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Review Article

Stroke Associated with COVID-19 Vaccines

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Objectives: Development of safe and effective vaccines against coronavirus disease 2019 (COVID-19) remains the cornerstone of controlling this pandemic. However, there are increasing reports of various types of stroke including ischemic stroke, and hemorrhagic stroke, as well as cerebral venous sinus thrombosis (CVST) after COVID-19 vaccination. This paper aims to review reports of stroke associated with COVID-19 vaccines and provide a coherent clinical picture of this condition. *Materials and methods:* A literature review was performed with a focus on data from recent studies. *Results:* Most of such patients are women under 60 years of age and who had received ChAdOx1 nCoV-19 vaccine. Most studies reported CVST with or without secondary ischemic or hemorrhagic stroke, and some with Vaccine-induced Thrombotic Thrombocytopenia (VITT). The most common clinical symptom of CVST seen after COVID-19 vaccination was headache. The clinical course of CVST after COVID-19 vaccination may be more severe than CVST not associated with COVID vaccination. Management of CVST following COVID-19 vaccination is challenging and may differ from the standard treatment of CVST. Low molecular weight heparin is commonly used in the treatment of CVST; however, it may worsen outcomes in CVST associated with VITT. Furthermore, administration of intravenous immunoglobulin and high-dose glucocorticoids have been recommended with various success rates. *Conclusion:* These contradictory observations are a source of confusion in clinical decision-making and warrant further study and development of clinical guidelines. Clinicians should be aware of clinical presentation, diagnosis, and management of stroke associated with COVID-19 vaccination.

Key Words: COVID-19—Vaccination—Stroke—Thrombosis

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Introduction

In the past two decades, coronaviruses have caused two serious pandemics, namely severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[1,2] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused coronavirus disease 2019 (COVID-19) in late 2019, which was later turned into a pandemic in March, 2020.[3] COVID-19 is now a global health issue[4,5] for which control measures such as the use of face masks, physical distancing, testing of exposed or symptomatic individuals, contact tracing, and quarantine seem insufficient.[6–14] Despite numerous efforts, there is no cure for the disease.[15] Thus far, vaccination has been the best strategy to end this pandemic; however, vaccination hesitancy can jeopardize the success of COVID-19 immunization programs.[16] Several COVID−19 vaccines have been developed and launched into the market, and some are still in the process of clinical trials. Information on vaccine safety or adverse effects has important impacts on public acceptance of the vaccines.[17,18]

COVID-19 produces various neurological manifestations.[19,20] Stroke is an important neurological complication of COVID-19 in the central nervous system (CNS),[20,21] but it also occurs subsequent to COVID-19 vaccination.[22] Ischemic stroke and intracerebral hemorrhage (ICH)[23]have been reported after COVID-19 vaccination.[24] Cerebrovascular venous sinus thrombosis (CVST) was first reported after Oxford-AstraZeneca vaccine inoculation (ChAdOx1 nCoV-19). Subsequently, 6 cases of CVST were reported after administration of Johnson & Johnson vaccination (Ad26.COV2.S).[25]

Vaccine-induced Thrombotic Thrombocytopenia (VITT) may also be associated with stroke following COVID-19 vaccination.[26–28] Management and treatment of stroke are usually challenging, but it is more so in VITT-associated stroke. This review paper summarizes reports of stroke after COVID-19 vaccination and gives account of its clinical picture, management, and treatment. For this review, we searched PubMed and Google Scholar databases for the following keywords: Stroke, cerebral venous sinus thrombosis, CVST, cerebral venous thrombosis, CVT, cerebrovascular accident, CVA, cerebrovascular event, thrombosis, ischemic stroke, intracerebral hemorrhage, intracranial hemorrhage, ICH, hemorrhage, vaccine, COVID-19, SARS-CoV-2, corona, complication, side effect.

Different types of COVID-19 vaccines: how they work

COVID-19 vaccines motivate the immune system to create antibodies against SARS-CoV-2. The vaccines use a harmless structure similar to spike (S) protein, which is present on the surface of SARS-CoV-2 and is used for viral endocytosis to the host cells. The COVID-19 vaccines include messenger RNA (mRNA), vector, protein subunit, and inactivated/weakened vaccines.[29,30] Engineered mRNA COVID-19 vaccines namely Pfizer-BioNTech (BNT162b2) and the Moderna (mRNA-1273) give the cells instructions to make S protein which may generate antibodies. After delivering instructions, the mRNA is broken down immediately and does not enter the nucleus of the host cells. In vector COVID-19 vaccines viz Ad26.COV2.S, Sputnik V (rAd26-S and rAd5-S), and ChAdOx1 nCoV-19 SARS-COV-2's, genetic material is inserted in a viral vector. The vector delivers the genetic material to the host cells that make copies of the S protein on their surfaces. The immune system then responds by creating antibodies and defensive white blood cells. Protein subunit COVID-19 vaccines such as Novavax (NVX-CoV2373) include only harmless S protein which stimulates the immune system. Inactivated or weakened COVID-19 vaccines do not cause disease, but still, stimulate the immune system.

Vaccine-induced neurological complications

SARS-CoV-2 infection induces important changes in the innate and adaptive immunity.[31] It results in overproduction of proinflammatory cytokines including interleukins (e.g., IL-1α, IL-1β, IL-6, IL-7), chemokines (e.g., CXCL1, CXCL2, CXCL6, CXCL8 /IL-8, CXCL10, CCL2/ MCP-1, CCL3 / MCP-1 A, CCL4/ MIP1B), and interferons (e.g., IFN-α2, IFN-β1, IFN-2).[32,33] Serum IL-6, a reliable prognostic factor for ischemic stroke,[20] rises in COVID-19.[34] It is thought that at least some neurological symptoms such as inflammation of the peripheral and central nervous systems are due to the release of these factors.[35] Moreover, lung tissue involvement can lead to hypoxia in the CNS which can present with sensory, cognitive, and motor impairment.[36]

Vaccination induces a series of immunological events which may cause neurological problems, for example, demyelinating diseases,[37–40] epileptic seizures,[41] Guillain-Barre syndrome,[42] and stroke.[43] The most common neurological symptoms after the vaccination include dizziness, headache, pain, muscle spasms, myalgia, and paresthesia, which are usually acute and transient.[43] Furthermore, in limited studies, tremor, diplopia, tinnitus, dysphonia, and seizures were seen after COVID-19 vaccination.[43] In a trial of the Pfizer−BioNTech (BNT162b2) mRNA vaccine, 7 out of 37,000 participants developed Bell's palsy, although the rate of the disease was not higher than expected in the general population.[44]

Stroke following COVID-19 vaccination

Stroke is a major cause of death and disability globally.[45] It can be classified into two main categories of ischemic and hemorrhagic stroke, the latter has higher mortality than the former.[46] CVST is a rare form of stroke that is generally seen in younger patients and predominantly women.[47–49] COVID-19 vaccines may trigger stroke with thrombotic thrombocytopenia with or without the presence of anti-platelet factor 4 antibody (anti-

PF4 antibody). Such association between thrombocytopenia and thrombosis with a catastrophic clinical picture has raised clinical attention. Association of thrombosis and thrombocytopenia rarely occurs in thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia (HIT), autoimmune HIT, antiphospholipid syndrome (APS),[50] and disseminated intravascular coagulation (DIC).[51] Unusual thrombotic events with thrombocytopenia following COVID-19 vaccination and the presence of anti-PF4 antibody have led to the concept of VITT, which is also called thrombosis with thrombocytopenia syndrome (TTS).[52] The clinical picture mirrors what is seen in HIT.[53] Anti-PF4 antibodies are typically detected in HIT[54] probably due to molecular mimicry between proteins on the virus and platelet antigens,[55,56] On another reading, the antibodies produced against the spike (S) proteins might cross-react with specific antigens expressed on the platelet surface.[28] However, in one preliminary report, Greinacher et al.[57] suggested that anti-PF4 antibody do not cross-react with the S protein.

Another hypothesis is that the breakdown of fibrin leads to the production of D-dimer.[58] Elevated D-dimer associated with thrombocytopenia is suggestive of activation of systemic anticoagulation. Therefore, increased D-dimer level may be a helpful parameter to distinguish idiopathic primary thrombocytopenia from secondary thrombocytopenia due to systemic thrombosis.[58] Furthermore, CSVT incidence is significantly correlated with D-dimer level.[59]

A prospective Chinese cohort study suggested that inactivated COVID-19 vaccine (BBIBP-CorV, Sinopharm) did not influence the profile of antiphospholipid antibody and anti-PF4-heparin antibody nor increased the risk of thrombosis.[60] Additionally, Campello et al.[61] suggested that significant activation of fibrinogen-driven coagulation, plasma thrombin generation, or clinically meaningful platelet aggregation did not occur after ChAdOx1 nCoV-19 or BNT162b2 vaccination. Nevertheless, Simpson et al.[62] evaluated associations between ChAdOx1 nCoV-19 or BNT162b2 vaccination and hematological and vascular adverse events. They demonstrated an association between vaccination with ChAdOx1 (but not vaccination with BNT162b2) and idiopathic thrombocytopenic purpura (ITP), arterial thromboembolic events and hemorrhagic events.

Using an animal model, Nicolai et al.[63] showed that intravenous injection of ChAdOx1 nCov-19 triggers platelet-targeted autoimmunity in the spleen that may result in thrombocytopenia syndrome. Hence, aspiration (to ensure the needle is not in a blood vessel) prior to injection of the vaccine could be a potential preventive measure for this important side effect.

Most of the reports of stroke after COVID-19 are from Europe. In addition, most of the patients were women within an age range of 18-77 years and within 1-24 days after the ChAdOx1 nCov-19 vaccination.

Ischemic stroke after COVID-19 vaccination

In ischemic stroke, a region of the brain is dispossessed of blood flow which can be due to thrombosis of an artery or, in rare instances, a vein. Thrombosis can occur in the vessels following COVID-19 vaccination. They are usually seen in the context of VITT. These cases were mostly diagnosed following ChAdOx1 nCoV-19 vaccine, especially with the involvement of the middle cerebral artery (MCA). The emergence of persistent or unusual neurological symptoms after receiving the COVID-19 vaccines should urgently be evaluated for VITT with neuroimaging techniques and laboratory tests.

De Michele et al.[64] carried out clot analysis after thrombectomy in patients with ischemic stroke following the ChAdOx1 nCoV-19 vaccine and suggested that the clot collected during the first thrombectomy was mainly composed of platelets (85% of the total material examined) and was massively infiltrated by neutrophils with scarce evidence of karyorrhexis. Histological features consistent with the presence of neutrophil DNA extracellular traps (NETs) were also observed. Furthermore, the clot collected during the second endovascular procedure was a red-blood-cell-rich thrombus (90% of red blood cells and 10% fibrin and platelets) with scarce neutrophils. Normally, platelet-rich thrombi are formed by Von Willebrand factor, neutrophil extracellular traps, and fibrin.[65] However, platelet/fibrin thrombi were also found in veins and arteries of multiple organs,[66] so-called "white clot syndrome".[67] Despite this, it would be difficult to account for their potential pathophysiological differences. In fact, the main difference between the clots is their age.[64]

Table 1 shows that most of the patients with ischemic stroke after COVID-19 vaccination were women within the age range of 26-60 years and after vaccination with ChAdOx1 nCoV-19 vaccines and within 1 to 21 days after the vaccination.

Hemorrhagic stroke after COVID-19 vaccination

Hemorrhagic strokes occur when a blood vessel ruptures. ICH and subarachnoid hemorrhage (SAH) can occur after COVID-19 vaccination, which can be primary or secondary to venous thrombosis.[23,71–76] While ICH after COVID-19 vaccination can occur in the context of VITT, Silva et al.[75] described primary hemorrhagic stroke following ChAdOx1 nCoV-19 vaccination in a patient without thrombocytopenia, coagulation disorder, or coagulation risk factors. Argument for such a causal relation is that arterial hypertension[77] and ICH[23,78] are complications of COVID-19 vaccination. More to the point, hypertension is an important risk factor of ICH.

Finsterer et al.[79] suggested that the second dose of SARS-CoV-2 vaccination may be followed by ICH even when the first dose was uneventful Table 2. summarizes reports of ICH following COVID-19 vaccination. As can

Table 1. *Summary of reports of ischemic stroke cases following the COVID-19 vaccination.*

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19 (AstraZeneca)	3	35-43 F = 2, M = 1	11-21	Case 1: headache, left hemiparesis, right gaze preference, and drowsiness Case 2: diffuse headache, left visual field loss, confusion, and left arm weakness Case 3: dysphasia	Case 1: MCA infarct Case 2: ICA infart and CVST Case 3: MCA infarct Thrombocytopenia, positive anti-PF4 antibody, and increased D-dimer in all three patients	Case 1: IVIg, plasmapheresis, Fondaparinux, and decompressive hemicraniectomy Case2: IVIg, plasmapheresis, methylprednisolone, and Fondaparinux Case 3: platelet transfusion, IVIg, and Fondaparinux	Case1: death Case 2: improved clinically Case3: discharged with favorable clinical outcome	Al-Mayhani et al., 2021[27]
	1	60 F = 1	8	headache and left-weakness and eye deviation to the right	Ischemic stroke in the territory of ICA and MCA Thrombocytopenia, positive anti-PF4 antibody, and increased D-dimer	Hydrocortisone, platelet concentrates, hemicraniectomy, and dalteparin	Death	Blauenfeldt et al., 2021 (53)
	1	26 F = 1	1	Persistent nausea and headache and right hemiplegia and aphasia	Ischemic stroke in the territory of MCA Thrombocytopenia, positive anti-PF4 antibody, decreased fibrinogen level	Corticosteroids, plasmatic exchange, and anticoagulants	Only gripping difficulties and minor phasic troubles were remaining	Garnier et al., 2021[68]
	23	21-77 (mean:46) F = 14 M = 9	6-24 (mean:12)	NM	Thirteen cases of CVST Two cases of ischemic stroke antiPF4 antibody was positive in 22 patients Thrombocytopenia in 22 patients, low fibrinogen levels in 13 patients, and increased D-dimer levels in 21 patients	NM	Seven patients died	Scully et al., 2021[69]
	1	31 M=1	8	Acute headache, aphasia, and hemiparesis	Occlusion of MCA with the source of thrombus ipsilateral in the carotid bulb, elevated D-dimer level slightly, and positive anti-PF-4 antibody	IV thrombolysis, Aspirin, Danaparoid, Phenprocoumon	Favorable clinical outcome	Walter et al., 2021[70]

Table 1 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
	2	Case 1 = 55, Case 2 = 57 F=2	Case 1 = 9, Case 2 = 10	Case 1: left hemiplegia, right gaze deviation, dysarthria, and left neglect Case 2: aphasia, right hemiparesis, generalized seizures, and coma	Ischemic stroke Thrombocytopenia, positive anti-PF4 antibody, and increased D-dimer level	Case 1: mechanical thrombectomy, platelet transfusion, IVbetamethasone, IVIg, plasma exchange, fondaparinux Case 2: IVIg and dexamethasone	Case 1: critical condition Case 2: Brain death	De Michele et al., 2021[64]

Note: MCA: Middle Cerebral Artery; CVST: Cerebral Venous Sinus Thrombosis; Anti-PF4-antibody: anti-platelet factor 4 antibody; IVIg: Intravenous Immunoglobulin; IV: Intravenous.

be noted, most of the cases were reported following administration of ChAdOx1 nCoV-19 vaccine and in people 30–57 years of age, 5–12 days after the vaccination Table 2. shows the summary of reports of ICH following the COVID-19 vaccination.

Cerebral venous sinus thrombosis after COVID-19 vaccination

CVST is a rare form of stroke occurring often in young and middle-aged women.[81] Partial or complete occlusion of cerebral venous sinus system or its small-caliber draining veins leads to venous hypertension, localized parenchymal edema, raised intracranial pressure (ICP), infarction, and rarely ICH. The most common manifestation of CVST is headache,[82] which may be generalized or focal and is often progressive. CVST has been reported in COVID-19 patients and is paradoxically associated with thrombocytopenia.[55,83] This phenomenon can be explained by systemic platelet consumption and sequestration through agglutination triggered by COVID-19 vaccine immunization process, which may lead to thrombosis.[58] The peculiarities of CVST following COVID-19 vaccination warranted the specific term of VITT.[58] VITT is characterized by its unusual sites of thrombosis and the absence of common risk factors of CVST after COVID-19 vaccination in these patients. The unusual sites can include the cerebral venous sinus, splanchnic venous system, pulmonary thromboembolism (PTE), deep vein thrombosis (DVT), or acute arterial thrombosis.[28,78,84–87] CVST after COVID-19 vaccination was first reported following vaccination with ChAdOx1 nCoV-19; however, it was subsequently reported following adenovirus-based vaccine Ad26.COV2.S.[88] European Medicines Agency (EMA) reported 169 possible cases of CVST from 34 million recipients of the ChAdOx1 nCoV-19 vaccine; 35 possible cases of CVST from 54 million recipients of the BNT162b2 mRNA vaccine, and 5 possible, but unvetted, cases of CVST from 4 million recipients of the mRNA-1273 vaccine.[28] Six possible cases of CVST were reported from more than 7 million recipients of the Ad26.COV2.S vaccine.[28]

The frequency of atypical thrombosis after COVID-19 vaccination should be weighed against thrombosis in the general population. These statistics should be considered in comparison with stroke that occurs in patients with COVID-19. In these patients, thrombosis occurs at least 100-fold more often in the unvaccinated people compared to the vaccinated.[89] According to EMA data, of nearly 25 million people vaccinated with ChAdOx1 nCoV-19 vaccine in the UK, 62 developed CVT, and 24 had splanchnic venous thrombosis. The incidence of CVT in the vaccinated people was 2.6 per million people within 4-month after vaccination with ChAdOx1 nCoV-19 vaccine. However, the estimated incidence of CVT was 3-4 cases per million per year in unselected populations.[90] In

contrast, mRNA vaccines, compared to hormonal contraceptive use, do not show a disproportional rate of thromboembolic events in younger women.[91]

A multicenter cohort study[92] collected data from 43 hospitals across the UK and between April 1st and May 20th, 2021, reporting 95 patients with stroke, of which 70 had VITT. The median age of the VITT group was 47 years, compared to that in the non-VITT group, which was 57 years (p=0·005). The primary outcome of death or dependency occurred more frequently in the patients with VITT-associated CVT (33/70), compared with the non-VITT control group (4/25) (p=0·0061). This adverse outcome was less frequent in the patients with VITT who received non-heparin anticoagulants (18/50), compared with those who did not receive non-heparin anticoagulants (15/20) (p=0·0031), and in those who received IVIg (22/55), compared with those who did not receive IVIg (11/15) (p=0·022). In this study, it was also suggested that non-heparin anticoagulants and immunoglobulin treatment might improve outcomes of VITT-associated CVT.

CVST after vaccination mostly occurs with adenoviral COVID-19 vector vaccines, especially ChAdOx1 nCoV-19 vaccine; nonetheless, CVST may also occur following mRNA-based COVID-19 vaccines. rAd26-S and rAd5-S is another recombinant adenovirus vaccine but no CVT cases have been reported following its use. Nonetheless, that is not to say that CVT does not occur following this vaccine.

CVST usually has a good prognosis. However, CVST after COVID-19 vaccination may follow a catastrophic course. The outcome for these patients may be poor due to refractory increased ICP; indeed, almost half of patients with CVT in the context of VITT die within a few days and death often occurs following brain infarction often associated with ICH.[69,78,93]

Table 3 summarizes reports of CVST following the COVID-19 vaccination. The table shows that most of the patients were female at 24-56 years of age. Most of these CVST cases were reported following ChAdOx1 nCoV-19 vaccine administration. Furthermore, all of the patients received the vaccine 7-20 days before the diagnosis of stroke.

Ischemic and hemorrhagic stroke subsequet to CVST after COVID-19 vaccination

Ischemic or hemorrhagic stroke may occur with CVST subsequent to COVID-19 vaccination. Obstruction of the brain's venous system increases ICP and may rupture blood vessels leading to hemorrhagic stroke. Furthermore, hypercoagulable state may cause further clot formation causing ischemic stroke. These complications have a direct impact on the treatment strategy.

Table 4 summarizes reports of CVST with ischemic or hemorrhagic stroke. The table shows that most of the patients were female at 18-77 years of age. Most of these CVST cases were reported following ChAdOx1 nCoV-19 vaccine administration. Moreover, these patients received the vaccine 2-24 days before the diagnosis of stroke.

Comparison of different vaccines associated with stroke

Since the basic characteristics of vaccine recipients are different, it is not easy to compare various COVID-19 vaccines triggering stroke. The manufacturing technology for mRNA-based vaccines is different from that for adenovirus-based vaccines, and hence the mechanism of thrombosis formation differs in these vaccines.[112] CVST after ChAdOx1 nCov-19 vaccination is more frequent and is associated with venous thrombotic events and a higher mortality rate than that after the BNT162b2 and mRNA-1273 vaccines.[94] In addition, thrombocytopenia and positive anti-PF4 antibodies have been reported more frequently after the ChAdOx1 nCov-19 vaccine than after the mRNA-based vaccine.[94] Furthermore, the clinical manifestations of CVST after ChAdOx1 nCov-19 vaccine and mRNA-based vaccine are different. CVST after ChAdOx1 nCov-19 vaccination has a clinical picture different from CVST patients unrelated to vaccination; however, CVST which occurs after receiving mRNA vaccines is similar to pre-COVID-19 CVST cases unrelated to vaccination.[94] These differences can even extend to differences between vaccines that are made with similar technology. Indeed, patients who received the Ad26.COV.2.S vaccine tend to develop clinical manifestations later than those receiving ChAdOx1 nCoV-19.[114] Additionally, D-dimer and activated Partial Thromboplastin Time (aPTT) levels might be lower in patients after Ad26.COV.2.S than subjects receiving ChAdOx1 nCoV-19.[114] Also, the probability of a positive platelet function test in ChAdOx1 nCoV-19 recipients is much higher than in the Ad26.COV.2.S recipients; nonetheless, in both groups, most patients are positive for HIT antibody test using ELISA.[114] Notably, patients with CVT after Ad26.COV.2.S administration is more likely to suffer ICH and internal jugular vein thrombosis than those with CVT after ChAdOx1 nCoV-19.[114] There are no significant differences between the two vaccines in mortality and presenting symptoms, viz headache, visual disturbance, hemiparesis, and fever.[114] Beyond the comparison between different COVID-19 vaccines, Pawlowski et al.[115] assessed the association of COVID-19 vaccines and non-COVID-19 vaccines with CVST in a cohort of 771,805 vaccination events across 266,094 patients in the Mayo Clinic Health System between 01/01/2017 and 03/15/2021 and found that the risk of CVST is similar in the 30 days prior to COVID-19 vaccination compared to that in the 30 days after vaccination. In addition, the risk of CVST within 30 days following COVID-19 vaccination is similar to the risk of CVST within 30 days after all analyzed non-COVID

Table 2. *Summary of reports of ICH following the COVID-19 vaccination.*

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19 (AstraZeneca)	1	In her thirties F = 1	10	Headache, lethargy, uncoordinated movements, reduced consciousness, aphasia, central left facial paresis with right gaze deviation, and left hemiparalysis	ICH (MCA) Thrombocytopenia and positive anti-PF4 antibody Thrombi in the transverse sinus in autopsy	IV tranexamic acid	Death	Bjørnstad et al., 2021[23]
	1	57 F=1	5	Fever, headache, left hemiparesis, vomiting, and somnolence	ICH	Decompressive craniectomy	On Day 15 left hemiparetic, obeying simple tasks, kept on tracheostomy	Silva et al., 2021[75]
mRNA-based SARS-CoV-2 vaccine	1	52 M=1	7	aphasia	ICH in temporal lobe	Sacubitril/valsartan, atorvastatin, and bisoprolol in the rehabilitation	Aphasia resolved	Finsterer et al., 2021[79]
ChAdOx1 nCoV-19 (Vaxzervia)	1	52 M = 1	12	Intense headache, GCS;6	ICH Thrombocytopenia, elevated fibrin D-dimer level, low fibrinogen level, slightly increased INR	Tranexamic acid, platelet concentrate	Death	Wolthers et al.,2021[80]

Note: MCA: Middle Cerebral Artery; Anti-PF4-antibody: anti-platelet factor 4 antibody; ICH: Intracerebral Hemorrhage; INR: International Normalized Ratio; IV: Intravenous; GCS: Glasgow Coma Scale.

vaccinations. Finally, the authors suggested that CVST is rare and not significantly associated with COVID-19 vaccination in their study.

Recommendations for diagnosis and management of CVST after COVID-19 vaccination

Many cases of stroke after COVID-19 vaccination is associated with VITT. Following the first post-COVID-19 vaccination VITT reports several international scientific societies and panels of experts made recommendations on the management of patients with suspected VITT syndrome from diagnosis to treatment. Management of stroke associated with VITT is challenging and complex. In addition, clinicians should be aware that management recommendations of CVST after COVID-19 vaccination markedly differ from the routine treatment of CVST.

The diagnosis of VITT is rather challenging owing to its diverse clinical manifestations. Clinicians should maintain a high degree of suspicion in patients with symptoms suggestive of thrombotic events after COVID-19 vaccination, and along with this, wise comprehensive diagnostic criteria can be advantageous. The Expert Hematology Panel (EHP) of UK[116] and the American Society of Hematology (ASH)[117] produced recommendations for the diagnosis of VITT that included receipt of a COVID-19 vaccine (Janssen/Vaxzevria) 4 to 30 days previously, thrombosis (often cerebral or abdominal), thrombocytopenia, and positive PF4-HIT test using ELISA. They also recommended urgent medical evaluation for VITT if any of the symptoms including severe headache, visual changes, abdominal pain, nausea and/or vomiting, backache, shortness of breath, leg pain or swelling, petechiae, or easy bruising develop 4 to 30 days after vaccination. Urgent diagnostic workup in suspected VITT also includes complete blood count (CBC) and peripheral blood smear, PF4-ELISA (HIT assay) using blood drawn prior to any therapies, fibrinogen level, and imaging for thrombosis based on signs/symptoms.[116,117] In addition to the above-mentioned recommendations for lab tests, a D-dimer check seems useful for the diagnosis of VITT associated with COVID-19 vaccination. Scully et al.[69] demonstrated that D-dimer levels in patients with thrombosis and thrombocytopenia after receiving the ChAdOx1 nCoV-19 vaccine were much higher than what was expected in patients with acute venous thromboembolism. In addition, the EHP[116] classifies clinical presentation of VITT as follows: patients presenting with acute thrombosis and new-onset thrombocytopenia within 28 days of receiving COVID-19 vaccination (possible case), patients with either a low platelet count without thrombosis or with a D-dimer count at or about normal levels (< 2000 μg/L) but with and normal fibrinogen (2−4 g/L) levels (unlikely case), increased D-dimers (>4000 μg/ L > 2000 with a strong clinical suspicion) (probable case), and cases usually present 5−28 days after vaccination and are characterized by thrombocytopenia, elevated D-dimer level and thrombosis, which often rapidly deteriorate (definite case). In addition to diagnostic criteria and laboratory findings, radiological imaging should be used to confirm the diagnosis. In the event of acute onset of CVST, a non-contrast brain computed tomography (CT) should be the first evaluation. Nevertheless, a non-contrast CT has poor sensitivity since it only displays indirect and suggestive alterations of CVST in 30% of patients.[118] Consequently, if CVST is suspected, non-contrast CT should be carried out along with a contrast CT scan to create a three-dimensional venous reconstruction (CT venography).[119−124] In patients with subacute onset, magnetic resonance imaging (MRI) is, however, the study of choice.[118] In a meta-analysis study, CT and MRI showed similar diagnostic performance for CVST diagnosis.[123] Although Kennedy et al.[125] reported a case of VITT following Ad26.COV2.S COVID-19 vaccination without radiographically thrombosis demonstrable by radiography (Brain MRI) at presentation. Withal, Ikenberg et al.[76] reported a patient whose initial brain MRI was seemingly normal, but follow-up brain MRI findings indicated an extensive CVST, and laboratory report confirmed VITT. Therefore, if clinical suspicion of CVST after COVID-19 persists, a repeat MRI is useful.

Treatment of stroke in the setting of VITT is challenging. What is important is to act according to the existing guidelines considering the specific condition of each patient. The key element of management of VITT-associated CVT is high-dose IVIg and anticoagulation using direct oral anticoagulants.[86,126,127] The use of non-heparin anticoagulants and IVIg can be related to a low probability of VITT-associated CVT death or dependency at the end of hospital admission.[92] IVIg prevents platelet activation by PF4 antibodies and rapidly restores the platelet count.[105] Immune globulin prevents antibody-mediated platelet clearance and may down-regulate platelet activation by immune complexes by blocking platelet FcRγIIA receptors.[127] Therefore, prompt initiation of IVIg (1g/kg over two days if needed) that is likely to influence the disease process, regardless of the severity of thrombocytopenia, and continuing to review the clinical course, is recommended for VITT.[128] Contrastingly, clinicians should avoid all forms of heparin (i.e. unfractionated heparin, even for line flushes, or LMWH e.g. enoxaparin) in VITT-associated CVT.[74] However, non-heparin-based anticoagulants such as direct thrombin inhibitors (including bivalirudin, argatroban, and dabigatran), direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban), and indirect antithrombin dependent Xa inhibitors (e.g., fondaparinux) are not contraindicated in VITT.[129] Administration of anticoagulation should not be avoided in VITT patients with low fibrinogen levels or bleeding associated with VITT, particularly if the platelet count is >20,000/μL or increases following IVIg initiation.[116,117]

Table 3. *Summary reports of CVST following the COVID-19 vaccination.*

Vaccine	Number of cases	Age, Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19, BNT162b2 mRNA, and mRNA-1273	A total of 213 ChAdOx1 nCoV-19 (187 patients), BNT162b2 mRNA (25 patients), and mRNA-1273 (1 patient)	Median of age: 46 75% women in ChAdOx1 nCoV-19 recipients and 77% in mRNA vaccine recipients	Nine days in the ChAdOx1 nCov-19 group and 7 days in the mRNA vaccine group	NM	CVST in all of the patients Thrombocytopenia in 107 patients amongst 187 patients receiving the ChAdOx1 nCoV-19 vaccine	NM	Of the 117 patients with a reported outcome in the ChAdOx1 nCov- 19 group, 44 died, compared to 2 deaths out of 10 deaths with reported outcome in the mRNA vaccine group and 3 deaths out of 100 patients with reported outcome in the pre- COVID- 19 group.	Krzywicka et al., 2021[94]
	1	49 M=1	20	New-onset of mild to moderate headache and giddiness	CVST	Clexane, clopidogrel, and apixaban	Symptoms gradually improved	Zakaria et al., 2021[95]
ChAdOx1 nCoV-19 (COVISHIELD)	1	56 M=1	14	Persistent holocranial headache associated with vomiting, and double vision in horizontal gaze	CVST	LMWH and warfarin	Significant improvement in clinical status	Dutta et al., 2021[96]
ChAdOx1 nCoV-19 (AstraZeneca)	1	52 M = 1	10	Nausea and thunderclap headache and pain on the left side of the neck	CVST Thrombocytopenia, positive anti-PF4 antibody, and elevated D-dimer level	Apixaban and IVIg	Discharged without any symptoms	Guan et al., 2021[97]
	2	NM	NM	NM	CVT thrombocytopenia	Heparin, corticosteroid, IVIg in one patient, and decompressive craniectomy in both patients	Death	Geeraerts et al., 2021[98]

(*Continued*)

Table 3 (*Continued*)

Vaccine	Number of cases	Age, Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
	1	36 F=1	14	Fever with vomiting and severe headache, and sudden onset of focal left-sided convulsions for 5 min followed by weakness in the left arm.	CVST Thrombocytopenia, hypofibrinogenemia, leukocytosis, anemia, increased D-dimer level, and liver enzymes, high creatinine severe acidosis (acute kidney injury), and prolonged PT, PTT, and INR	Enoxaparin, antibiotics, and antivirals	Death	Aladdin et al., 2021[99]
	2	24,39 F = 2	8, 12	Case 1: severe holocephalic headache (before admission), new left dull occipital headache(during admission) Case 2: severe persisting headache	Case 1: CVST Case 2: CVT with related small frontal right juxtacortical hemorrhage Thrombocytopenia, positive anti-PF4 antibody, increased D-dimer and decreased fibrinogen level	Case 1: danaparoid, dexamethasone, IVIg, argatroban, and dabigatran Case 2: IVIg, dexamethasone, and argatroban	Cases 1 and 2: discharged without any symptoms	Gattringer et al., 2021[100]
Ad26.COV2.S (Johnson & Johnson/ Jansen)	1	40 F = 1	12	Headache, sinus pressure, myalgias, and sore throat with tonsillar exudate, photophobia, and intermittent dizziness	CVST Thrombocytopenia increased D-dimer levels, and mild elevation of serum transaminases	Bivalirudin, IVIg, prednisone	Resolution of headache and a steady improvement in laboratory markers of thrombocytopenia	Clark et al., 2021[101]

Table 3 (*Continued*)

Vaccine	Number of cases	Age, Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
	1	48 F = 1	14	New-onset headache	CVST Severe thrombocytopenia, low fibrinogen level, prolonged activated partial thromboplastin time, and marked elevation of the D-dimer level	UFH, Argatroban and IVIg	Remained critically ill	Muir et al., 2021[102]
	1	43 F=1	10	Generalized headache, fever, body aches, chills, and mild dyspnea, and lightheadedness	CVST Thrombocytopenia, positive anti-PF4 antibody, and elevated D-dimer level	IVIg and fondaparinux	TIA one day after discharge	Malik et al., 2021[103]

Note: CVST: Cerebral Venous Sinus Thrombosis; Anti-PF4-antibody: anti-platelet factor 4 antibody; TIA: Transient Ischemic Attack; LMWH:Low Molecular Weight Heparin; IVIg: Intravenous Immunoglobulin; UFH: Unfractionated Heparin; NM: Not Mentioned; CRP: C-Reactive Protein); mRNA: messenger Ribonucleic Acid; COVID-19: coronavirus disease 2019; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; INR: International Normalized Ratio; aPTT: activated Partial Thromboplastin Time.

Table 4. *Summary of reports of CVST with ischemic or hemorrhagic stroke.*

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19 (AstraZeneca)	23	21-77 (mean:46) F = 14 M = 9	6-24 (mean:12)	NM	Thirteen cases of CVST Two cases of ischemic stroke Positive antiPF4 antibody in 22 patients Thrombocytopenia in 22 patients, low fibrinogen levels in 13 patients, and increased D-dimer levels in 21 patients	NM	Seven patients died	Scully et al., 2021[69]
ChAdOx1 nCoV-19 (AstraZeneca)	1	50 M = 1	11	Headache, slight deviation of the right buccal rim, loss of strength in the right lower limb, unstable walking, and slight visual impairment	ICH CVST Thrombocytopenia, low fibrinogen level, increased amounts of D-dimer, CRP, and homocysteine	Bilateral decompressive craniectomy	Brain death	Castelli et al., 2021[71]
ChAdOx1 nCoV-19 (AstraZeneca)	1	54 F = 1	12	Left side signs	ICH CVST Thrombocytopenia, and elevated D-dimer level	NM	Death	D'Agostino et al., 2021[72]
ChAdOx1 nCoV-19 (AstraZeneca)	1	50 M=1	11	Headache, unconsciousness	ICH CVST Thrombocytopenia, positive anti-PF4 antibody, increased prothrombin time and D-dimer, low fibrinogen level, hypohomocysteinemia, and low folic acid level	Red blood cell and platelet apheresis transfusion, infusion of fibrinogen concentrate, neurosurgical intervention	Death	Franchini et al., 2021[73]

Table 4 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19 (AstraZeneca)	2	Case 1 = 25, Case 2 = 32 M=2	Case 1 = 6, Case 2 = 9	Case 1: thunderclap headache, left- incoordination, and hemiparesis Case 2: headache with photophobia, neck stiffness, visual disturbances, associated with a non-blanching petechial rash over lower limbs, bleeding of gums, left hemiparesis and hemisensory loss, and focal motor seizures	ICH, SAH CVST Thrombocytopenia and low fibrinogen level	Case 1: no specific hematological or immunological treatments were administered Case 2: UFH, platelet transfusions, dexamethasone, IVIg	Brain stem death	Mehta et al., 2021[74]
ChAdOx1 nCoV-19 (AstraZeneca)	1	In early 30s F=1	10	Mild myalgia, holocephalic headache, chills, and persisting headaches	CVST ICH Thrombocytopenia, positive anti-PF4 antibody, elevated D-dimer level	Argatroban, IVIg, and argatroban	Persistent minimal gait ataxia and amnestic deficits	Ikenberg et al., 2021[76]
ChAdOx1 nCoV-19 (AstraZeneca)	1	69 F=1	13	Headache associated with behavioral symptoms and decreased level of consciousness	CVST ICH Thrombocytopenia, positive anti-PF4 antibody	NM	Brain death	Jamme et al., 2021[104]
ChAdOx1 nCoV-19 (AstraZeneca)	1	33 M=1	12	Headache, vomiting, sudden onset of a tingling in the right arm, mental change, drowsiness, dysarthria, and right hemiparesis	ICH, SAH, and CVT Thrombocytopenia, elevated D-dimer level, low fibrinogen level, and positive anti-PF4 antibody	FFP, platelet concentrate, IVIg, methylprednisolone, and thrombectomy	Death	Choi et al., 2021[105]

(*Continued*)

Table 4 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19	3	22-46 F=3	7-17	Case 1: new frontally accentuated headache, a self-limited generalized epileptic seizure Case 2: severe headache, mild aphasia, hemianopia to the right, somnolence Case 3: severe headache, acute somnolence and right-hand hemiparesis	Case 1:CVST, SAH Case 2: CVST. ICH Case 3: CVST Thrombocytopenia and positive anti-PF4 antibody in all the three patients	Case 1: endovascular rheolysis, levetiracetam, enoxaparin, and dabigatran Case 2: enoxaparin, danaparoid, and dabigatran Case 3: danaparoid, endovascular rheolysis, enoxaparin, and dabigatran	Case 1: mRS 0 Case 2: mRS 1 Case 3: mRS 0	Wolf et al., 2021[106]
ChAdOx1 nCoV-19 (AstraZeneca)	11	22-49 F = 9: M = 2	5-16	NM	CVST in 9 patients ICH in one patient Thrombocytopenia in all of the patients, and positive anti-PF4 antibody in one patient	NM	Death in 6 patients, recovery in 4 patients, No information about one patient	Greinacher et al., 2021[78]

Table 4 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19 (AstraZeneca)	4	41-67 F = 4	5-11	Case 1: headache, somnolence, dysphasia, right hemiparesis, and arterial hypertension Case 2: headache Case 3: headache and diplopia Case 4: headache, dysarthria, left- hemiplegia, and conjugated gaze palsy	Case 1: CVST and ICH Case 2: cortical infarctions and aortic arch thrombi Case 3: no pathology in imaging findings Case 4: ischemic stroke in ICA and MCA territory with hemorrhagic transformation Thrombocytopenia, increased D-dimer level, positive anti-PF4 antibody in all of the patients	Case 1: heparin and eculizumab Case 2: argatroban and IVIg Case 3: argatroban Case 4: argatroban and IVIg	Case 1: Recovering Case 2, 3, and 4: Recovered	Tiede et al., 2021[107]
ChAdOx1 nCoV-19 (AstraZeneca)	4	37-54 F= 4	7-10	Case 1: fever and persistent headaches Case 2: headaches, reduced consciousness Case 3: headache Case 4: hemiparesis	Case 1: CVST and ICH Case 2: CVST and hemorrhagic infarction Case 3: CVT and hemorrhagic infarction Case 4: ICH and CVT Thrombocytopenia and positive anti-PF4 antibody in all of the patients	Case 1: platelet transfusions and decompressive craniectomy Case 2: hemicraniectomy, dalteparin, methylprednisolone, IVIg Case 3: dalteparin, prednisolone and IVIg Case 4: platelet transfusion, methylprednisolone, IVIg, thrombectomy, UFH, and decompressive hemicraniectomy	Case 1: death Case 2: death Case 3: full recovery Case 4: death	Schultz et al., 2021[93]

(*Continued*)

Table 4 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
ChAdOx1 nCoV-19 (AstraZeneca)	1	27 M=1	12	Intermittent headache associated with eye floaters and vomiting.	CVST ICH Thrombocytopenia, positive anti-PF4 antibody, raised D- dimer, low platelets, and fibrinogen levels	IVIg, dabigatan, idarucizumab, and prednisolone	Death	Suresh et al., 2021[26]
ChAdOx1 nCoV-19 (AstraZeneca)	1	62 M = 1	13	Fever, weakness in the right arm, and mental confusion	CVST, SAH, Large parietal hematoma (after receiving heparin), Acute myocardial infarction Increased CRP, leukocytosis, thrombocytopenia, increased D-dimer level, increased high-sensitivity cardiac troponin I level, positive anti-PF4 antibody	Antibiotics, platelet concentrate, UFH, intravenous methylprednisolone	Death	Bérezné et al., 2021[108]
ChAdOx1 nCoV-19 (Covishield)	1	32 F = 1	11	Headache associated with blurredvision and giddiness, weakness on the left upper and lower limb	CVST and ICH Thrombocytopenia, increased D-dimer, positive anti-PF4 antibody	Enoxaparin, parietal decompressive hemicraniectomy, fondaparinux, IVIg, tracheostomy	Discharged with home neurorehabilitation service	Kotal et al., 2021[109]

Table 4 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
Ad26.COV2.S (Johnson & Johnson/ Jansen)	12	18-60 F = 12	6-15	Eleven patients initially presented with headache and one patient initially showed back pain and later developed a headache	CVST (of the 12 patients with CVST, seven also had ICH) Thrombocytopenia and elevated D-dimer level and decreased fibrinogen level	Heparin treatment (later changed to non-heparin anticoagulant) in 6 patients; No anticoagulant therapy in 2 patients Non-heparin anticoagulant initially for CVST treatment in 4 patients. In addition to anticoagulation, seven patients received IVIg of which three also received systemic corticosteroids and four had platelet transfusions.	Death (n = 3), ICU care (n = 3), non-ICU hospitalization (n = 2), and discharged (n = 4)	See et al., 2021[110]
mRNA-1273	1	45 M = 1	8	Headache, neck pain, altered mental, state after a witnessed seizure (GCS: 3)	ICH,SAH, and CVST	Heparin and coumadin	Discharged with no neurological sequel	Syed et al., 2021[111]
BNT162b2 mRNA(Pfizer)	2	47, 67 F=2	3, 6	Case 1: persistent headache, nausea, photophobia, and sudden left motor deficit Case 2: sudden right lower limb clonic movements followed by motor deficit, loss of consciousness, and headache	Case 1: CVST and SAH Case 2: CVST	Case 1: enoxaparin and warfarin Case 2: enoxaparin, and dabigatran	Case 1: slight gait instability at two-month follow-up Case 2: discharged without neurological deficits	Dias et al., 2021[112]

(*Continued*)

Table 4 (*Continued*)

Vaccine	Number of cases	Age Gender (F, M)	Interval (days) between vaccination and diagnosis	Clinical presentation	Imaging and lab findings	Treatment	Outcome	Author, year, ref
BNT162b2 mRNA (Pfizer-Biontech	3	54-62 F = 2 M = 1	2-9	Case 1: headache, vomiting, and left hemiparesis Case 2: headache and vomiting Case 3: right ataxic hemiparesis	Case 1: ICH and CVST Case 2: ICH, SAH, and CVST Case 3: ICH, SAH, and CVST	Case 1: UFH and LMWH Case 2: UFH, LMWH, warfarin, and decompressive craniectomy Case 3: LMWH, warfarin	Cases 1 and 2: Left hemiparesis, on rehabilitation Case 3: Full recovery	Fan et al., 2021[113]

Note: MCA: Middle Cerebral Artery; ICA: Internal Carotid Artery; CVST: Cerebral Venous Sinus Thrombosis; CVT: Cerebral Venous Thrombosis; Anti-PF4-antibody: anti-platelet factor 4 antibody; ICH: Intracerebral Hemorrhage; SAH: Subarachnoid Hemorrhage; LMWH: Low Molecular Weight Heparin; IVIg: Intravenous Immunoglobulin; UFH: Unfractionated Heparin; ICU: Intensive Care Unit; mRS: modified Rankin Scale; NM: Not Mentioned; CRP: C-Reactive Protein; FFP: Fresh Frozen Plasma; GCS: Glasgow Coma Scale.

Furthermore, continuing systemic anticoagulation for at least three months in patients with documented thrombosis in the context of VITT is recommended.[130] However, warfarin is not recommended in this setting due to a paradoxical increase in thrombotic tendency.[129] In order to continue these VITT treatment recommendations, platelet transfusions should be avoided unless the bleeding is associated with paradoxical thrombosis, and risk/benefit assessment should be conducted in patients with severe bleeding and/or the need for surgical intervention.[116,117] Severe bleeding and/or the need for surgical intervention may favor platelet transfusion following the initiation of IVIg, non-heparin anti-coagulation, and fibrinogen replacement if its level is less than 1.5 g/L.[116,117] Platelet transfusion should be considered in life-threatening bleeding situations.[128] In other words, platelet transfusion is an optional treatment to support anticoagulation, and its superiority to critical care by argatroban (low dose) without platelet transfusion has not yet been confirmed.[116,117] Expressly, if urgent neurosurgical intervention is needed, platelet transfusion to >100 × 109/L and cryoprecipitate to maintain fibrinogen over 1.5 g/L should be considered.[116,117] However, since it is still unclear that platelet transfusion can exacerbate CVST, a definite recommendation cannot be given.[128] In addition, fibrin injection is controversial, and it should be measured to ensure that its level does not drop below 1.5 g/L.[128] Moreover, steroids may be useful, although whether their benefits outweigh the potential harm is uncertain.[128] Plasma exchange could also be helpful in patients with severe or resistant diseases. For VITT patients who are refractory relative to repeated doses of IVIg treatment and plasma exchange, treatment with rituximab may be helpful.[128] In addition to pharmacological treatments, non-pharmacological methods such as Endovascular Mechanical Thrombectomy (EMT) can be efficient for selected patients. EMT can restore normal venous outflow, decrease venous congestion, and reduce increased ICP through rapid and definite recanalization of occluded venous sinuses.[131,132] Wolf et al.[106] reported 3 cases of CVT after COVID-19 vaccination who were successfully treated by endovascular rheolysis. Although the outcome of EMT in the case report by Choi et al[105] was not satisfactory, they suggested that if the EMT is done at early stages, and before the beginning of cortical venous occlusion, the outcome might be better. Therefore, if VITT-associated CVT is clinically suspected and the symptoms deteriorate quickly, early EMT intervention is necessary.[105] Another non-pharmacological procedure is decompressive craniectomy, which should be decided based on the patient's condition. The association between decompressive hemicraniectomy and the poor outcome probably reflects the selection of patients with the most serious CVT for this invasive procedure.[92]

Anticoagulation with argatroban can be a useful treatment option for VITT among other medications. This is

because, first of all, it has a short half-life, which is useful in case of bleeding complications.[100] Second, it also inhibits platelets.[133] Third, a thrombin inhibitor acts at the bottom of the coagulation cascade with less potential effect on the other coagulation factors.[100] Furthermore, bivalirudin can be used as a heparin alternative in VITT for its immediate onset of action, renal elimination, short half-life (w25 min), and ease of reversibility in the event of life-threatening bleeding.[101]

Conclusion

Many recent studies reported the occurrence of stroke after administration of COVID-19 vaccination. All forms of stroke including ischemic, ICH, and CVST have been encountered. Most of the evidence pertaining to stroke following COVID-19 vaccination are case reports, therefore, the incidence of stroke after COVID-19 vaccination is not precisely known. Most patients who suffered from stroke after COVID-19 vaccination were women, under 60 years of age, and after the ChAdOx1 nCoV-19 vaccine.

Clinicians should be aware of the possible stroke after COVID-19 vaccination to ensure rapid diagnosis and treatment. CVST is an important phenomenon that may occur after COVID-19 vaccination and is mostly associated with VITT. The diagnosis of VITT-associated stroke should be made with high suspicion because of its rapid and diverse clinical manifestations. Stroke should be considered when a patient develops any neurological complaints, especially constant headaches, within 4 weeks of COVID-19 vaccination. These patients should urgently be evaluated for possible VITT with laboratory tests such as platelet count, D-dimer, anti-PF4 antibody, fibrinogen level, and brain imaging, especially cerebral venography. Concurrent thrombosis including DVT, PTE, and splanchnic venous thrombosis should be ruled out in patients who suffered from VITT-associated CVST. Furthermore, other differential diagnoses including APS, DIC, ITP, thrombotic-thrombocytopenic purpura, atypical hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria, and underlying malignant diseases should be taken into account. Notably, the latest guidelines should be considered for VITT management; however, clinicians should eventually act according to the specific condition of each patient. Since the management of VITT is challenging, they should be managed by a multidisciplinary team from different disciplines including hematology, neurology, stroke, neurosurgery, and neuroradiology. Finally, since the advantages of COVID-19 vaccination outweigh the risk of stroke or any other neurological complication, the public should be reassured that the vaccination program is still the best way to combat COVID-19.

Declaration of Competing Intrest

The authors declare no conflict of interest with respect to the present review study.

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