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Case report

SARS-CoV-2 vaccination associated venous sinus thrombosis in three patients

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Abstract
Introduction: There is increasing evidence that vaccinations against the severe acquired respiratory syndrome coronavirus type-2 (SARS-CoV-2) virus can be followed by venous sinus thrombosis (VST). Here we report on three patients who developed VST shortly after SARS-CoV-2 vaccinations.
Case series: An 80-year-old male, a 58-year-old male, and a 34-year-old female developed VST 14 to 24 days after the first dose of an mRNA-based SARS-CoV-2 vaccine. All three patients profited from analgesics, heparinisation, and oral anticoagulation, but made only an incomplete recovery at the time of discharge. Arguments for a causal relationship are: VST was time-linked to vaccination in the three patients; VST was previously reported after SARS-CoV-2 vaccination; SARS-CoV-2 infections can be complicated by VST; and SARS-CoV-2 can be associated with hypercoagulability. The fact that no hypercoagulability occurred in a pilot study after SARS-CoV-2 vaccination and that there has been no evidence of an increased prevalence/incidence of VST after vaccination since the introduction of the SARS-CoV-2 vaccination speak against a causal relationship.
Conclusions: SARS-CoV-2 vaccinations can occasionally be followed by a VST. There are more arguments for than against a causal relationship.

Keywords: Coronavirus; COVID-19; Hypercoagulability; SARS-CoV-2; Thrombosis

Highlights:
- SARS-CoV-2 vaccinations can be complicated by cerebral venous sinus thrombosis.
- SARS-CoV-2 vaccination associated venous sinus thrombosis is attributed to hypercoagulability.
- SARS-CoV-2 vaccination associated venous sinus thrombosis is treated with heparin followed oral anticoagulation.

Abbreviations:
COVID-19 – Coronavirus diseases 2019; CSF – Cerebro-spinal fluid; CT – Computed tomography; ECG – Electrocardiogram; EEG – Electroencephalography; IVIGs – Intravenous immunoglobulins; MRI – Magnetic resonance imaging; PF – Platelet factor; SARS-CoV-2 – Severe, acute, respiratory syndrome-coronavirus-2; VST – Venous sinus thrombosis

Introduction

Venous sinus thrombosis (VST) has been repeatedly reported as a complication of severe acquired respiratory syndrome coronavirus type-2 (SARS-CoV-2) infections (Dakay et al., 2021; Medicherla et al., 2020). Additionally, there is accumulating evidence that VST can also be a complication of SARS-CoV-2 vaccinations (Bikdeli et al., 2022; Ciccone, 2021; Kerr et al., 2022; Zakaria et al., 2021). The incidence of VST after a first vaccine dose within one month of administration is 0.55 per 100,000 for all vaccine brands, and 1.52 per 100,000 for the Astra Zeneca vaccine (AZV) (Schulz et al., 2021). Given an incidence of 0.02–0.15 per 100,000 for VST in the general population, the risk of VST increases after SARS-CoV-2 vaccination (Schulz et al., 2021). However, other studies have found only a slightly increased risk of VST after vaccination (Kerr et al., 2022), or no increased incidence of VST after SARS-CoV-2 vaccinations at all (Pawlowski et al., 2021). Symptoms and signs of VST usually resolve after anticoagulation with heparin or oral anticoagulants. However, when VST is associated with vaccine-induced thrombotic thrombocytopenia (VITT), the consequences can be fatal. Here we report a case series of three patients who developed a VST shortly after the first dose of SARS-CoV-2 vaccination. Written informed consent for publication of the results was obtained from the patients.

Case presentation

Two of the three cases were male, and one was female. Age ranged from 34 to 80 years. In two of the patients VST was

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diagnosed upon MR venography, and in one case upon CT venography. All three patients received heparin, being replaced by dabigatran.

Case 1

The first patient is an 80-year-old, polymorbid male who experienced a previously unknown, holocrane headache with left temporal predominance. His previous history was positive for multiple granulomas of the lung of unknown dignity, diverticulosis, colonic adenoma, steatosis hepatis, cholecystolithiasis, prostate carcinoma, and pre-diabetes. He received the first dose of an mRNA-based SARS-CoV-2 vaccine [Biontech Pfizer vaccine (BPV)] 21 days prior to presentation, and shortly before admission he had been treated with ampicillin for a suspected hypo-pharyngeal abscess for 8 days. On admission, he had motor aphasia, ataxia on the right lower limb, marked left temporo-occipital tenderness, and deficient attention, concentration, and photosensitivity. Cerebral MRI revealed thrombotic occlusion of the left transverse sinus up to the left bulb of the jugular vein, and on a follow up MRI a subacute left occipito-temporal ischemic lesion (hyperintensity on diffusion weighted imaging, hyperintensity on the apparent diffusion coefficient map). Long-term electrocardiography (ECG) recording revealed paroxysmal atrial fibrillation. Echocardiography exclusively showed a mildly enlarged left atrium. Electroencephalography (EEG) recordings repeatedly revealed paroxysmal activity in a left parieto-temporal projection. CSF-investigations revealed pleocytosis of 174/3 cells and mild protein elevation. The thrombocyte count, leukocyte counts, and fibrinogen level were normal, D-dimer was slightly increased [0.98 mg/l (*n*, <0.5 mg/l)]. C-reactive protein (CRP) was elevated on admission but normalised subsequently. Additionally, a paraproteinemia type kappa was detected. The patient profited from heparin, which was replaced by dabigatran 300 mg/d after five weeks, but did not lead to complete recovery yet. Additionally, upon discharge the patient was orally taking valproic acid (2500 mg/d), perampanel (10 mg/d), topiramate (400 mg/d), citalopram (15 mg/d), pantoprazole (40 mg/d), bisoprolol (1.25 mg/d), and folic acid (5 mg/d).

Case 2

The second patient is a 58-year-old male with a previous history of autoimmune thyroidopathy, diabetes, arterial hypertension, hyperlipidemia, thrombosis in the right lower leg 21 years earlier, gastro-esophageal reflux, severe depression and post-traumatic stress reaction, nicotine abuse, and obesity, who was admitted for diffuse headache (visual analogue scale (VAS) 10 initially and 7 on admission), nausea, emesis, and postural vertigo starting 14 days prior to admission. Symptoms began 24 days after the first dose of an mRNA-based SARS-CoV-2 vaccine (BPV). Clinical exam revealed positional tremor, retropulsion and dextropulsion on the treadmill test, and gait disturbance exclusively. A cerebral CT venography revealed thrombosis of the transverse and sigmoid sinuses bilaterally. Thrombocyte counts, leukocyte counts, and fibrinogen levels were within normal limits, the D-dimer was slightly increased to 1.07 mg/l (*n*, <0.5mg/l). CRP was slightly elevated on admission but normalised subsequently. The thyroidea-stimulating hormone was elevated to 4.73 µU/ml (*n*, 0.2–3.7 µU/ml). The patient profited from parenteral heparin followed by dabigatran 300 mg/d for 6 months. Upon discharge his oral medication included metformin (2000 mg/d), atorvastatin (40 mg/d), tizanidine (2 mg/d), pantoprazole (40 mg/d), sertraline (60 mg/d), mirtazapine 30 mg/d, trazodone 225 mg/d, risperidone (10 mg/d), and quetiapine (700 mg/d). At discharge only the positional tremor persisted.

Case 3

The third patient is a 34-year-old, previously healthy female who was admitted for headache and cervicalgia, neck stiffness, photosensitivity, and vertigo. Five days prior to admission she had been seen by an oto-rhino-laryngologist who prescribed tizanidine without benefit. She had received the first dose of an mRNA-based SARS-CoV-2 vaccine (BPV) 14 days prior to the onset of the clinical manifestations. Clinical neurologic exam was normal after resolution of the initial manifestations upon application of metamizol. MR venography surprisingly revealed a thrombotic occlusion of the left transverse and sigmoid sinuses without acute parenchymal damage (normal diffusion weighted imaging, normal apparent diffusion coefficient, normal susceptibility weighted imaging) (Fig. 1). D-dimer was slightly elevated to 1.71 mg/l (*n*, <0.5 mg/l). The thrombocyte count, leukocyte count, CRP, and fibrinogen levels were normal. Initially, the patient received danaparoid. After anti-platelet factor (PF)-4 antibodies came back negative, heparin was started. A control MRI, 16 days after the first one, showed almost complete recanalization of the previously occluded sinuses. Additionally, she tested positive for hepatitis-B. After heparin, dabigatran 300 mg/d was prescribed for six months. No other medication was indicated. At discharge the patient only complained about vertigo upon verticalisation.

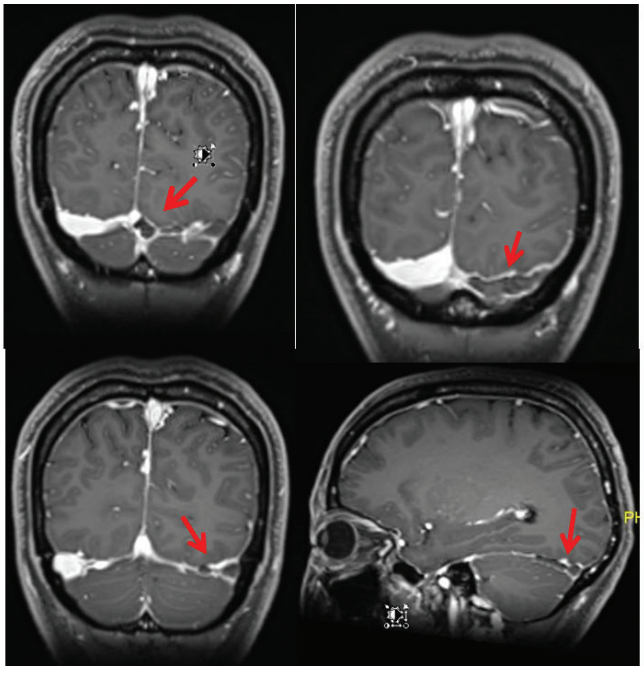

Fig. 1. Cerebral MR venography showing thrombosis of the left transverse sinus in patient 3

Discussion

The three patients are interesting as they show that SARS-CoV-2 vaccinations can be followed by VST within a timeframe of 14–24 days after the vaccination. Whether there was a causal relation between the vaccinations and the occurrence remains speculative. There are arguments both in favour and against a causal relation. Arguments in favour are that the VST was time-linked to the vaccination; SARS-CoV-2 infections can be complicated by hypercoagulability (Burley et al., 2021); post-SARS-CoV-2 vaccination VST has been previously reported (Ciccone, 2021; Zakaria et al., 2021); and VST has been repeatedly reported as a complication of SARS-CoV-2 infections (Dakay et al., 2021; Medicherla et al., 2020). As of the end of June 2021, >300 cases with SARS-CoV-2 associated VST were reported in 26 publications (Finsterer, 2022). Hypercoagulability has been explained by direct activation of platelets, enhanced coagulation, by indirect activation (for example: cytokine storm) of endothelial cells by SARS-CoV-2, shifting endothelium from an anti-thrombotic to a pro-thrombotic state, and by direct activation of complement pathways, promoting thrombin generation (Steadman et al., 2021). Arguments against a causal relation are that hypercoagulability was absent after SARS-CoV-2 vaccination in a recent pilot study (Campello et al., 2021), and that currently no reliable data are available showing that the prevalence or incidence of VST has truly increased since the introduction of SARS-CoV-2 vaccines. One of these studies included 101 patients who received the AZV and 89 patients who received the BPV (Campello et al., 2021). Thrombin receptor activating peptide (TRAP)-, adenosine di-phosphate (ADP)-, and arachidonic acid induced aggregation (ASPI)-induced platelet aggregation, as well as platelet count were similar among vaccinated and control subjects (Medicherla et al., 2020). Endogenous thrombin potential (ETP) was also comparable among these groups (Campello et al., 2021). It was concluded that, after vaccination with the BPVr or AZV, no significant activation of fibrinogen-driven coagulation, plasma thrombin generation, or clinically meaningful platelet aggregation vaccines was observed (Campello et al., 2021).

Causes of VST other than the vaccination are manyfold. They include coagulopathy (coagulation factor deficiency, thrombophilia, hyperhomocystemia), infections (otitis, sinusitis, tonsillitis, tooth infections, meningitis, hepatitis, herpes, zytomegaly, endocarditis, tuberculosis, funghi, parasites), cardiac disease, hematological disorders, immunodeficiency (lupus, Sjögren syndrome), drugs (chemotherapeutics, anti-conceptive pill, gluocorticoids), interventions (brain surgery, lumbar puncture, central venous catheter), vasculitis, traumatic brain injury, diabetes, and smoking. Most of these causes were excluded in the three patients. The hypopharyngeal abscess in patient-1 was only suspected and never confirmed. Alternative causes in patient-2 were smoking and diabetes, and in patient-3 chronic hepatitis. Diabetes in patient-2 was well controlled. Hepatitis in patient-3 was congenital and did not require any treatment. Smoking in patient-2 could have been causative but this is regarded unlikely. All patients were drinking sufficiently, had normal hemodynamic parameters, no severe acute infection, no history of inactivity of immobilisation, and no hereditary coagulation disorder.

Another alternative cause of VST in the three patients could have been VITT. VITT is associated with elevated D-dimer and elevated anti-PF-4 antibodies. It is frequently complicated by thrombosis, including VST (Dix et al., 2022). About half of the patients with VITT experience a VST (Palaiodimou et al., 2021). Because platelet counts were within normal limits in each of the 3 patients, and since D-dimer was only slightly elevated in each of the three patients, VITT was ruled out as an alternative cause of VST in all three patients. Patients with VITT experience thrombosis in different locations with different symptoms. They require different therapy to patients without VITT (Zamboni et al., 2022). Patients with VST and VITT experience severe headache, bleeding, isolated thrombocytopenia, and mortality is increased to non-VITT (Pang et al., 2022; Thiele et al., 2022). Patients with VST due to VITT should be treated with non-heparin anticoagulants, and intravenous immunoglobulins platelet transfusions should be avoided (Ferro et al., 2021).

Conclusions

SARS-CoV-2 vaccinations can be complicated by VST. VST can occur in all age groups, both genders, predominantly after the first dose, and with all available vaccine specifications. Currently, it is possible to raise more arguments in favour than against a causal relation between SARS-CoV-2 vaccination and VST.

Conflict of interests

The author has no conflict of interests to declare.

Ethics approval

Ethics approval was in accordance with ethical guidelines. The study was approved by the institutional review board.

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