Cerebral Venous Sinus Thrombosis After a Third Dose of mRNA COVID-19 Vaccine in an Adolescent: A case report

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Case Report

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Abstract

**Background:** Several effective vaccines against Coronavirus disease 2019 (COVID-19) have been developed to control the spread of the disease. A few cases of thrombosis have been reported post-vaccination, especially among young adult women immunized with viral vector-based vaccines; although pediatric cases of cerebral venous sinus thrombosis (CVST) have been rarely reported after messenger ribonucleic acid (mRNA) vaccine administration.

**Case presentation:** Here, we report a case of CVST in a 14-year-old girl immunized with the BNT16B2b2 vaccine. Other than this recent COVID-19 vaccination, there were no precipitant risk factors in her medical history. Laboratory work-up showed low levels of protein S activity. Further research revealed no pathological gene mutation. She was treated with anticoagulant therapy and discharged with mildly impaired coordination/movement of the fingers.

**Conclusion:** CVST may occur following a mRNA COVID-19 vaccination, even among children. Further investigations are needed to establish whether thrombotic events are merely incidental or are a complication associated with mRNA-based vaccines.

**Article Summary**

Our patient did not have a typical thrombosis with thrombocytopenia syndrome profile, indicating a peculiar pathophysiology following third mRNA COVID-19 vaccination.

**Background**

Since the first reported case in 2019, coronavirus disease 2019 (COVID-19) has spread worldwide, resulting in rapid production of several effective vaccines. Five such vaccines have been authorized by the Japanese Ministry of Health, Labor, and Welfare for use in adults: Pfizer-BioNTech, Moderna, AstraZeneca, Johnson and Johnson/Janssen, and Novax. Each has a different action mechanism. The Pfizer-Biotech and Moderna vaccines are both messenger ribonucleic acid (mRNA) -based, while the AstraZeneca and Johnson and Johnson/Janssen vaccines are replication-incompetent adenoviral vector-based. Novax is a recombinant nanoparticle vaccine. All are designed to produce coronavirus spike proteins and trigger an immune response. Only the Pfizer-BioNTech vaccine has been approved in Japan for use in children aged 6 months through 17 years.

Initial trials of these vaccines reported rare cases of anaphylaxis and low rates of serious adverse events. However, as the vaccines began to be used widely, some serious adverse effects were reported, including myocarditis and cerebral venous sinus thrombosis (CVST).

CVST is a rare but serious neurovascular condition defined as occlusion of venous sinuses, leading to increased venous pressure. This disrupts venous return, resulting in infarction and hemorrhage. Thrombosis of the cerebral venous sinus is an uncommon form of stroke, usually affecting young adult
women. Risk factors for pediatric CVST include birth complications, infection of the head or neck, cancer, traumatic head injury, acquired or inherited thrombophilia, and use of hormonal contraceptives. Due to the seriousness of CVST, studies have focused on its incidence after vaccinations. A few cases of thrombosis with thrombocytopenia syndrome (TTS) were reported following vaccinations with adenovirus vector-based vaccines. Several mechanistic models have been proposed to explain such vaccine-induced immune thrombosis. Immune tolerance and production of autoantibodies specific for platelet factor-4 (PF4) in such cases resemble heparin-induced thrombocytopenia (HIT). However, there has been no reported case of CVST in a child/adolescent receiving an mRNA COVID-19 vaccine.

Here, we report a case of CVST following administration of a third dose of the BNT162b2 (Pfizer-BioNTech) vaccine to a 14-year-old girl with no particular medical history. This is the first pediatric case of CVST associated with an mRNA vaccine and, as such, provides insight into the elusive mechanisms underlying CVST following a mRNA vaccination.

**Case Presentation**

A 14-year-old, right-handed, healthy Japanese girl presented with a 1-day history of persistent headache, vomiting, paresthesia of the bilateral extremities, and seizure. She reported no recent infection, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Both medical and surgical history were unremarkable. Regarding drug history, she received the Pfizer-BioNTech mRNA COVID-19 vaccine 7 days prior to presentation, and reported no use of oral contraceptive pills or any other medications of clinical relevance. Her family history was unremarkable. On examination, her temperature was 36.4°C, pulse 75 beats per minute, blood pressure 118/82 mmHg, and oxygen saturation 96% on ambient air. Cardiopulmonary examination indicated no murmurs, and bilateral auscultation showed clear lung fields. An abdominal examination demonstrated a soft, non-tender abdomen, with no organomegaly. Neurological examination revealed disturbed consciousness and bilateral weakness of the upper extremities; muscle strength was 4 in the upper limbs and 5 in the lower limbs for manual muscle testing.

Laboratory findings, including complete blood counts, and the results of coagulation tests and blood chemistry, are summarized in the Table. The data revealed elevation of D-dimer (6 times the upper normal limit on hospitalization day 3). On hospitalization day 2, the platelet count was slightly low at 169 × 109/L. The following test results were normal: white blood cell count, hemoglobin, platelet count, prothrombin time, partial thromboplastin time, fibrinogen, blood urine nitrogen, creatinine, electrolytes, bilirubin, lactate dehydrogenase, alkaline phosphatase, albumin, total protein, aminotransferases of aspartate aminotransferase, and alanine aminotransferase.

Non-contrast brain computed tomography (CT) and brain magnetic resonance imaging showed hemorrhage in the right temporal region and angioedema in the left frontal and temporal regions on hospitalization day 1. Brain CT angiography revealed a filling defect within the superior sagittal sinus.
Fig. 1). These findings are consistent with CVST. Since no clear precipitating factors were found in her clinical history, we ordered a thrombophilia (protein C and S, anti-thrombin III, anti-B2GP1 immunoglobulin G/immunoglobulin M, anticardiolipin, and lupus anticoagulant) work-up. Protein S activity on admission was low and returned to normal on hospitalization day 4. However, low values presented again during her follow-up as an outpatient. We also measured anti-platelet factor-4 (PF-4) antibodies, which were negative. A polymerase chain reaction assay for SARS-CoV-2 was negative.

After CVST was confirmed, we wondered whether vaccine-induced TTS was a possible cause. Therefore, we administered argatroban (0.7 mcg/kg/d) and levetiracetam (40 mg/kg/d). The patient did not meet the Center for Disease Control and Prevention criteria for a TTS case definition due to the absence of a low platelet count and negativity for anti-PF-4 antibodies; however, we continued argatroban for 11 days and then switched to warfarin. Her headache and upper limb paralysis improved greatly, and subsided completely by hospitalization day 3. MRI performed on hospitalization day 7 and MR venography on hospitalization day 17 showed improvement of the abnormal hyperintensity area at sagittal sinus (Fig. 2). The patient was discharged with only mildly impaired coordination/movement of the fingers on hospitalization day 17. Further investigation for protein S deficiency revealed there was no mutation of protein S (PS) gene (PROS1 gene).

**Discussion And Conclusion**

To the best of our knowledge, this is the first pediatric case of CVST associated with a mRNA vaccine. The patient experienced CVST with elevated D-dimers, but without severe thrombocytopenia or anti-PF4 antibodies.

In most instances, CVST is triggered by single or multiple pre-disposing factors, or even by transient factors such as a systemic or local infection. At least one precipitant risk factor is identified in more than 85% of the cases, and multiple risk factors are found in approximately half.\(^5,11,12\) In our patient, a recent mRNA COVID-19 vaccination and low level of PS activity were noted by precise history and detailed laboratory work-up. CVST is a rare, although increasing, adverse event that can occur after a COVID-19 vaccination. Most COVID-19 vaccine-related cases of CVST are associated with vector-based vaccines. They are usually accompanied by TTS.\(^2,6,13,14\) The median platelet count at diagnosis is approximately 20,000 to 30,000×10^9/L, and in almost every patient, high levels of antibodies to PF4 are identified by enzyme-linked immunosorbent assay. However, our patient developed CVST without TTS following her third dose of a mRNA COVID-19 vaccine (BENT126b2; Pfizer-BioNTech). To date, there are a few reports of adult cases of mRNA COVID-19 vaccine-related CVST in the absence of TSS.\(^14–16\)

The estimated incidence of CVST is 0.4 to 0.7 per 100,000 children per year.\(^11,12\) The reporting event rate of CVST after the Pfizer-BioNTech vaccine from December 12, 2020 to 16 March 16, 2021, was 0.4% (4/1197), less than that for viral vector vaccine-related CVST within the same period, which was 1.1% (7/639).\(^17\) Likewise, an CVST analysis after vaccination in European countries noted that it occurred far more frequently after an AstraZeneca (vector-based) vaccination than after a mRNA vaccination.\(^6\)
Nevertheless, SARS-CoV-2 infection itself is associated with a markedly increased incidence of CVST when compared with the general population, patients with influenza, and people who have received the Pfizer-BioNTech or Moderna vaccines.\textsuperscript{18} These data suggest that healthcare providers, parents, and patients should be aware of the safety profiles for COVID-19 vaccines, although the benefits overweight the risks associated with a SARS-CoV-2 infection.

The main mechanism of CVST associated with viral vector vaccines is vaccine-induced immune thrombotic thrombocytopenia, which is similar to HIT.\textsuperscript{5} The mechanism underlying mRNA vaccine-related CVST is unclear, although the following have been proposed: first, the interaction between the spike glycoprotein and platelets leads to platelet aggregation\textsuperscript{19}; second, binding of the spike glycoprotein to the angiotensin converting enzyme receptor activates endothelial cells and up-regulates expression of cell adhesion molecules, which promotes thrombogenesis and causes CVST\textsuperscript{20}; and third, in vitro studies have shown that spike proteins can activate the alternative complement pathway, which plays a role in immune-mediated thrombogenesis.\textsuperscript{21} In our patient, in addition to these hypotheses, acquired PS deficiency secondary to the immune-mediated reaction to the mRNA vaccine may have contributed to the CVST onset.

PS deficiency is caused by inherited or acquired deficiencies, such as, liver disease, severe infection or other illness, and pregnancy and certain medications. Inherited PS deficiency is uncommon. \textit{PROS1} is found on chromosome 3 (3q11.1) and, to date, the reported detection rate of causative gene mutation in suspected PS deficiency is approximately 50%.\textsuperscript{22} Therefore, inherited PS deficiency was not excluded completely. The exact mechanism of acquired PS deficiency is not known, although it may be acquired through the induced autoantibodies and epigenetic etiology.

Since thrombotic events following administration of a mRNA COVID-19 vaccine are very rare, causality cannot be confirmed. This case may add to the evidence supporting a possible relationship between mRNA COVID-19 vaccines and thrombotic events, and raises the awareness of health care providers associated with pediatric care, as well as parents and patients, regarding this rare, critical adverse event; early recognition allows early treatment to prevent complications. In conclusion, CVST may occur following any COVID-19 vaccination, even among children. Our patient lacked the typical TTS profile, which can occur following administration of vector-based vaccine (low platelet counts and the presence of anti-PF4 antibodies). This may indicate a peculiar pathophysiology associated with thrombotic events following a mRNA vaccination. Further investigations are needed to establish whether thrombotic events are merely incidental or are a complication associated with mRNA-based vaccines.

**Abbreviations**

COVID-19: coronavirus disease 2019

CT: computed tomography
CVST: cerebral venous sinus thrombosis
HIT: heparin-induced thrombocytopenia
mRNA: messenger ribonucleic acid
PF4: platelet factor-4
PS: protein S
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
TTS: thrombosis with thrombocytopenia syndrome

Declarations

Ethics approval:
This study was approved by Hyogo Prefectural Kobe Children’s Review Board (no. R4-64).

Consent to participate and consent for publication:
Informed consent was obtained from patient and patient’s parents.

Availability of data and materials:
Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to 4t0121@gmail.com.

Competing interests:
The authors declare that they have no competing interests.

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Author’s contributions:
SM conceptualized the study, collected, analyzed, and interpreted data, drafted the initial manuscript, and critically reviewed and revised the manuscript.

JK, SH, KK, DH, YK, and MK collected data, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted, and agree to be accountable for all
aspects of the work.

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References


Figures
Figure 1

Brain CT on hospitalization day 1:

Non-contrast CT, revealing right temporal lobe intracerebral hemorrhage [A]. CT angiography, revealing a filling deficit within the superior sagittal sinus (arrowhead) [B]. A triangular filling defect in the in the superior sagittal sinus as the positive empty delta sign (arrow) [C].
Figure 2

Brain MRI during hospitalization

T2 FLAIR-weighted magnetic resonance imaging (MRI) on hospitalization day 7 showing an abnormal hyperintensity area (arrow) in the dilated superior sagittal sinus and intracranial hemorrhage in the subacute phase [A]. An MRI venogram on hospitalization day 17, demonstrating the absence of opacification in the superior sagittal sinus (arrowhead) and intracranial hemorrhage in the chronic phase [B].