Stroke

SPECIAL REPORT

Diagnosis and Management of Cerebral Venous Sinus Thrombosis With Vaccine-Induced Immune Thrombotic Thrombocytopenia

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Cerebral venous sinus thrombosis (CVST) is a rare manifestation of cerebrovascular disease.[1–4] Recent reports from the Centers of Disease Control and the US Food and Drug Administration identified 6 cases of CVST associated with thrombocytopenia in US patients who had received the Ad26.COV2.S (Janssen) coronavirus disease 2019 (COVID-19) vaccine. Similar thromboembolic events were reported in Europe following ChAdOx1 nCoV-19 (AstraZeneca) vaccination. Both the Ad26.COV2.S and ChAdOx1 nCoV-19 vaccines contain adenoviral vectors. In contrast, there have been no cases of CVST reported with thrombocytopenia following administration of 182 million mRNA severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) vaccines.[5] While awaiting further information on the causal nature of the relationships of vaccines to CVST with thrombocytopenia, clinicians should be aware of the symptoms to facilitate recognition of potential cases of CVST in patients receiving these vaccinations. The goal of this report is to heighten awareness of the apparent association between adenovirus SARS-CoV2 vaccinations and CVST with vaccine-induced immune thrombotic thrombocytopenia (VITT) and suggest approaches to management.

CVST EPIDEMIOLOGY AND RISK FACTORS

CVST is an uncommon cerebrovascular disorder.[1–4] There are other terms used in literature, including dural sinus thrombosis, venous sinus thrombosis, and cerebral venous thrombosis. Previous studies and systematic reviews highlighted the epidemiology and risk factors.[1–4] CVST most commonly affects young adults (mean age 35–40 years), predominantly women of childbearing age.[1,6,7] Risk factors for CVST are similar to those for venous thromboembolism; over 80% of patients with CVST have at least one identifiable risk factor for thrombosis and half have multiple predisposing factors. Most common transient risks factors include temporary medical conditions, such as pregnancy and puerperium, exposure to drugs (oral contraceptives, chemotherapy), central nervous system or ear and face infections, and head trauma.[1,6,8] Chronic risk factors include hereditary or acquired thrombophilias, autoimmune diseases, and cancer.[1,6,8] Thrombocytopenia is an uncommon primary cause of CVST.[9] Before the COVID-19 pandemic, registries showed a low prevalence and magnitude of the association between thrombocytopenia and CVST (Table 1).

It is important to recognize that infection with SARS-CoV2, or COVID-19, is a risk factor for CVST. A retrospective analysis using electronic health records showed the incidence of CVST after COVID-19 was 39.0 per million people (95% CI, 25.2–60.2) compared with any 2-week period in the pre-COVID-19 epoch (0.41 per million people).[15] One study (initially published as a preprint) showed that the incidence of CVST associated with COVID-19 was 10-fold higher than after receiving BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccines (39.0 per million people [95% CI, 25.2–60.2] versus

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
CVST	cerebral venous sinus thrombosis
DOAC	direct oral anticoagulant
HIT	heparin-induced thrombocytopenia
PF4	platelet factor 4
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
VITT	vaccine-induced immune thrombotic thrombocytopenia

4.1 per million people [95% CI, 1.1–14.9], adjusted RR, 6.36; $P<0.001$).[15]

SYMPTOMS OF CVST

The signs and symptoms of CVST are diverse and may mimic many other neurological disorders, making diagnosis challenging. Symptoms reflect the location of the vein or sinus affected; in some cases, multiple locations may be affected simultaneously. Presentations of CVST may be roughly divided into 4 syndromes: (1) isolated headache or increased intracranial pressure; (2) focal neurological presentations; (3) subacute encephalopathy; and (4) cavernous sinus syndrome/multiple cranial neuropathies.

Headache is frequent in CVST, present in ≈90% of patients.[9] Headache may be accompanied by increased intracranial pressure, due to failure of blood to drain properly from the brain, with papilledema and sixth nerve palsies. In one series of 160 consecutive patients with sinus thrombosis, 37% had isolated intracranial hypertension without focal signs or symptoms.[16] Most had papilledema, and sixth nerve palsies could be either unilateral or bilateral. Visual loss from optic nerve damage also occurred in some cases. In another study, however, 17 (14%) of 123 consecutive patients with CVST presented with isolated headache, without evidence of increased intracranial pressure, indicating the need for a high index of suspicion for the disorder in patients presenting with headache.[17] In 15 of these 17 patients, the lateral sinus was involved. The headache in CVST may be diffuse or localized, it is persistent and often progresses over days to weeks.[18] In some cases, it is intermittent. Severity is variable. It is usually refractory to analgesics. The headache may worsen with recumbency or Valsalva maneuver, as is typical with increased intracranial pressure. More acute presentations consistent with migraine or thunderclap headache may occur. On rare occasions, scalp edema or dilated scalp or orbital veins may also be seen.

Patients often present with focal neurological deficits and seizures. Focal deficits depend on the area of the brain affected but most often include hemiparesis, aphasia, or visual loss. One feature that may distinguish the focal deficits of CVST from those of more commonly encountered ischemic infarcts and primary intracerebral hemorrhage is their bilateral nature, particularly when the superior sagittal sinus, which drains both hemispheres and is the most commonly involved venous sinus (62%), is affected.[9] Another distinguishing characteristic is their progressive nature, as the deficit in arterial occlusions tends to be maximal at onset, particularly for cardiac emboli. In the International Study on Cerebral Vein and

Table 1. Thrombocytopenia and CVST

	Unrelated to COVID-19 vaccines			COVID-vaccine era		
	Asian CVT registry[10]	VENOST registry[11]	ISCVT registry[9]	COVID-vaccine[12]	COVID-vaccine[13]	COVID-vaccine[14]
N	812	1144	624	11	5	6
Age in years, mean (SD) or median (range)	31 (NA)	80% aged <50 y (NA)	39 (NA)	36 (22–49)	39 (32–54)	33 (18–48)
Sex, female (%)	479 (59)	777 (68)	465 (75)	9 (82)	4 (80)	6 (100)
No. of countries	9	1	21	2	1	1
Ethnic groups (%)	South-Asian	White (100)	White (79)	NR	NR	NR
			Black (5)			
			Hispanic (9)			
			Asian (3)			
			Others (3)			
Geographic location	Asia	Turkey	Europe	Germany and Austria	Norway	United States
N (%) thrombocytopenia	3 (0.3)	NR (thrombocytosis reported as 1.1%)	NR (thrombocytosis reported as <3%)	10/11 (91)	5/5 (100)	6/6 (100)
Number PF4 positive (%)	NR	NR	NR	9/11 (82)	5/5 (100)	5/6 (83)

Numbers between brackets represent %, unless otherwise indicated. COVID-19 indicates coronavirus disease 2019; CVT, cerebral venous thrombosis; CVST, cerebral venous sinus thrombosis; ISCVT, International Study on Cerebral Vein and Dural Sinus Thrombosis; NR, not reported; PF4, platelet-activating antibodies directed against platelet factor 4; and VENOST, Multicenter Cerebral Venous Thrombosis Study.

Dural Sinus Thrombosis, symptom onset was <48 hours in about 1/3 of patients, 48 hours to 30 days in just over half of patients, and >30 days in almost 10% of patients. Seizures also occur more commonly with CVST (≈40%) than with other stroke subtypes.[9]

Some patients with thrombosis of the deep cerebral veins may develop a subacute encephalopathy, with confusion and lethargy.[1] This syndrome is due to edema of bilateral thalami, basal ganglia, or other deep structures drained by these veins. If untreated, the syndrome can progress to coma and death. Imaging may appear to show devastating injury, but with timely treatment, recovery can be complete as edema resolves.

CVST ASSOCIATED WITH VACCINE-INDUCED THROMBOCYTOPENIA

The Ad26.COV2.S (Janssen) and ChAdOx1 nCoV-19 (AstraZeneca) vaccines contain replication-incompetent adenoviral vectors, human Ad26.COV2.S and chimpanzee ChAdOx1, respectively, that encode the spike glycoprotein on SARS-CoV2. It is believed that leakage of DNA from the adenovirus infected cells binds to PF4 (platelet factor 4) and triggers the production of autoantibodies.[5]

CLINICAL CHARACTERISTICS OF CVST WITH VITT

Among the symptoms of the women who experienced CVST after receiving the Ad26.COV2.S (Janssen) adenovirus-based SARS-CoV2 vaccine in the United States, the most common symptom was headache.[5] Symptom onset occurred 6 to 13 days after receipt of the vaccine. The age range was 18 to 48 years. Five of 6 patients presented with headache, one of whom also had vomiting and one lethargy. A sixth patient had back pain. Two had hemiparesis, one aphasia, one neglect, and one loss of consciousness. Two patients had abdominal pain due to portal vein thrombosis. Several of the cerebral sinuses were affected. Patients were treated with heparin (n=4), nonheparin anticoagulants (n=5), platelets (n=3), intravenous immunoglobulin (n=3). At least one patient died. Additional clinical details are described in Table 2.

Similar reports from Europe describe thrombocytopenia and venous thrombosis after the ChAdOx1 nCoV-19 vaccine (AstraZeneca). Symptoms began 5 to 24 days after the first dose of the 2-shot vaccination. All had thrombocytopenia. In Germany, 11 patients (9 women) aged 22 to 49 developed venous thrombosis. Nine had CVST, 3 had splanchnic-vein thrombosis, and 3 had pulmonary embolism.[12] In Norway, 5 patients presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of ChAdOx1 nCoV-19 (AstraZeneca) vaccine. The patients were 32 to 54 years of age.[13] In the United Kingdom, 23 patients with antibodies to PF4 after ChAdOx1 nCoV-19 vaccination were described. The age range was 21 to 77 years and 61% were female. Of the 22 patients who presented with thrombosis, 13 had suspected CVST, others had pulmonary embolism (n=4) deep venous thrombosis and bilateral adrenal hemorrhage consistent with infarction (n=1), middle cerebral artery territory ischemic stroke (n=2), and portal vein thrombosis (n=2).[19]

DIAGNOSTIC TESTING

In cases of suspected CVST, either magnetic resonance imaging with venogram or computed tomography with venogram can accurately detect CVST.[1] A conventional angiogram is rarely necessary. Blood tests should include complete blood count with platelet count and peripheral smear, a prothrombin time, partial thromboplastin time, fibrinogen, D-dimer, and a PF4 antibody ELISA. In a UK study, PF4 testing with the chemiluminescence HemosIL AcuStar HIT IgG assay (Werfen) was negative but testing with an ELISA was positive. ELISAs included the Lifecodes PF4 IgG assay (Immucor) and the Asserachrom HPIA IgG assay (Stago).[19] Finally, a confirmatory PF4 platelet activation assay (serotonin release assay, P-selectin expression assay, or HIPA) can be obtained if locally available, and the PF4 ELISA is low positive or if there is uncertainty regarding the diagnosis.

MANAGEMENT

Acute Management

There is limited information about optimal treatment of CVST with VITT, but recommendations follow those of heparin-induced thrombocytopenia (HIT) given similarities in the 2 conditions.[12,13,20] It is strongly suggested that care be provided collaboratively by vascular neurology and hematology, vascular medicine, or other consultant with expertise in managing HIT with cerebral or systemic thrombosis.

Based upon evidence of response in HIT, although there are no published data on efficacy in VITT, intravenous immunoglobulin 1 g/kg body weight daily for 2 days, has been recommended after laboratory testing for PF4 antibodies has been sent.[12,20,21] No heparin products in any dose should be given. Some experts recommend administration of steroids.[22]

Anticoagulation should follow recent guidelines on HIT with thrombosis that recommend alternative anticoagulants to heparin including argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC) at therapeutic anticoagulant dose intensity.[23] Dosing strategy may require alteration if there is severe thrombocytopenia (ie, <20 000 per mm^3) or low fibrinogen. Anticoagulation should be used in CVST even in the presence of secondary intracranial hemorrhage as it is necessary to

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Table 2. Characteristics of Post-Ad26.COV2.S Vaccine (Janssen) Patients With CVST (n=6)[5]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Presenting symptoms	Headache, lethargy	Headache	Headache, vomiting, fever	Headache, chills, myalgia	Headache, chills, dyspnea, fever	Back pain, bruising
Location of CVST	Right transverse and sigmoid sinuses	Left transverse and sigmoid sinuses, straight sinus, confluence of the sinuses	Superior and inferior sinuses, straight sinus	Right transverse and sigmoid sinuses	Right transverse and sigmoid sinuses	Right transverse sinus
Systemic thrombosis	None	None	None	Portal vein and Pulmonary artery	Bilateral lower extremity and internal jugular vein	Portal vein
Location of intracerebral hemorrhage	Right temporoparietal	Left temporal	Bilateral frontal and intraventricular	None	None	Occipital
Platelet count nadir (per mm^3)	12 000	69 000	18 000	127 000	10 000	14 000

CVST indicates cerebral venous sinus thrombosis.

prevent progressive thrombosis to control this bleeding.[1] In severely ill patients, parenteral agents with short half-life are preferred. Platelet transfusion should be avoided.

Subacute/Chronic Management

Once there is full platelet count recovery, most patients can be transitioned to an oral anticoagulant if there are no contraindications. The American Society of Hematology 2018 HIT guideline panel provided a conditional recommendation for HIT patients with thrombosis to prefer a DOAC over vitamin K antagonist.[23] With CVST in the absence of HIT, some experts recommend a DOAC over vitamin K antagonist based upon three factors, observational study data documenting efficacy and safety, one randomized controlled trial, and the known lower rate of cerebral hemorrhage with DOACs compared with vitamin K antagonist's.[24] In the RE-SPECT open-label randomized trial (A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis) of 120 patients with acute CVST, after an initial course of 5 to 15 days of heparin or low molecular weight heparin, patients were randomized to dabigatran 150 mg twice daily or warfarin.[6] Over 6 months, the primary outcome (major bleeding or recurrent venous thromboembolism) occurred in one (1.7%) patient with dabigatran and 2 (3.3%) patients with warfarin. These were all major bleeding events, and there were similar rates of recanalization and functional recovery in the 2 groups. Taken together, we suggest consideration of patient factors and use of a DOAC or vitamin K antagonists once there is full platelet count recovery.

REPORTING

Reporting of certain vaccine side effects is required of US clinicians, and we recommend all thrombosis cases after SARS-CoV2 vaccines (as well as any suspected adverse events) be reported to the Department of Health and Human Services Vaccine Adverse Event Reporting System: https://vaers.hhs.gov/reportevent.html. In addition, analysis of all CVST cases during the COVID pandemic would provide a better estimate of incidence and reduce case ascertainment bias.

LIMITATIONS AND FUTURE DIRECTIONS

Much about COVID-19 associated neurological complications remains unknown. There is a considerable risk to patients if scientific data are taken out of context and without appropriate caveats.[25] For example, reports of vaccine-associated CVST may increase vaccine hesitancy, yet the risk of CVST associated with COVID-19 infection is far greater than that associated with vaccination.[15] The particular comorbidities that might predispose to CVST after vaccination are unknown. Although the presence of PF4 antibodies has been confirmed in cases of vaccine-associated CVST with thrombocytopenia, the true prevalence and risk of this antibody are unknown, and case selection bias affecting current knowledge is possible. Asymptomatic individuals after vaccination have not been tested, so whether an association between the vaccine and PF4 antibody, thrombocytopenia, and thrombosis exists or not is not definitive.

Future research must address several critical questions. Most importantly, unbiased population surveys are needed to assess the true risk, if any, of vaccination and CVST. Since spurious associations are always possible in rare disease research, the true prevalence of PF4 antibody formation, thrombocytopenia, and CVST after vaccination must be clarified. Further case series must be viewed with the utmost care and skepticism until population prevalence rates are measured in an unbiased manner. Other research questions concern the mechanisms of venous thrombosis in infected persons. There is a rich literature possible, with many fruitful directions to pursue. Investigators should be encouraged, and funded, to delineate the molecular and cellular mechanisms underlying CVST in COVID-19 or after vaccination.

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ARTICLE INFORMATION

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