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Cerebral Venous Thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine

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The development of SARS-CoV-2 vaccines has raised several concerns regarding venous thromboembolism, namely cerebral venous thrombosis. Although cerebral venous thrombosis has been reported after administration of a viral vector vaccine, due to a possible auto-immune mechanism inducing thrombocytopenia, the same has not happened in mRNA vaccines. We report two cases of cerebral venous thrombosis, shortly after administration of mRNA vaccine. In both patients, there was no evidence of thrombocytopenia or antiplatelet antibodies, and alternative causes for cerebral venous thrombosis were found. As such, despite the temporal relation of both cases to vaccine administration, these types of cerebral venous thrombosis do not seem to be pathophysiological different from cerebral venous thrombosis not associated to SARS-CoV-2 vaccination. Continuous pharmacovigilance is necessary to monitor possible new events and clarify this association.

Keywords: Cerebral Venous Thrombosis—COVID-19—SARS-CoV-2—Thromboembolism

SARS-CoV-2 vaccine development raised several concerns regarding adverse events, particularly venous thromboembolism.[1,2] Cerebral venous thrombosis (CVT) was recently reported in patients vaccinated with AstraZeneca's vaccine and Janssen's vaccine.[3–6] This side effect has not been previously reported in mRNA vaccines. We hereby report two CVT cases in patients who took an mRNA vaccine (BNT162b2, Comirnaty®, Pfizer/BioNTech).

Case 1: A 47-year-old female, who had iron-deficiency anemia due to adenomyosis and used combined oral contraceptives, developed persistent headache, nausea and photophobia six days after the first vaccine dose. Three days later, she presented a sudden left motor deficit. Papilledema, left visual extinction, right gaze deviation, and left hemiparesis were documented. Brain MRI with venography revealed thrombosis of superior sagittal, right lateral, transverse, sigmoid sinuses and jugular vein and left sigmoid sinus, together with right frontal subarachnoid hemorrhage and a cortical venous infarct. Admission PCR test for SARS-CoV-2 was negative. Complete blood count revealed microcytic hypochromic anemia (9.3 g/dL) and normal platelet count (343.000/μL). Coagulation tests-aPTT, Quick test, fibrinogen-were normal. Prothrombotic screening-lupus anticoagulant, anticardiolipin antibodies, protein C, RAPC, antithrombin III, and prothrombin mutation-was negative except for low protein S (0.40, N>0.54). Autoimmune screening-immunoglobulins, complement, antinuclear antibodies-was negative. A chest-abdomen-pelvis CT excluded occult neoplasms. She started acetazolamide and enoxaparin 60 mg bid, later switched to warfarin. At two-month follow-up, slight gait instability was the only deficit. Antiplatelet-PF4-antibodies, measured 2 months after the event with ELISA technique, were negative. Anti-SARS-CoV-2 IgG was positive at low titers [anti-RBD IgG 17 U/mL (N<10), anti-S1 IgG 11 U/mL (N<10), anti-S2 and anti-N negative]. The second dose of the vaccine was never administered.

Case 2: A 67-year-old female had a history of multiple cerebral cavernous malformations, hypertension, diabetes, dyslipidemia, viral myocarditis, and depression. Three days after the second vaccine dose, she presented

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with sudden right lower limb clonic movements, followed by motor deficit, loss of consciousness and headache. Tongue bite was evident. Brain MRI showed thrombosis of high convexity cortical veins, superior sagittal, right transverse, and sigmoid sinus and jugular vein. There were no signs of hemorrhage. Admission PCR test for SARS-CoV-2 was negative. Complete blood count, including platelet count (164.000/μL) and coagulation tests were normal. An elevation of erythrocyte sedimentation rate was noticed (53 mm/1st hour), with no other elevation of inflammatory biomarkers. Prothrombotic and autoimmune screening were unremarkable. Electroencephalography showed focal polymorphic delta slowing, located in the right frontal-temporal region, and epileptiform discharges. A chest-abdomen-pelvis CT showed a probable renal cell carcinoma. She started levetiracetam 500 mg bid and enoxaparin 80 mg bid, later switched to dabigatran 150 mg bid. Antiplatelet-PF4-antibodies, 20 days after the event, were negative. Anti-SARS-CoV-2 IgG was positive (anti-RBD IgG >100 U/mL, anti-S1 IgG >100 U/mL, anti-S2 72 U/mL, anti-N negative). She was discharged without neurological deficits, awaiting an urgent Urology referral.

Discussion

The Pfizer/BioNTech vaccine contains mRNA particles that are translated into a spike protein, whose immune recognition leads to antibody production.[7] Before translation, mRNA may bind to pattern recognition receptors inducing pro-inflammatory cascades.[8] This immune response might, theoretically, contribute as a trigger for thromboembolic events. This mechanism is different from the AstraZeneca vaccine (ChAdOx1 nCoV-19, Vaxzevria®) and Janssen vaccine (Ad26.COV2.S), which use a viral vector.

Up to 08/05, 70 cases of CVT with AstraZeneca's vaccine have been reported in EudraVigilance and 5 cases with Janssen's, most occurring in women aged under 60, up to 2 weeks post-vaccination.[3,5,9] These cases had thrombocytopenia and antiplatelet-PF4-antibodies, with a probable auto-immune mechanism leading to an atypical form of immune thrombocytopenia.[10] Although the exact pathophysiological mechanism for this type of thrombosis is still not clear, patients seem to benefit from immunomodulatory therapy (with intravenous immunoglobulin and high dose corticosteroids), and a proposed treatment mechanism with immunomodulation and non-heparin-anticoagulation has recently been published[11].

However, our cases did not exhibit thrombocytopenia nor antiplatelet antibodies. There was no clinical or laboratory worsening after the start of enoxaparin. Moreover, both had good clinical outcome, with no or minor neurological deficits, and had additional CVT risk factors: combined hormonal contraception and a likely malignant renal neoplasm. Thus, despite the temporal relation with vaccination, these cases do not seem to be pathophysiologically different from regular CVT. Continuous pharmacovigilance is necessary to monitor adverse events and clarify this association.

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Informed consent

The patients gave their consent to the publication of the data. Details that might disclose the identity of the subjects under study have been omitted.

Ethical approval

Not applicable.

Guarantor

LD.

Contributorship

LD researched literature. RR, JM, DF, PRS, AP, GG, LF, VF, and MC were involved in the clinical care and management of the patients. LD, RR and MC acquired, analysed, and interpreted the data and drafted the manuscript. RR and MC provided supervision and a critical revision of the paper. LD wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript. Written consent for publication was obtained from the patients.

Declaration of Competing Interest

The authors declare no conflict of interest.

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