[10] Stage 2 hypertension is a frank manifestation of renal vascular disease in children, which is consistent with the admitting presentation in our case.[11]

Aside from hypertension, the case presents another possible mechanism for development of pICH, which is the existing SARS-CoV-2 infection. Less than two years into the COVID-19 pandemic, multiple authors have reported on COVID-19 patients presenting with neurologic manifestations secondary to intracerebral hemorrhage in the general population.[12] A meta-analysis by Margos et al. showed the prevalence of ICH in hospitalized COVID-19 patients to be around 0.25%, with around 75.5% of these ICH cases being primary ICH.[13] A preponderance of elderly males with mean age of 59 to 67.4 years old was noted among all studies surveyed, and history of hypertension was present in 52% of recorded cases.[13] Corollary to this, about 48% of ICH cases in hospitalized COVID-19 cases have no known history of any hypertension, which may support a hypothesis of primary causation by COVID-19. In a cross-sectional analysis of 282,718 patients hospitalized for COVID-19 in the United States, the incidence of ICH was 0.2%, which is similar to that of the previously mentioned meta-analysis, with the same gender and age preponderance.[14] There is a paucity of data regarding the location of ICH in COVID-19 patients, more so in pediatric cases. Due to the relative novelty of the disease, the question of causality versus coincidence still arises. However, elucidation of the role of angiotensin-converting enzyme 2 (ACE2) receptor in viral entry, and the resulting RAAS dysregulation, direct vascular endothelial dysfunction, and decreased Angiotensin (1-7) [Ang(1-7)] contributes merit to the hypothesis of a causative or contributory role for SARS-CoV-2 infection in the development of intracerebral hemorrhage.[12,15] Specifically, binding of the SARS-CoV-2 spike protein to the ACE2 receptor leads to a cascade of events resulting in viral entry and replication, lymphopenia secondary to decreased lymphopoiesis, and increased lymphocyte apoptosis, disruption of the epithelial-endothelial barrier, an exaggerated immune response, and consumptive coagulopathy.[3] Decreased Ang (1-7) also impairs its signaling to the Mas receptor, which leads in turn to impaired vasodilatation, possibly producing a generalized hypertensive effect.[3]

Mechanisms of pICH development in this case, therefore may be both directly and indirectly related to SARS-CoV-2 infection, in that the hypothesized ACE2 receptor-mediated cerebrovascular endothelial dysfunction may directly cause intracerebral hemorrhage, and also cause a decrease in the production of Ang (1-7) which causes a defective activation of the Mas receptor, which blocks its vasodilatory, neuroprotective, and antifibrinolytic actions, leading to further exacerbation of the patient's pre-existing hypertension secondary to the right renal arterial stenosis.[12] As of this writing, no studies have yet been published which describe new-onset hypertension in COVID-19 patients or blood pressure patterns of either hospitalized or home isolated COVID-19 cases.

CONCLUSION

Spontaneous intracerebral hemorrhage in pediatric patients is a rare condition. The case of a 7-year-old Filipino SARS-CoV-2 positive male presenting with new-onset headache and seizures due to pICH and hypertension secondary to renal artery stenosis was presented. The pathophysiology for increased risk for pICH in COVID-19 infection with renovascular hypertension is multifactorial but could be influenced by the ACE2-mediated RAAS dysregulation secondary to binding of the SARS-CoV-2 spike protein. Correct and prompt identification of COVID-19 and comorbid conditions in pediatric patients may lead to better risk stratification, monitoring, prevention, and management of pICH in these patients.

Ethical Considerations

Informed consent was obtained from the patient's mother prior to using the case for the purpose of this study.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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