CASE

Cerebral Venous Sinus Thrombosis With Severe Thrombocytopenia

A Fatal Adverse Event After Johnson & Johnson COVID-19 Vaccination

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Approximately 7.98 million doses of the Johnson & Johnson adenovirus vector SARS-CoV-2 vaccine (J&J vaccine) have been administered since emergency use authorization by the FDA on February 27, 2021.[1,2] On April 13, 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 after vaccination with J&J, with 3 reported fatalities.[2] We report one of those fatalities in a 35-year-old woman who developed CVST with thrombocytopenia after vaccination with the J&J vaccine.

PRACTICAL IMPLICATIONS

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

Case

A 35-year-old woman with a medical history of migraine headaches and chronic thrombocytopenia presented to the emergency department (ED) with severe headache 7 days after 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 body mass index was 36.6. She described her headache as being more severe and retro-orbital compared with her typical migraine. Physical examination 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). Noncontrast 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 after migraine treatment. She returned to a separate ED 20 hours later with persistent headache. No repeat imaging or laboratory studies were completed. The patient continued to have a normal neurologic examination. She was again discharged after symptomatic relief.

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Fourty-eight hours after initial ED visit and 16 hours after discharge from the second ED visit, the patient experienced an acute loss of consciousness with an onset of generalized tonic-clonic seizure activity. On arrival to the ED, she was unresponsive with no purposeful movements. Neurologic examination revealed a Glasgow coma score of 3 with corneal, gag, and cough reflexes absent. Pupils were 6 mm and fixed. Noncontrast 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 (Figures 1C and 2B). Subsequent CT angiogram and venogram of the head revealed findings consistent with superior sagittal, transverse, and sigmoid sinus thrombosis (Figure 1D).

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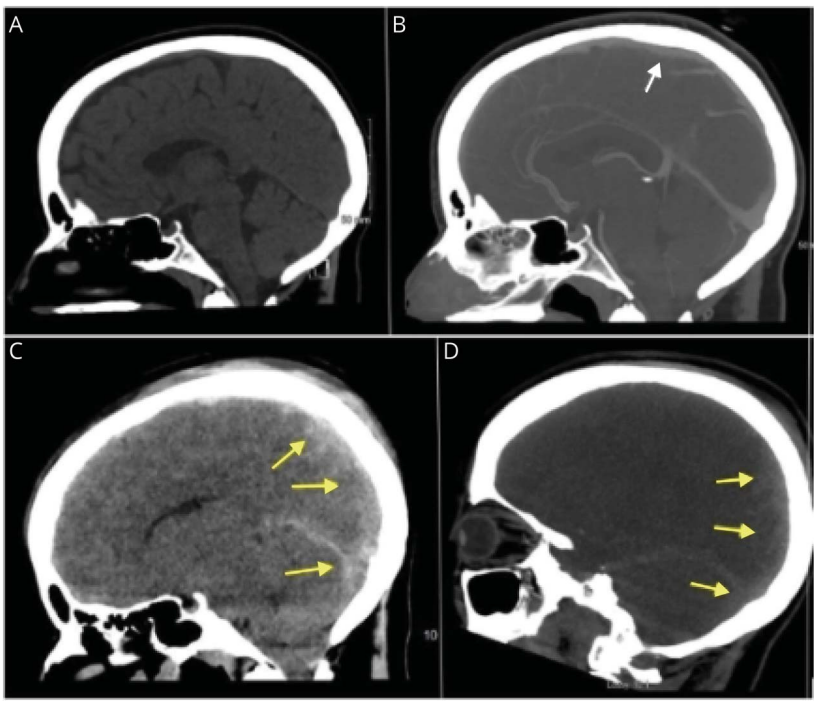
Table 1 Laboratory Data

Variable	Reference range	3 Months prior	1st ED visit	3rd ED visit—admission	
				1st day	2nd day
Platelet count (per mm^3)	140,000–450,000	164,00	114,000	10,000	16,000
Hemoglobin (g/dL)	12–16	11.2	11.0	12.2	10.7
White blood cell count (per mm)	4,000–10,000	6,650	9,700	9,900	20,700
International normalized ratio				1.2	1.8
Prothrombin time (s)	10.5–13.0			14.0	21.4
Partial thromboplastin time (s)	26.0–36.0			24.4	30.5
D-dimer (ng/mL)	<230				13,476
Fibrinogen (mg/dL)	210–450			128	319
Blood urea nitrogen (mg/dL)	7–24	16	14	12	13
Creatinine (mg/dL)	0.5–1.5	0.9	0.8	0.6	1.6
Bicarbonate (mmol/L)	21–29	22	19	16	19
Aspartate transaminase (IU/L)	12–32	17	24	17	56
Alanine transaminase (IU/L)	12–39	20	30	24	35
Total Bilirubin (mg/dL)	0.3–1.2	<0.2	0.2	0.3	1.0
Heparin-induced thrombocytopenia antibody (Optical density—OD)	<0.4			2.240	

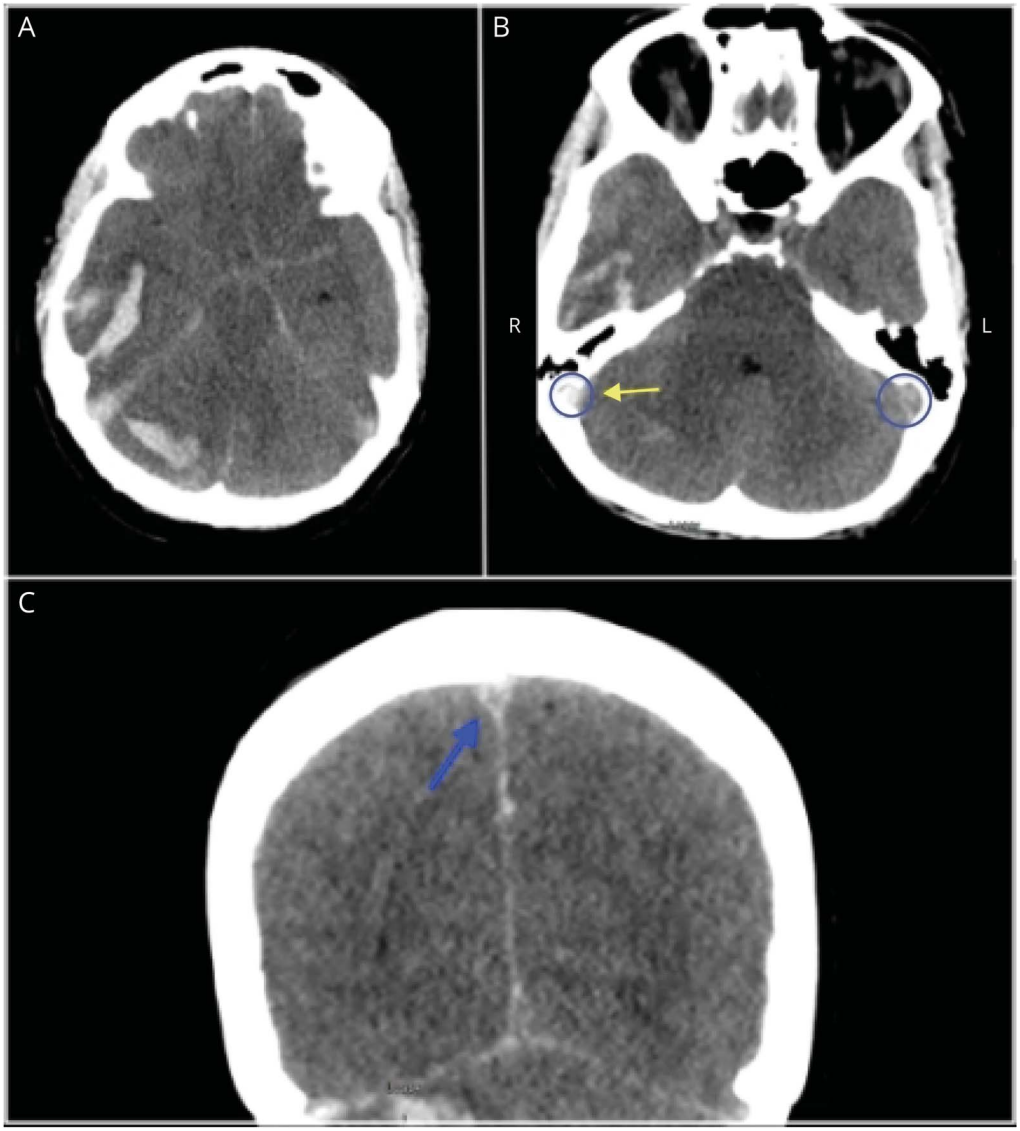
Laboratory evaluation revealed a platelet count of 10 K/uL, fibrinogen of 128 mg/dL, and D-dimer of 13476 ng/dL. Heparin-induced thrombocytopenia antibody assay was very elevated at 2.240 OD (normal <0.4). The patient had no exposure to heparin products. Evaluation by neurology and neurosurgery did not recommend any neurosurgical

Figure 1 Noncontrast CT Head and CT Venogram Sagittal View, a Comparison Between First and Third ED Visit



(A) Noncontrast head CT performed on 1st ED visit; no abnormal density noted within the sinuses. (B) CT venogram postcontrast performed on the initial ED visit, note appropriate opacification of sinuses. (C) Noncontrast head CT was performed on the third ED visit; the arrow points toward abnormal density within superior sagittal and transverse sinus. (D) CT venogram postcontrast performed on the third ED visit; a lack of contrast opacification of sinuses and persistent density as demonstrated on noncontrast CT head consistent with cerebral venous sinus thrombosis.

Figure 2 Coronal and Axial View of Noncontrast Head CT Performed on the Third Visit



(A) Axial view of noncontrast head CT with findings consistent with intraparenchymal and subarachnoid hemorrhage. (B) Axial view of noncontrast head CT showing prominent density in the right sigmoid sinus (indicated by arrow sign) compared with the left sigmoid sinus, indicating right sigmoid sinus thrombosis. (C) shows coronal view of noncontrast head CT; the arrow indicates delta sign suggestive of dural sinus thrombosis.

intervention secondary to futility. The patient had an ongoing absence of cortical activity with the 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 13, 2021.[3] It was this health alert that caused the emergency room physician to pursue CT venography on initial presentation. In addition, our patient's case was included in the meeting of the Advisory Committee on Immunization Practices on April 23, 2021, and the patient meets all the criteria described by Bussel et al.[4] 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. First, 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. Second, the initial platelet decline was not dramatic, despite being lower than her most recent assay (114 K/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. Although the sensitivity of CT venography for CVST ranges from 90–100%, echoplanar T2 susceptibility-weighted imaging combined with magnetic resonance venography are considered the most sensitive test for the diagnosis of CVST.[5]

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 the 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 nonheparin therapies (i.e., argatroban or bivalrudin) is essential for effective management.

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Christopher Goshgarian, MD	Mercy Health Saint Mary's Department of Neurology, Grand Rapids, MI	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
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