

Venous sinus thrombosis after the first dose of Pfizer BioNTech vaccine

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SUMMARY

mRNA vaccines including Pfizer BioNTech and Moderna have categorically been considered safe when it comes to preventing COVID-19. However, there is still a small associated risk of thromboembolic phenomenon including venous sinus thrombosis with it and our case report highlights one.

We describe a patient who developed severe progressive headache, tinnitus and visual disturbance symptoms post-Pfizer-SARS-CoV-2 vaccination. His medical history included essential tremors, hypertension, type 2 diabetes mellitus, chronic kidney disease stage 3, anxiety, depression and long-term catheterisation. Systemic examination revealed hypotonia, generalised reduced power and central diplopia along with peripheral visual field defect in the left eye. He was extensively investigated, the COVID-19 PCR test was negative and all routine blood tests were in the normal range except a marginally raised D-dimer of 779 ng/mL. CT head was unremarkable. He was also tested for myasthenia gravis; however, acetylcholine receptors antibodies were negative and nerve conduction studies were normal. Subsequent MRI of the brain with venography confirmed venous sinus thrombosis. A 24-hour Holter monitoring test did not reveal any cardiac rate or rhythm abnormality. He was treated with apixaban as per a neurologist's advice. His clinical condition started to improve and was later discharged from the hospital with an outpatient neurologist clinic follow-up.

BACKGROUND

In late 2019, a new disease emerged from Wuhan (a city in the Hubei Province of China), this was identified due to SARS-CoV-2 resulting in acute severe pneumonia and respiratory failure. In February 2020, WHO named it COVID-19 and due to its rapid spread declared it a global pandemic.

So far, vaccines have been considered the most promising approach for suppressing the pandemic and are strongly recommended. Different vaccines have been used, for example, Pfizer-BioNTech, Moderna, Johnson & Johnson, AstraZeneca vaccine and so on. In large placebo-controlled trials, these vaccines were highly effective in preventing laboratory-confirmed COVID-19, especially severe/critical disease.¹⁻³

Both local, as well as systemic side effects, have been reported after receiving these vaccines. Local and systemic adverse effects (pain, fever, fatigue, headache) are common but usually non-severe. Johnson & Johnson and AstraZeneca COVID-19 vaccines are, however, associated with an extremely

small risk of thrombosis with thrombocytopenia, but their benefits outweigh this rare risk.^{3,4}

We are presenting a rare case of cerebral venous sinus thrombosis (CVST) that appeared after receiving the Pfizer-BioNTech COVID-19 vaccine.

CASE PRESENTATION

A Caucasian male in his 80s presented to the accident and emergency department with a 2-week history of severe progressive headache more pronounced in the retro-orbital region, associated with tinnitus and visual disturbance. Symptoms started the next day after receiving the first dose of the Pfizer BioNTech vaccine. There was no relief with over the counter analgesia and symptoms worsened causing more psychological distress, impaired concentration and sleeping difficulties. Medical history included essential tremors, hypertension, type 2 diabetes mellitus, chronic kidney disease stage 3, anxiety, depression and long-term catheterisation. He was fully compliant with his regular medications and there was no recent evidence of trauma. He was living alone in his house and mobilising independently.

His initial observations showed raised blood pressure, systemic examination revealed central diplopia and peripheral visual field defect, intentional tremors, positive Romberg's sign, reduced power in all four limbs, reduced reflexes and down-going planters.

INVESTIGATIONS

He was extensively investigated and all routine blood tests were in the normal range except slightly raised D-dimers (table 1).

COVID-19 PCR test was negative.

CT head showed mild cerebral and cerebellar volume loss but unremarkable otherwise.

He was also investigated for myasthenia gravis, however, acetylcholine receptors antibodies were negative and nerve conduction studies showed no evidence of clinically significant peripheral neuropathy or generalised neuromuscular junction disorder. A 24-hour Holter monitoring test did not reveal any cardiac rate or rhythm abnormality. Brain MRI with venography revealed absent venous flow in the left transverse sinus and the left jugular vein (figure 1A,B) with an impression of cerebral venous sinus thrombosis.

TREATMENT

There was a discussion with the on-call neurosurgical and neurology team and it was agreed that



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Table 1 Laboratory investigations of the patient

Full blood count	Results		Normal values
Haemoglobin	121	g/L	130–170
White cell count	9.7	10 ⁹ /L	4.0–10.0
Platelet count	195	10 ⁹ /L	150–400
Haematocrit	36	%	40–50
Red cell count	4.39	10 ¹² /L	5.00–6.00
Mean cell volume	83	fL	83–101
Mean cell Hb	28.0	pg	27–32
Neutrophils	7.49	10 ⁹ /L	1.5–6.5
Lymphocytes	1.28	10 ⁹ /L	1.1–3.5
Monocytes	0.72	10 ⁹ /L	0.21–0.92
Eosinophils	0.15	10 ⁹ /L	0.02–0.67
Basophils	0.05	10 ⁹ /L	0.00–0.13
ESR	6	mm/hour	1–30
Serum biochemistry			
CRP	3	mg/L	0–5
Estimated GFR	31	mL/min	
Sodium	139	mmol/L	133–146
Potassium	3.9	mmol/L	3.5–5.3
Urea	* 9.4	mmol/L	2.5–7.8
Creatinine	* 165	umol/L	59–104
Total protein	66	g/L	60–80
Albumin	43	g/L	35–50
Calcium	* 2.17	mmol/L	2.25–2.55
Corrected calcium	* 2.15	mmol/L	2.20–2.60
Inorganic phosphate	1.07	mmol/L	0.8–1.5
Total bilirubin	10	umol/L	0–21
Alkaline phosphatase	99	IU/L	30–130
Alanine transaminase	16	IU/L	5–41
Glucose	5.7	mmol/L	
Serum vitamin B12	501	ng/L	197–771
Vitamin D	81.1	nmol/L	25–50
Clotting profile and D-dimer			
INR—clotting profile	0.9	Ratio	0.8–1.2
APTT—clotting profile	30	s	22–30
D-dimer	779	ng/mL	500

APTT, activated partial thromboplastin clotting time; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; INR, international normalized ratio.

there was no other contributing factor than the recent Pfizer COVID-19 vaccine. A multidisciplinary team decision agreed on treatment with a course of apixaban (5 mg two times per day) for 3 months. After starting apixaban, patient's condition started to improve slowly and later he was discharged home with routine outpatient neurology follow-up. Apixaban was advised due to its lower risk of major bleeding and also as characteristics of our case were similar to a normal non-vaccine-related CVST.

DISCUSSION

CVST is a rare condition with a background incidence of about 15 cases per million people each year according to recent studies from Australia and the Netherlands.⁵ CVST is a rare cause of stroke that generally affects younger adults and women more than men. Although the pathophysiology is not fully understood, prothrombotic conditions are the most common implicated risk factor for CVST. Patients with hereditary thrombophilia have increased chances of developing any form of thrombosis, including CSVT. G20210A prothrombin polymorphism, factor V Leiden and antiphospholipid syndrome are the most usual

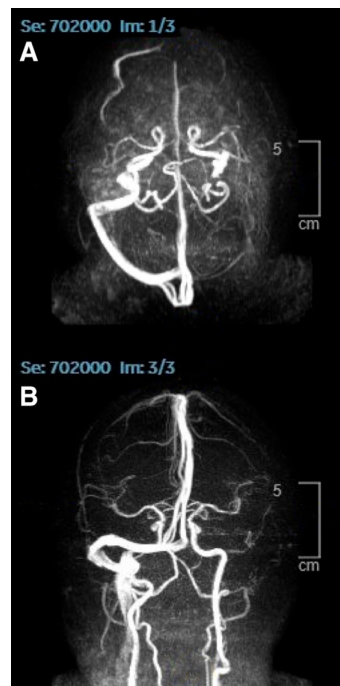


Figure 1 Magnetic resonance venography (MRV) of the cerebral venous sinuses shows absent flow in the left transverse sinus and left jugular.

causes. Protein C, S deficiency and antithrombin III deficiency are less commonly encountered risk factors.⁶

Studies and clinical data have confirmed that COVID-19 has been associated with hypercoagulability, with a high incidence of the thromboembolic phenomenon.

Since April 2021, CVST (along with low platelets) link has been established with Astra Zeneca vaccine and Johnson & Johnson (Janssen) COVID-19 vaccine, this was named as vaccine-induced immune thrombotic thrombocytopenia (VITT).^{4,7} This vaccine-associated syndrome provokes immune-mediated thrombotic thrombocytopenia via IgG antibodies that recognise platelet factor (PF) 4 and activate platelets through their Fcγ receptors.^{4,7–10} Therefore, the pathogenesis of VITT has been considered similar to that of heparin-induced thrombocytopenia.

CVST has also been reported in a very small number of individuals who have received the mRNA vaccines.¹¹ The pathophysiological mechanism leading towards the development of CVST post mRNA-based vaccination remains unclear. One possibility is that before translation, mRNA may induce pro-inflammatory cascades after binding to pattern recognition receptors. A spike protein translated by the mRNA may facilitate platelets aggregation and dense granule secretion¹² and activate the alternative pathway.¹³ Furthermore, the spike protein in epithelial cells promotes IL-6 trans-signalling by activation of the angiotensin II type 1 receptor axis to initiate the collaboration of a hyper-inflammatory response.¹⁴ These might be responsible for the trigger of thrombus formation, which is quite dissimilar from the pathogenesis of VITT mediated by PF4-reactive antibodies.⁴

A USA-based retrospective cohort study (April 2021) was also conducted (537 913 COVID-19 cases) to look at the incidence of CVST and portal vein thrombosis 2 weeks after receiving mRNA-based COVID-19 vaccine. This study suggested that the risk of CVST in the 2 weeks after vaccination with the Moderna and Pfizer vaccines is very low (about 4 per million people), while the incidence of CVST in the 2 weeks after COVID-19 diagnosis

is about 8–10 times as high as this (39 per million people). Both of these risks were higher than in the general population over 2 weeks (0.4 per million).¹⁵

In a recent US study (June 2021), 3 cases of CVST were observed within the 30 days following Pfizer-BioNTech vaccination (2 females, 1 male) including one individual with a prior history of thrombosis and another individual with recent trauma in the past 30 days. However, there was no statistically significant difference found in the incidence rates of CVST in 30-day time windows before and after vaccination.¹⁶

While it is important to consider this reporting in pharmacovigilance decision-making, there is reason to interpret such reports with caution. Spontaneous adverse event reporting is prone to reporting bias and increased event reporting with lay press attention or the introduction of a novel agent.^{17–19}

So far, there is not much data available for post-Pfizer vaccine CVST and it needs further research and studies.

Learning points

- ▶ The SARS-CoV-2 infection has been associated with hypercoagulability, with a high incidence of venous thromboembolism including pulmonary embolism and deep vein thrombosis with a glaring-associated thrombocytopenia.
- ▶ Physicians should also be alert for signs and symptoms related to cerebral venous sinus thrombosis (CVST), for example, headache or other neurological symptoms when they occur in patients who have recently been vaccinated with the COVID-19 vaccines, for example, AstraZeneca vaccine, Pfizer and so on.
- ▶ Features of CVST after mRNA-based COVID-19 vaccines are similar to those of non-vaccine-related CVST including a normal platelet count. Therefore, anticoagulation may be appropriate and should not be avoided in contrast to patients with vaccine-induced immune thrombotic thrombocytopenia after virus vector COVID-19 vaccination, in which heparinisation or platelet transfusion is contraindicated.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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