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SPONTANEOUS INTRACRANIAL HYPOTENSION COMPLICATED BY A CEREBRAL VENOUS THROMBOSIS FOLLOWING AN mRNA COVID-19 VACCINATION: COINCIDENCE VS CAUSE?

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ABSTRACT

Spontaneous intracranial hypotension (SIH) is a rare cause of persistent headache, particularly among young and middle-aged people. A potentially life-threatening complication of SIH is a cerebral venous thrombosis (CVT). The authors present a case in which a patient presented with SIH complicated by CVT one week after receiving a booster dose of mRNA COVID-19 vaccine. According to our literature review, this is the first such case report.

KEYWORDS

Spontaneous intracranial hypotension, cerebral venous thrombosis, mRNA COVID-19 vaccine, headache

LEARNING POINTS

- Spontaneous intracranial hypotension is rarely complicated by cerebral venous thrombosis (CVT).
- The majority of cerebral venous thrombosis cases post-COVID-19 vaccination occurred in patients administered with adenoviral vaccines. CVT following administration of mRNA COVID-19 vaccines is rare.
- Clinicians should consider COVID-19 vaccine-induced CVT in recently vaccinated patients; MRI plays an important role in accurate diagnosis.

INTRODUCTION

Spontaneous intracranial hypotension (SIH) is a rare condition caused by spontaneous spinal cerebrospinal fluid (CSF) leaks through the dural defects. The incidence of SIH is estimated at 5 in 100,000 per year; women are affected more commonly than men, with peak incidence at around the age of 40 years[1]. The most typical presenting symptom of SIH is orthostatic headache; however, other associated symptoms include neck stiffness, nausea and vomiting. A potentially life-threatening complication of SIH is cerebral venous thrombosis (CVT). CVT occurs in approximately 2% of patients with SIH[2], and magnetic resonance imaging

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(MRI) plays an important role for its accurate diagnosis as it is often difficult to diagnose clinically due to the vague nature of clinical presentation.

During the recent COVID-19 pandemic, while a large part of the population across the world has received the COVID-19 vaccination to overcome the pandemic, an emerging concern about thromboembolic side effects of these vaccines has been noticed. A systemic review of cases of CVT following COVID-19 vaccination[3] found that though it is more commonly associated with adenoviral vaccines, mRNA vaccines are not devoid of such complications.

We present a case in which a patient presented with SIH complicated by CVT one week after receiving a booster dose of mRNA COVID-19 vaccine. According to our literature review, this is the first such case report.

CASE DESCRIPTION

A 42-year-old woman presented to our hospital with a complaint of severe headache and vomiting for 5 days. Her headache would increase by lifting her head or sitting up. Her present symptoms started 1 week after receiving a booster dose of mRNA COVID-19 vaccine (Pfizer-BioNTech). She had on and off headaches and neck pain in the past. She had no pertinent past medical history, trauma, lumbar puncture or oral contraception. She never underwent a nasal swab. A neurological examination revealed an orthostatic headache and absence of focal neurological deficit.

The patient was investigated with magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) of the brain *(Fig. 1A and 1B)*. Drooping splenium of the corpus callosum was noted along with effaced perimesencephalic

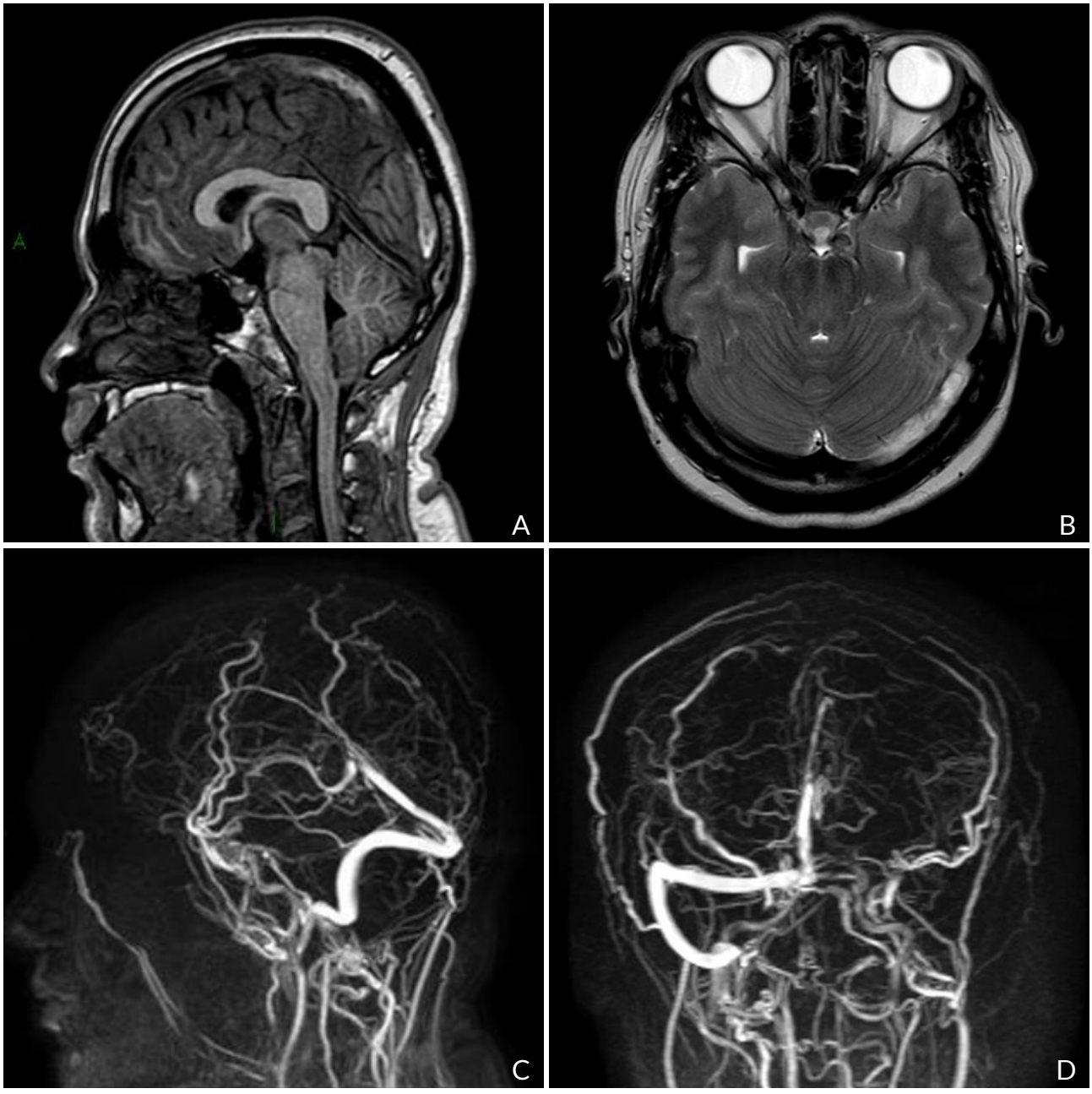

Figure 1. Sagittal T1WI (A) and axial T2WI (B) images reveal drooping of the splenium of corpus callosum, brain stem sagging, effaced perimesencephalic and prepontine cisterns along with T1 & T2 hyperintense thrombus filling the superior sagittal and left transverse sinuses. Sagittal (C) and coronal (D) MR venography shows lack of flow-related enhancement in the superior sagittal, left transverse and sigmoid sinuses.

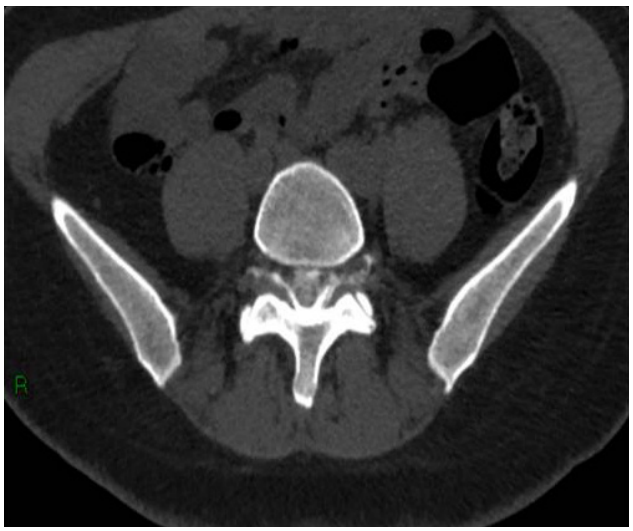

Figure 2. An axial CT myelography image depicts CSF leakage along bilateral lumbar nerve roots.

and prepontine cisterns. The pontomesencephalic angle and mammillopontine distance were grossly reduced, representing brain stem sagging, and cerebellar tonsils were reaching caudally 3 mm below McRae's line. A contrast-enhanced MRI was not performed. This constellation of findings represents intracranial hypotension. In addition, small haemorrhagic subdural collections were seen over the frontal convexities. There was no cerebral infarct or intraparenchymal haemorrhage.

The MRI also revealed a T1 and T2 hyperintense thrombus filling the superior sagittal, left transverse and sigmoid sinuses. On MRV, these sinuses did not exhibit flow-related enhancement *(Fig. 1C and 1D)*. The right transverse, sigmoid and straight sinuses were patent with normal signal on the venogram.

The only significant abnormality on blood investigation was raised D-dimer (791 ng/ml). In particular, there was no thrombocytopenia. Two days after the MRI, a lumbar puncture was performed in the supine position; CSF opening pressure was very low and not detectable. A few drops of CSF were sent to the lab and the CSF analysis was unremarkable. A CT myelogram *(Fig. 2)* was performed, which showed epidural CSF leakage along the bilateral nerve roots from L1 to L5 vertebral levels.

Based on the findings of CSF leakage on the CT myelogram, the patient was treated with an epidural blood patch for SIH. She was also started on anticoagulation for CVT. Follow-up MRI and MRV *(Fig. 3)* conducted after 6 months showed recanalisation of the superior sagittal, left transverse and sigmoid sinuses. There was resolution of subdural collections, and features of SIH were no longer seen. The patient has been on regular follow-up in our neurology clinic and her symptoms have been relieved significantly.

DISCUSSION

SIH is caused by spontaneous CSF leaks[1], which generally occur due to dural defects and onset of symptoms may be preceded by trivial traumatic events. These dural defects may be present in the setting of connective tissue disorders such as Marfan syndrome, Ehler-Danlos syndrome type II and autosomal dominant polycystic kidney disease, or may be associated with isolated joint hypermobility or spontaneous retinal detachment. Spinal meningeal diverticula have also been described in neurofibromatosis type 1 and Lehman syndrome. A distinct and uncommon cause of spontaneous intracranial hypotension not associated with a primary dural defect is the presence of a congenital osseous spur[4] as well as acquired degenerative disc disease piercing the dura[5]. CSF venous fistula is an important cause of SIH that may occur without epidural CSF leak[6], and can be

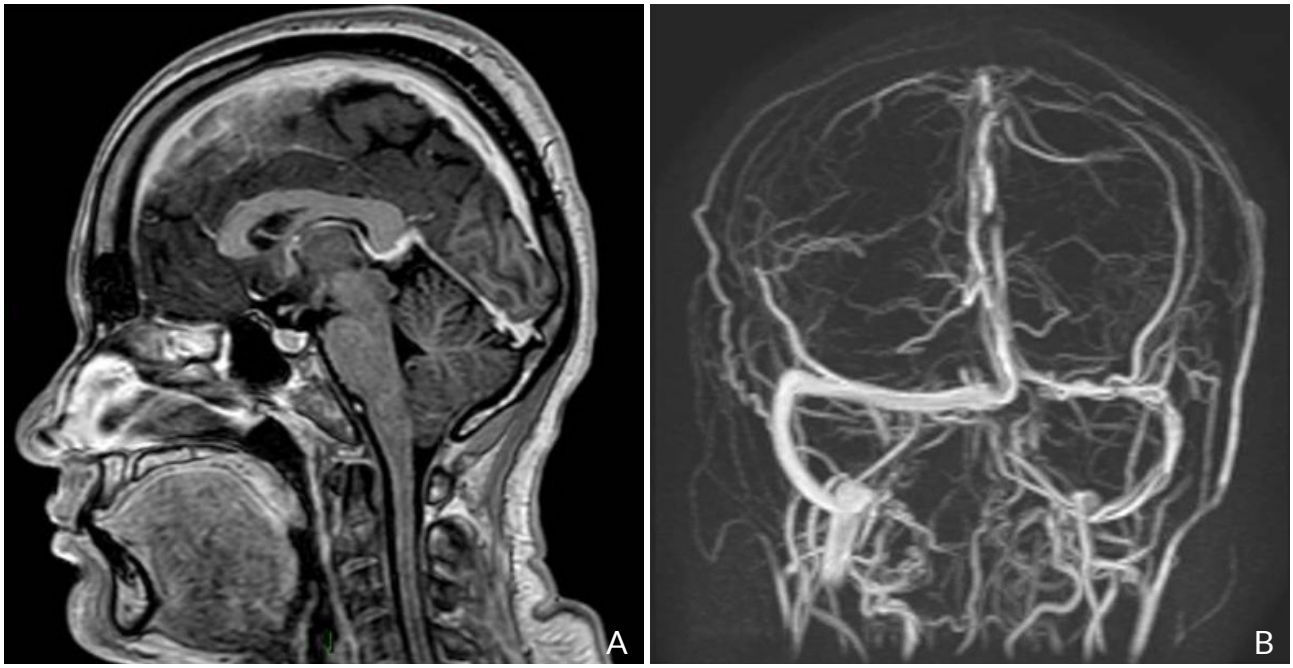

Figure 3. A contrast-enhanced T1 sagittal image (A) shows resolution of features of SIH and normal contrast-enhancement of venous sinuses. A coronal MRV image (B) shows recanalisation of the superior sagittal, left transverse and sigmoid sinuses.

detected by CT myelography or modified conventional myelography. A CT myelogram performed on our patient did not reveal any CSF venous fistula, but rather displayed epidural CSF leakage along the bilateral nerve roots from L1 to L5 vertebral levels. There were no clinical features of any overt connective tissue disorders. Iatrogenic CSF leak from the anterior skull base after repeated nasal swab tests for COVID-19 has been reported[7]; however, our patient did not have any history of a nasal swab. In the literature, we could find only one case report of SIH developing following severe COVID infection[8], and there is no case report of SIH following COVID vaccination. According to our literature review, this is the first reported case of SIH complicated with CVT following recent administration of the Pfizer mRNA COVID-19 vaccination. SIH is a known risk factor for CVT but only 2% of SIH cases are complicated by CVT. Hence, it is difficult to ascertain whether it was just a coincidence that symptoms started one week after vaccine administration, or the vaccine was causally related with incidence of CVT.

The majority of CVT cases post-COVID-19 vaccination occurred in patients administered with adenoviral vaccines. CVT following administration of mRNA COVID-19 vaccines is rare. An observational cohort study from Singapore reported the incidence of CVT following mRNA COVID-19 vaccinations to be 2.59 per 100,000 person-years[9]. In the same study, the incidence rate of CVT after COVID-19 infection was 83.3 per 100,000 person-years, which was significantly higher compared with that after mRNA-based COVID-19 vaccination. While CVT after adenoviral vaccines is considered to be mediated by vaccine-induced immune thrombotic thrombocytopenia (VITT)[10], the exact mechanism of mRNA vaccine-induced CVT is not clear and it is not associated with thrombocytopenia[11].

The pathophysiology of CVT in patients with SIH is multifactorial, including venous stasis, vascular distortion and increased venous blood viscosity[12]. First, as dictated by the Monro Kellie doctrine[13], as the CSF volume decreases because of CSF leaks, causing dilatation of intracranial veins and sinuses, leading to a slowing of the venous blood flow velocity and eventually resulting in a hypercoagulable state. Second, the sagging of the brain and traction on cerebral veins in SIH may lead to mechanical distortion of the vessel wall with increased propensity for thrombus formation. Third, CSF leakage reduces absorption of CSF into the cerebral venous sinuses and consequently increases blood viscosity, leading to hypercoagulability[14].

It is very possible that CVT in our reported patient was triggered by her recent COVID-19 vaccine; however, it is difficult to prove that the vaccine was causally related with the CVT. We do recognise that this presentation could be coincidental and not directly associated with the mRNA vaccination. To objectively address this dilemma of coincidence or causal relationship of SIH and CVT with vaccination, we applied the adverse drug reaction probability scale as proposed by Naranjo et al.[15] and based on previous reports, a reasonable time gap between vaccine administration and onset of clinical symptoms and MRI confirmation of diagnosis; a score of +2 and +3 was calculated for development of SIH and CVT respectively. These scores suggest that it is possible that SIH with CVT may be causally related with COVID-19 vaccination; however, there is not enough evidence to suggest a definite causal relationship.

To conclude, we report a rare case of SIH complicated with CVT presenting one week after receiving an mRNA COVID-19 vaccination. This is not to deter the usage of mRNA vaccination as demonstrated by a much higher risk for CVT for patients who are infected with COVID-19. Nevertheless, clinicians should consider COVID-19 vaccine-induced CVT in recently vaccinated patients; MRI plays an important role in accurate diagnosis. Early diagnosis and treatment may ultimately improve health outcomes.

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