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# Pontocerebellar venous infarction caused by COVID-19 in a 13-year-old girl with underlying asymptomatic developmental venous anomaly

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ABSTRACT

*Introduction:* COVID-19-associated coagulopathy (CAC) presents as a highly activated thrombotic status, leading to severe clinical outcomes. We report a unique pediatric case of pontocerebellar venous infarction caused by COVID-19 (omicron mutation) and accompanied by abnormal brain venous structure.

*Case:* A 13-year-old unvaccinated girl with high-grade fever and altered mental status visited our emergency department. In her initial serologic results, all the inflammatory markers were elevated; interleukin-6 was remarkably elevated (above 5000 pg/mL). On brain CT, a suspicious subtle hypo-attenuated lesion in the right interior cerebellar hemisphere area was observed; brain MRI revealed bilateral asymmetric hyperintense lesions in the mid-pons, and extensive cerebellar hemorrhage and engorged venous structure. Despite intensive medications and treatments, the patient failed to maintain her vital signs with a mechanical ventilator because of aggravated pneumonia and bilateral pleural effusion, and she died ten days after her hospital admission.

*Conclusion:* In our patient, a rapid systemic cytokine storm reaction occurred, and presumably, the resulting inflammation sequentially caused the coagulopathy cascade. One of the significant risk factors was an asymptomatic developmental venous anomaly (DVA) of the cerebellum. The asymptomatic DVA concomitant with COVID-19 may be associated with thrombosis and needs further brain imaging studies.

## Introduction

Coagulopathy is highly observed in patients with COVID-19, it is one of the critical manifestations and can rapidly progress to severe illness or fatality (Awad et al., 1993). In particular, incidence of cerebrovascular stroke in patients with COVID-19 increased approximately 7.6 times more than in those affected by influenza (Fotuhi et al., 2020). A previous study of an animal model with coronavirus showed that the urokinase pathway regulates the severity in knockout mice (Glass et al., 2004). The mechanisms of COVID-19-associated coagulopathy (CAC) still remain to be elucidated, however, a specultaive pathophysiology theory suggests that the cytokine surge during COVID-19 may damage endothelium and secondarily activate fibrin-mediated coagulation pathway (Griffiths et al., 2013). Various neurological manifestations were reported to be associated with COVID-19 (Iba et al., 2020), an cases of vascular infarction in children have resulted in severe clinical outcomes (Jensen et al., 2021).

We report the case of a 13-year-old girl that tested positive for COVID-19 (omicron mutation) with suspicion of an undetected cerebellar venous anomaly who developed pontocerebellar venous infarction.

## Case

A 13-year-old unvaccinated girl with no prior medical history presented to our emergency department with a high-grade fever (40 °C) and altered mental status. Her mother, who lived with her, was diagnosed with COVID-19 without any symptoms one day earlier. On initial physical examination, her Glasgow Coma Scale was 11 (E4/M4/V3), blood pressure was 90/50 mmHg, heart rate was 180 beats/minute, and respiration rate was 20 breaths/minute. The presence of SARS-CoV-2 viral nucleic acid in the nasopharyngeal swab was confirmed by using real-time reverse-transcriptase polymerase chain reaction (PCR). Her initial serologic results were as follows: (i) white blood cell count: 5110/$\mu$L; (ii) platelet count: 168 × 103 /$\mu$L; (iii) C-reactive protein: 11.7 mg/L (0–5); (iv) procalcitonin: 1.55 ng/mL (0–0.05); (v) D-dimer: 13.67 $\mu$g/mL (0–0.5). Specifically, interleukin-6 was elevated well above 5000 pg/mL (normal range in blood, 0–7.0).

Although her high-grade fever subsided owing to intravenous administration of antipyretics, her mental status remained altered and inappropriate for stimulation. The initial brain computed tomography (CT) scan

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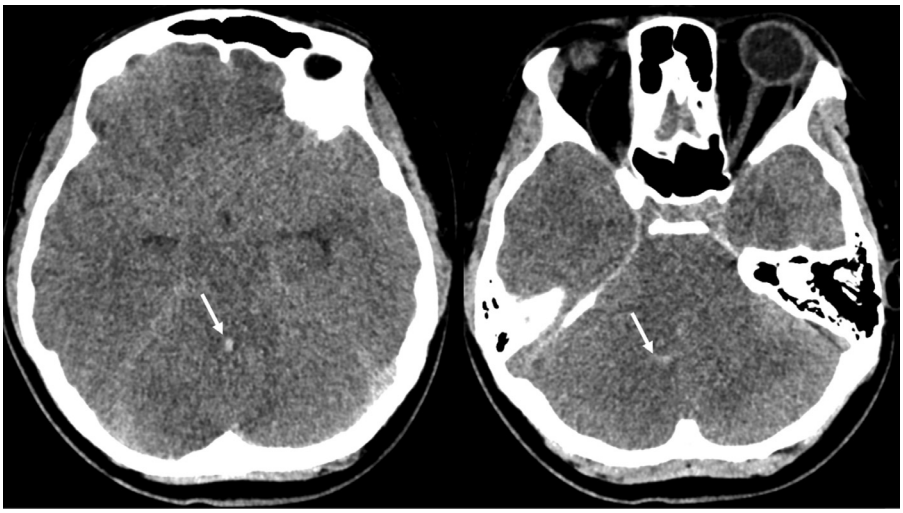

**Fig. 1.** Brain computed tomography scan of the patient.
Abnormal linear hyperdensity in the median cerebellum, extending to the right paramedian cerebellar hemisphere, suggesting thrombosed vessels.

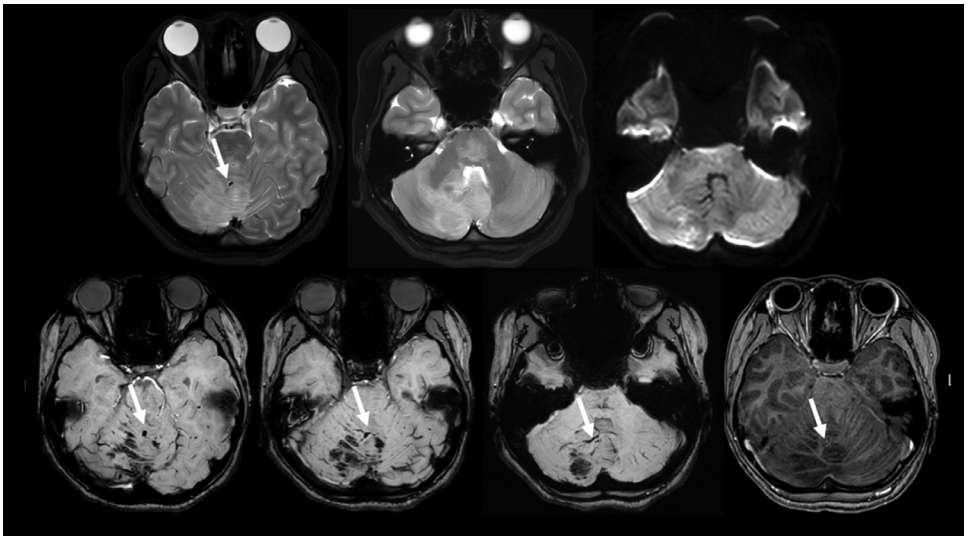

**Fig. 2.** Brain magnetic resonance imaging of the patient.
The multifocal pontocerebellar lesions are considered to be a hemorrhagic venous infarction related to the thrombosed cerebellar DVA. In the upper row (T2 and diffusion-weighted imaging) and lower imaging row (susceptibility-weighted imaging and enhanced T1), dark signal intensity (*white arrow*) suggest thrombosed DVA.

presented a suspicious subtle hypo-attenuated lesion in the right interior cerebellar hemisphere area (**Fig. 1**). Immediately, mannitol, broad-spectrum antibiotics, dexamethasone, and remdesivir 20 mg/kg were administered intravenously. We decided to perform emergency extraventricular drainage because her pupil size was dilated by 5 mm bilaterally with no light reflex, and cerebrospinal fluid (CSF) analysis showed the following: red blood cell count: 980 /mm3; white blood cell count: 32 /mm3 (predominantly monocytes and macrophages: 96%); protein: 144.9 mg/dL; glucose: 17 mg/dL; CSF PCR of SARS-Cov-2 was negative.

Initial brain magentic resonance imaging (MRI) revealed bilateral asymmetric hyperintense lesions and swelling in the mid-pons, cerebellar hemispheres with extensive hemorrhage, multifocal diffusion restriction foci in T2 and fluid atteuated inversion recovery axial images. Medical cerebellar venous engorgement was confirmed based on the venous structure connected to the straight sinus, which is most likely a cerebellar venous anomaly (**Fig. 2**).

Patient's serologic markers and coagulation factors were highly elevated (aspartate transaminase [AST]: 24,592 U/L, alanine trasaminase [ALT]: 10,115 U/L, lactate dehydrogenase [LDH]: 21,210 U/L, lactic acid: 12.9 mmol/L; prothrombin time [PT]: 37.7 s/INR 4.03, activated partial thromboplastin time [aPTT]: 69.9 s) despite injecting medications, including methyprednisolone pulse therapy, intravenous immunoglobulin, and low molecular weighted heparin in the intensive care unit. Continuous renal replacement therapy was performed because of oliguria and rapidly aggravated lactic acidosis. The electroencephalogram revealed extremely low voltage in cerebral cortex activities. On the fourth day in the ICU, the patient failed to maintain her blood pressure, heart rate, and respiratory rate with the mechanical ventilator owing to aggravated pneumonia and bilateral pleural effusion; she died ten days after her hospital admission.

## Discussion

CAC presents as a highly activated thrombotic status (Awad et al., 1993), and COVID-19-associated stroke has been reported mainly in severe clinical cases (Fotuhi et al., 2020). The pathophysiology of how COVID-19 penetrates the central nervous system can be explained by three significant hypotheses as follows: (i) by binding with and inhibiting nasal epithelial cells; (ii) by the formation of clots in small or large vessels; and (iii) by cytokine-induced damage to the blood-brain barrier (Mucha et al., 2020). Microthrombi caused by the immune response to COVID-19 result in blockage of small or large cerebral blood vessels, according to the post-morterm autopsy of COVID-19 infected patients (Mukerji and Solomon, 2021). In addition, virus particles pass through the olfactory bulb and cause cytokine-induced reactions, which damage the blood-brain barrier and stimulate astrocytes or microglia, permitting immune cascades in inter or intra-cranial space (Nagu et al., 2021).

The cytokine surge by the invasion of SARS-CoV-2 may prompt coagulopathy in patients with underlying venous malformation. In our patient, a rapid systemic cytokine storm occurred owing to COVID-19, and it is presumed that the resulting inflammation sequentially caused the coagulopathy cascade. Moreover, one of the significant risk factors in our patient was an asymptomatic venous anomaly of the cerebellum. Developmental venous anomalies (DVA), a type of congenital venous anomalies, are considered to be a risk factor for spontaneous thrombosis (Octavius et al., 2021). The reported incidence of DVA is below 2.5%, and DVA could be dispositioned various areas (Patel et al., 2015); genetic signals at the embryonic stage are suggested to maintain the persistent abnormal angioarchitecture (Sarwar and McCormick, 1978). The hemodynamic disturbances due to abnormal smooth muscle cells and connective tissue of dilated veins may lead to the formation of thrombosis (Schupper et al., 2020).

Over 50% of asymptomatic intracranial venous malformations were detected incidentally by radiography study (Patel et al., 2015; Töpper et al., 1999). The dysmorphisms of DVA present with various prognoses, and most cases reported favorable outcomes (Octavius et al., 2021). However, enormous immune cascades by SARS-CoV-2 induced immune cells to activate coagulation by thrombus formation, resulting in venous infarction. According to the autopsy reports of patients with COVID-19, infiltration of immune cells in the perivascular areas with microthrombi was found in cases of the intracranial infarct (Vogrig et al., 2021). Therefore, when exposed to SARS-CoV-2, patients with asymptomatic DVA could have an unfavorable prognosis due to cytokine surges by immune cascades and vulnerability to coagulopathy. In conclusion, the asymptomatic DVA concomitant with COVID-19 in present patient may have resulted in the occurrence of intracranial thrombosis, which resulted in lethal outcomes. As a key takeaway, we suggest that in patient with COVID-19 having altered mental status, brain imaging, including angiography, should be urgently performed.

## Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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