Cerebral Venous Sinus Thrombosis With Severe Thrombocytopenia: A Fatal Adverse Event Following Johnson & Johnson COVID-19 Vaccination

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Neurology® Clinical Practice Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
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Andrew Jameson: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design

Number of characters in title: 132

Abstract Word count: 190

Word count of main text: 888

References: 5

Figures: 2

Tables: 1

Supplemental: Will include signed patient consent-to-disclose form and the CARE case report guideline.


Acknowledgements: We would like to thank Tracy Koehler for her assistance in manuscript formatting and preparation.

Study Funding: The authors report no targeted funding

Disclosures: There are no financial disclosures for any author relevant to this manuscript.

Practical Implication
A high index of suspicion is required to identify the very rare case of CVST following vaccination with an adenovirus vector SARS-CoV-2 vaccine. Headache is very common following vaccination, but onset is within 24 hours. While headache related to CVST starts 5-7 days after vaccination. This distinction can help clinicians risk stratify headache following SARS-CoV-2 vaccine administration.

Introduction

Approximately 7.98 million doses of the Johnson and Johnson adenovirus vector SARS-CoV-2 vaccine (J&J vaccine) have been administered since EUA authorization by the FDA on February
27, 2021\(^1,2\). On April 13\(^{th}\), the CDC/FDA recommended a pause in administration after 6 cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia were identified through the vaccine adverse event reporting system in women aged 18-48. To date, 15 cases of thrombosis with thrombocytopenia syndrome (TTS) have been reported following vaccination with J&J, with three reported fatalities\(^2\). Here we report one of those fatalities in a 35-year-old woman who developed CVST with thrombocytopenia following vaccination with the J&J vaccine.

**Case Presentation**

A 35-year-old woman with a medical history of migraine headaches and chronic thrombocytopenia presented to the emergency department with severe headache 7 days following vaccination with the J&J Covid-19 vaccine. The patient was not pregnant, had no history of hypercoagulability and no use of hormone replacement therapy however her BMI was 36.6. She described her headache as being more severe and retro-orbital compared to her typical migraine. Physical exam was remarkable only for mild neck stiffness. Laboratory evaluation revealed a platelet count of 114K/ul (106 K/ul in 2015, although January 2021 was up to 164 K/ul; Table 1). Non-contrast head CT was normal (Figure 1A) and a CT venogram head did not reveal any evidence of cerebral venous thrombosis (Figure 1B). She was discharged to home with improvement in symptoms following migraine treatment. She returned to a separate emergency department (ED) 20 hours later with persistent headache. No repeat imaging or laboratory studies were completed. Patient continued to have a normal neurologic exam. She was again discharged after symptomatic relief.

48 hours after initial ED visit and 16 hours after discharge from the second ED visit, the patient experienced an acute loss of consciousness with onset of generalized tonic-clonic seizure activity. On arrival to the ED, she was unresponsive with no purposeful movements. Neurologic exam revealed a GCS of 3 with corneal, gag, and cough reflexes absent. Pupils were 6 mm and fixed. Non-contrast head CT revealed right temporal intraparenchymal hemorrhage and extensive subarachnoid hemorrhage (Figure 2A). There was also evidence of elevated intracranial pressure (sulci effacement) and resultant transtentorial herniation with obliteration of the basilar cisterns. A hyperdensity involving the superior sagittal sinus, right transverse sinus and right sigmoid sinus suggested cerebral venous thrombosis (Figure 1C and 2B). Subsequent CT angiogram and venogram of the head revealed findings consistent with superior sagittal, transverse, and sigmoid sinus thrombosis (Figure 1D).

Laboratory evaluation revealed platelet count of 10 K/ul, fibrinogen of 128 mg/dl and D-dimer of 13476 ng/dl. Heparin-induced thrombocytopenia antibody assay was very elevated at 2.240 OD (normal <0.4). The patient had no exposure to heparin products. Evaluation by neurology and neurosurgery did not recommend any neurosurgical intervention secondary to futility. The patient had ongoing absence of cortical activity with absence of all cortical and brainstem reflexes. Nuclear medicine perfusion imaging documented the absence of cerebral perfusion.
Discussion
The timeline of symptom onset and patient characteristics closely match the case description described in the CDC Health Alert released on April 13th, 2021. It was this health alert that caused the emergency room physician to pursue CT venography on initial presentation. Additionally, our patient’s case was included in the meeting of the Advisory Committee on Immunization Practices on 4/23/2021 and the patient meets all the criteria described by Dr. James Bussel, et al in the case definition published by the American Society of Hematology.

Despite the significant concordance with the previously described cases, there are differences in our case that bear mentioning. Firstly, the patient had a normal CT venogram despite the presence of a severe thunderclap headache. This case raises the possibility that symptoms can precede objective findings of central venous thrombosis. Secondly, the initial platelet decline was not dramatic despite being lower than her most recent assay (114K/ul). The fact she had a history of chronic thrombocytopenia certainly provided a false sense of assurance. Finally, the rapid clinical decline demonstrated by our patient necessitates a high degree of suspicion for timely diagnosis. In a patient without an alternative diagnosis, serial laboratory and radiographic evaluation may be required despite initial studies offering reassurance. While CT venography for CVST ranges from 90-100%, echoplanar T2 susceptibility-weighted imaging combined with MRV are considered the most sensitive test for the diagnosis of CVST.

In summary, the development of thrombosis with severe thrombocytopenia points toward activation of platelet aggregation. The clinical similarities of TTS to heparin-induced thrombocytopenia are striking. Rapid laboratory and radiographic evaluation are necessary for appropriate management. Platelet count, D-dimer, fibrinogen, HIT antibody assay, and CT or MRI venogram are necessary for evaluation of high-risk patients recently vaccinated with an adenovirus vector vaccine against SARS-CoV-2. It is necessary for clinicians to recognize this entity as platelet transfusion or heparin-based anticoagulation could have devastating effects. Timely treatment with intravenous immunoglobulin and anticoagulation with non-heparin therapies (i.e. argatroban or bivalrudin) is essential for effective management.
References:


   https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia


   https://doi.org/10.1161/str.0b013e31820a8364
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<th>Variable</th>
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<th>3&lt;sup&gt;rd&lt;/sup&gt; ED visit - Admission</th>
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Figure Legends

Figure 1:
Title: Noncontrast CT Head and CTV Sagittal view, a comparison between 1st and 3rd ED visit.

Legend: (Image A) shows Non-contrast Head CT performed on 1st ED visit, no abnormal density noted within the sinuses. (Image B) shows CT Venogram post Contrast performed on initial ED visit, note appropriate opacification of sinuses. (Image C) Non-contrast Head CT performed on third ED visit, arrow points towards abnormal density within superior sagittal and transverse sinus. (Image D) CT Venogram post-contrast performed on third ED visit, lack of contrast opacification of sinuses and persistent density as demonstrated on non-contrast CT head consistent with cerebral venous sinus thrombosis.
**Figure 1:**

Title: Coronal and Axial view of non-contrast Head CT performed on 3rd visit.

Legend: (Image A) shows axial view of non-contrast Head CT with findings consistent with Intraparenchymal and subarachnoid hemorrhage. (Image B) Axial view of non-contrast Head CT showing prominent density in the right sigmoid sinus (indicated by arrow sign) compared to the left sigmoid sinus, indicating right sigmoid sinus thrombosis. (Image C) shows coronal view of non-contrast Head CT, arrow indicates Delta sign suggestive of Dural sinus thrombosis.
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Neurol Clin Pract published online October 7, 2021
DOI 10.1212/CPJ.0000000000001137

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