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Review Article

Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review

Maryam Sharifian-Dorche a,b, Mohammad Bahmanyar c, Amirhossein Sharifian-Dorche b, Pegah Mohammadi d, Masood Nomovi e, Ashkan Mowla f, *

a Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada
b Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
c Department of Pathology and Laboratory Medicine, St Paul’s Hospital, University of British Columbia (UBC), Vancouver, British Columbia, Canada
d Department of Medicine, Eisenhower Medical Center, Rancho Mirage, CA, USA
e Department of Internal Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
f Department of Neurological Surgery, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA

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ABSTRACT

Introduction: The common reported adverse effects of COVID-19 vaccination consist of the injection site’s local reaction followed by several non-specific flu-like symptoms. However, rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) after viral vector vaccines (ChAdOx1 nCoV-19 vaccine, Ad26.COV2 vaccine) have been reported. Herein we systemically reviewed the reported cases of CVST and VITT following the COVID-19 vaccination.

Methods: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched PubMed until May 19, 2021, and the following Keywords were used: COVID Vaccine & Neurology, AstraZeneca COVID vaccine, ChAdOx1 nCoV-19 COVID vaccine, AZD1222 COVID vaccine, Janssen COVID vaccine, Johnson & Johnson COVID vaccine, Ad26.COV2 COVID vaccine. The authors evaluated the abstracts and titles of each article for screening and inclusion. English reports about post-vaccine CVST and VITT in humans were collected.

Results: Until May 19, we found 877 articles with the searched terms. We found 12 articles, which overall present clinical features of 36 patients with CVST and VITT after the ChAdOx1 nCoV-19 vaccine. Moreover, two articles were noted, which present 13 patients with CVST and VITT after Ad26.COV2 vaccine. The majority of the patients were females. Symptom onset occurred within one week after the first dose of vaccination (Range 4–19 days). Headache was the most common presenting symptom. Intracerebral hemorrhage (ICH) and/or Subarachnoid hemorrhage (SAH) were reported in 49% of the patients. The platelet count of the patients was between 5 and 127 cells × 10⁹/l, PF4 IgG Assay and d-Dimer were positive in the majority of the reported cases. Among 49 patients with CVST, at least 19 patients died (39%) due to complications of CVST and VITT.

Conclusion: Health care providers should be familiar with the clinical presentations, pathophysiology, diagnostic criteria, and management consideration of this rare but severe and potentially fatal complication of the COVID-19 vaccination. Early diagnosis and quick initiation of the treatment may help to provide patients with a more favorable neurological outcome.

1. Introduction

The COVID-19 (coronavirus disease) pandemic had a devastating impact on public health, social life, and economy worldwide [1–4]. The development of vaccines has been shown to be the only effective tool to combat the situation. Vaccines prevent severe illness from SARS-COV-2 infection [5,6]. Thus far, two types of COVID-19 vaccines are developed. Messenger RNA (mRNA) vaccines such as Pfizer/BioNTech’s (BNT162B2) and Moderna’s (mRNA-1273) and viral vector vaccine such as Oxford-AstraZeneca vaccine (AZD1222 (ChAdOx1)) and Johnson &

* Corresponding author at: Division of Endovascular Neurosurgery, Department of Neurological Surgery, Keck School of Medicine, University of Southern California (USC), 1200 North State St., Suite 3300, Los Angeles, CA 90033, USA.
E-mail address: mowla@usc.edu (A. Mowla).

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Johnson COVID-19 vaccine (JNJ-78436735 (Ad26.COV2.S)) [7].

Safety concerns have been raised regarding the vaccines since they have been used. The common adverse effects post COVID-19 vaccination consist of the injection site’s local reaction followed by non-specific systemic symptoms such as headache, fatigue, myalgia, and fever. These symptoms may occur soon after vaccination and resolve in a short period [6]. However, some rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been reported, mainly with viral vector vaccines [6]. Among these reports, there are patients with VITT and cerebral venous sinus thrombosis (CVST), a severe and rare neurological condition [8,9].

In this study, we systematically reviewed the CVST cases reported post-COVID-19 vaccination so far. We described their clinical and laboratory features and also discussed the diagnostic and management implications.

2. Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Fig. 1) statement [10]. We searched PubMed until May 19, 2021, and the following keywords were used: COVID Vaccine & Neurology, AstraZeneca COVID vaccine, ChAdOx1 nCoV-19 COVID vaccine, AZD1222 COVID vaccine, Janssen COVID vaccine, Johnson & Johnson COVID vaccine, Ad26.COV2 COVID vaccine. The authors evaluated the abstracts and titles of each article for screening and inclusion. English reports on post-vaccine CVST and VITT in humans (original articles, case series, case reports, letters, correspondence, or short communications presenting at least 1 case of CVST after the COVID-19 vaccine) were collected. Included articles were reviewed in full text. Relevant references in each article were also checked. Duplicated results were removed. Data from each article was extracted into the Microsoft Excel software.

3. Results and discussion

Until May 19, 2021, we found 877 articles with the searched words. COVID Vaccine & Neurology(175 articles), AstraZeneca COVID vaccine (226 articles), ChAdOx1 nCoV-19 COVID vaccine(86 articles), AZD1222 COVID vaccine(69 articles), Janssen COVID vaccine(160 articles), Johnson & Johnson COVID vaccine(140articles), Ad26.COV2 COVID vaccine(21 articles). Among these articles, we selected the relevant reports.

3.1. AstraZeneca COVID-19 vaccine (ChAdOx1)

The Oxford–AstraZeneca COVID-19 vaccine (AZD1222, ChAdOx1, and Vazzevia) is a viral vector vaccine to prevent COVID-19. Overall this vaccine efficacy more than 14 days after the second dose was about 66.7% [11].

Common side effects including injection-site reaction and pain, headache, malaise, and nausea, all generally resolving within a few days [6]. However, there are few reports of VITT after vaccination [9].

According to the “European Medicine Agency’s Pharmacovigilance...
Risk Assessment Committee,” from the 34 million people that received the AstraZeneca COVID-19 vaccine in the European Economic Area and the United Kingdom as of April 4, 2021, 169 cases of CVST and 53 cases of splanchnic vein thrombosis were reported. Most of these cases occurring within the first two weeks of vaccination and in women <60 years [6].

Table 1 summarizes the articles that report CVST, associated venous infarct and hemorrhagic stroke, arterial infarct and ICH (intracerebral hemorrhage), and VITT after the AstraZeneca COVID-19 vaccine. In this group, we found 12 articles, which present the clinical features of 41 (36 CVST, 4 infarctions, 1 ICH) patients. Among 36 patients with CVST, 16 patients had an ICH and/or Subarachnoid Hemorrhage (SAH) (44%). From all reported cases (41 patients), 18 patients (44%) died.

3.2. Johnson & Johnson COVID-19 vaccine (Ad26.COV2)

Johnson & Johnson COVID-19 vaccine is a viral vector vaccine based on a human adenovirus. It has been modified to contain the gene for making the spike protein of the SARS-CoV-2 that causes COVID-19 [24]. The vaccine’s efficacy is about 66.1% against symptomatic moderate and severe SARS-CoV-2 infection and about 85.4% against hospitalization or death [25].

Common side effects after vaccination include injection site reactions, fever, chills, and malaise, but there are rare reports of venous thrombosis after vaccination [26].

Table 2 summarizes the articles which report CVST and associated venous infarct and hemorrhagic stroke and VITT after Johnson & Johnson COVID-19 vaccine. In this group, we found 2 articles that present 13 patients. All of these patients were females. Among 13 reported patients with CVST, 8 patients had ICH/SAH (61%).

3.3. CVST

In general, CVST affects young adults, especially young women. In most cases, the patients have an identifiable risk factor for thrombosis, such as pregnancy, puerperium, autoimmune diseases, oral contraceptives, etc. [28-31]. Diagnosis might be challenging at times. The symptoms of CVST may mimic other neurological disorders and might reflect the location of the involved vein or sinus [30]. However, headache is a frequent symptom and present in the majority of the patients [28]. With the progression of the disease, patients may develop focal neurological deficits due to venous infarction and seizure, which is more common in CVST compared to the other subtypes of stroke. With timely diagnosis and treatment, full recovery might happen [32].

Infection with SARS-CoV-2 has also been shown to contribute to the development of CVST in multiple studies [8,32].

3.4. History and clinical characteristics of reported cases of CVST associated with VITT

Thrombotic thrombocytopenia after vaccination is not a new event in the history of vaccination [33]. One of the first reports was from Brown et al. in 1973, who reported thrombotic thrombocytopenia after influenza vaccination [34]. There are also other reports of similar events after H1N1, Rabies, and pneumococcal vaccination [35-38]. In these reports, corticosteroids, plasmapheresis, and rituximab were suggested as treatment options. However, CVST was not reported in these patients [34,37].

SARS-CoV-2 VITT is a newly described phenomenon post-viral vector COVID-19 vaccines. In contrast to the previous reports of thrombotic thrombocytopenia after vaccination, in these patients, cases of CVST have been reported post-COVID-19 vaccines.

In this study, all reported cases of VITT and CVST are announced after AstraZeneca (ChAdOx1) and Johnson & Johnson (Ad26.COV2) vaccination. The majority of reported patients with CVST associated with VITT were females, 54 cases reported in total (49 cases of CVST, 4 cases of infarction, and 1 case of ICH), 36 females, 9 males, and 9 unknown sex. Oral contraceptives (2 cases), Contraceptive vaginal ring (1 case), Hormone-replacement therapy (1 case), and Obesity (6 patients) were the most relevant predisposing conditions in the patients.

Symptom onset occurred within one week after the first dose of vaccination (Range: 4–19 days). Headache was the most frequent presenting symptom in the patients with CVST. In addition, other symptoms such as malaise, vomiting, lethargy, loss of consciousness, blurred vision, hemiparesis, abdominal pain, and back pain were reported in some patients. Abdominal pain and back pain were reported in the patient with concurrent portal vein thrombosis.

Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) were seen as consequences of CVST in a large group of patients (24 patients, 49% of the patients with CVST). Middle cerebral artery (MCA) infarct was reported in 4 patients after the ChAdOx1 nCoV-19 vaccine (AstraZeneca) (Tables 1 and 2).

Pulmonary embolism, splanchnic vein thrombosis, lower extremity deep venous thrombosis, bilateral adrenal hemorrhage, portal vein thrombosis, iliofemoral vein thrombosis, internal jugular vein thrombosis, and Ischemic bowel infarct are other sites of thrombosis in the reported patients (Tables 1 and 2).

Platelet count was between 5 and 127 cells×10^11/L, and PF4 IgG Assay and d-Dimer were positive in most reported cases. Among 54 patients evaluated in this study, at least 21 (38.8%) patients died (19 cases of CVST(39%), one case of infarction (25%), and one case of ICH) (Tables 1 and 2). Such a high mortality rate among CVST patients indicates the importance of early diagnosis and treatment of CVST and VITT post-COVID-19 vaccination [12].

3.5. Pathophysiology

VITT clinically resembles spontaneous autoimmune heparin-induced thrombocytopenia (HIT). HIT is caused by platelet-activating immunoglobulin G (IgG) antibodies against platelet factor 4 (PF4) complexed with heparin. This complex then binds to the platelet FcγRIIA receptors and causes platelet activation and formation of platelet microparticles [39]. These microparticles initiate the formation of blood clots and inducing a prothrombotic cascade, which consequently decreases platelet count and causes thrombocytopenia. Moreover, the reticuloendothelial system, particularly the spleen, removes the antibody-coated platelets and aggravates thrombocytopenia [6,20,39,40].

It has also been demonstrated that some patients present with clinical symptoms and laboratory features of HIT despite not having previously received heparin and recognized as spontaneous autoimmune HIT. Sera from these patients contain antibodies that activate platelets strongly even in the absence of heparin. Most reported spontaneous HIT patients had preceding orthopedic surgery (release of knee cartilage glycosaminoglycans or RNA, owing to tourniquet-related cell damage) or infection (exposure to microorganism) [41].

AstraZeneca COVID vaccine (ChAdOx1) and Johnson & Johnson (Ad26.COV2) vaccines contain replication-incompetent adenoviral vectors; chimpanzee ChAdOx1 and human Ad26.COV2 S respectively. These two factors encode the spike glycoprotein on SARS-CoV-2 [32].

Interactions between the vaccine and platelets or PF4 could play a role in the pathogenesis of VITT. The possible explanation for this phenomenon is that the free DNA in the vaccines could bind to PF4 and trigger these PF4-reactive autoantibodies in the VITT setting [19] (Fig. 2).

An important observation in VITT post-COVID-19 vaccination is the preponderance of thrombosis in the cerebral venous sinuses. Although HIT is a prothrombotic condition, it has not been reported to preferentially present in association with CVST. Moreover, brain imaging of the patients with post-COVID-19 vaccination associated with VITT and CVST detected a high rate (49% in this study) of ICH and SAH [20].
Table 1
Clinical and laboratory findings of the patients with thromboembolic events after vaccination with The Oxford–AstraZeneca COVID-19 vaccine. F: Female, M: Male, N/A: not applicable, CVST: cerebral venous sinus thrombosis, MCA: Middle cerebral artery, ICH: Intracerebral Hemorrhage, SAH: Subarachnoid hemorrhage, PF4: Platelet Factor-4.

| No | Authors          | Total no./sex/age | Preexisting conditions / medications | Time from vaccination (days) | Clinical presentations | Imaging findings | Lab findings | Outcome |
|----|------------------|-------------------|--------------------------------------|-----------------------------|------------------------|------------------|-------------|---------|
| 1  | Scully et al.    | 11 F Mean age: 39.3 (Range:26–55) | 5 M Mean age: 32 (Range:21–48) | 11.7 (Range:6–19) days | N/A                   | 13 CVST (In 2 cases with ICH and 1 with SAH) | Platelet count: Mean: 48 (Range:7–113) cells × 10^9/l | Alive: 11 patients Died: 5 Patients (4 CVST, 1 ICH) |
| 2  | Schultz et al.   | 4 F Mean age: 43 (Range:37–54) | Hypertension oral contraceptive pill (OCP), Contraceptive vaginal ring, Hormone-replacement Therapy, Anti-hypertensive agents | 8.7 (Range:7–10) days | Headache (in all cases), visual disturbances, drowsiness, abdominal pain, Hemiparesis | CVST in: Cortical veins, transverse sinus, sigmoid sinus, Inferior sagittal sinus, vein of Galen and straight sinus all with ICH | Platelet count: Mean: 31.2 (Range:19–70) cells × 10^9/l | Alive: 3 patients Died: 1 Patient |
| 3  | Bayas et al.     | 55 y/o F          | –                                    | 10 days                     | conjunctival congestion, retro-orbital pain, and diplopia | Bilateral superior ophthalmic vein thrombosis Ischemic stroke in the left parietal lobe, MCA territory Right MCA infarct | Platelet count: 30 cells × 10^9/l | Alive |
| 4  | Blauenfeldt et al. | 60 y/o F | Hashimoto’s thyroiditis and Hypertension | 9 days | left-sided weakness, eye deviation to the right | CVST in left transverse and sigmoid sinuses And ICH | Platelet count: drops to 5 cells × 10^9/l | Died |
| 5  | Castelli et al.  | 50 y/o M          | –                                    | 11 days                     | Headache Deviation of the right buccal rim loss of strength in the right lower limb Slight visual impairment. Left side weakness | CVST in left transverse and sigmoid sinuses And ICH | Platelet count: 20 cells × 10^9/l | Died |
| 6  | D’Agostino et al. | 54 y/o F | Meniere’s disease | 12 days                     | CVST multiple subacute intra-axial hemorrhages in atypical locations SAH acute basilar thrombosis superior sagittal sinus thrombosis non-occlusive thrombosis of the vein of Galen myocardial infarction thrombus within the aortic arch and left portal branch and right | d-Dimer: Positive | Thrombocytopenia | Died |

(continued on next page)
3.6. Diagnosis

Despite the high mortality associated with VITT and CVST post-COVID-19 vaccination, prompt recognition and early management will likely lead to better neurological outcomes. Key diagnostic criteria of VITT include the following items (must meet all four criteria):

1- The patient has received the AstraZeneca COVID (ChAdOx1) or Johnson & Johnson (Ad26.COV2) vaccines within the last 30 days (between 4 and 30 days).

2- Presence of moderate to severe thrombocytopenia. However, in some cases, this thrombocytopenia may be mild, particularly in the beginning stages of VITT.

3- The presence of thrombosis often in the forms of CVST (Patients may present with headache) or splanchnic veins thrombosis(patients may present with abdominal or back pain (or both) and nausea and vomiting). Arterial thrombosis occurs less commonly.

4- Positive PF4 “HIT” (heparin-induced thrombocytopenia) ELISA [42].

Despite transient headaches being a common adverse effect of vaccination, if a patient has a continuing headache, blurred vision, petechiae, easy bruising, or bleeding after AstraZeneca COVID...

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### Table 1 (continued)

| No | Authors                  | Total no./sex/age | Preexisting conditions / medications | Time from vaccination (days) | Clinical presentations | Imaging findings                                                                 | Lab findings                                             | Outcome |
|----|--------------------------|-------------------|--------------------------------------|-----------------------------|------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------|---------|
| 7  | Franchini et al. [18]    | 50 y/o M          | 1 case with chronic neurological disorder 1 case with type 1 von Willebrand disease and positive anticardiolipin antibodies | 7 days                      | Headache               | suprahepatic vein and Bilaterally, adrenal hemorrhage CVST in left transverse and sigmoid sinuses intra-parachymal hemorrhage in the left cerebral hemisphere | Platelet count: 15 cells × 10^9/l PF4 IgG Assay: Positive d-Dimer: Positive | Died    |
| 8  | Greinacher et al. [19]   | 9 Patients        |                                       | 9.3 (Range:5–16) days       |                       | 9 CVST Pulmonary embolism splanchnic vein thrombosis Aortoiliac thrombosis intra-ventricular, iliofemoral vein, Multiple organ thromboses | Platelet count: 27.3 cells × 10^9/l (Range 8–75) PF4 IgG Assay: 7 Positive 2 unknown d-Dimer: Positive in all cases | 5 Died  |
| 9  | Mehta et al. [20]        | 2 M Mean Age: 28.5 y/o (Range: 25–32) | Primary sclerosing cholangitis        | 7.5 days (6–9)              | Headache               | CVST in Superior sagittal sinus, cortical veins, and Superior sagittal sinus With ICH and SAH | Platelet count: 24.5 cells × 10^9/l (Range 19–30) PF4 IgG Assay: 1 Positive d-Dimer: 1 Positive 1 unknown d-Dimer: Positive | 2 Died  |
| 10 | Wolf et al. [21]         | 3F 34.6 y/o (Range: 22–46) |                                       | 6.3 days (4–8)              | Headache in all cases , epileptic seizure , aphasia and hemianopia | CVST In ascending cerebral veins, superior sagittal sinus, transverse sinus, and also sigmoid sinus with ICH and SAH CVST in Transverse sinus, frontal lobe, and pulmonary artery. With ICH And SAH | Platelet count: 75.5 cells × 10^9/l (Range 60–92) PF4 IgG Assay: Positive d-Dimer: Positive | All Alive|
| 11 | Bjernstad-Tuveng TH et al. [22] | 30s y/o F Mild preeclampsia in a previous pregnancy |                      | 7 days                      | Headache               |                                                                      |                                                        | Died    |
| 12 | Tobaiga et al. [23]      | Age between:18–64 1F N/A N/A N/A |                                      | 7 days                      | Headaches most frequent | CVST:36 MCA infarct: 4 ICH:1 (CVST+ICH/SAH: 16) | Platelet count: 39 cells × 10^9/l (5–113) PF4 IgG Assay: Positive 27 Negative: 2 Unknown:11 d-Dimer: Positive: 35 Unknown:5 | Alive:21 Died:18:16 CVST, 1 ICH, 1 Infarct Unknown:2 |

Total 41 In 32 patients, sex was reported (23 F, 9 M) 7 days Range (4–19)
Table 2
Reports of CVST post-Johnson & Johnson COVID-19 vaccination. F: Female, M: Male, N/A: not applicable, CVST: cerebral venous sinus thrombosis, ICH: Intracerebral Hemorrhage, PF4: Platelet Factor4.

| No | Authors | Total no. sex/age | Preexisting conditions / Medications | Time from vaccination (days) | Clinical presentations | Imaging findings | Lab findings | Outcome |
|----|---------|-------------------|-------------------------------------|-----------------------------|------------------------|------------------|--------------|---------|
| 1  | See et al. [9] | 12 F 8 (18-39) 4(>40) | Obesity in 6 patients combined oral contraceptives (OCP) in 1 patient | 8.8 days (Range: 6-13) | Headache 11 patients Other symptoms: Back pain, Abdominal pain, lethargy, myalgia, nausea, vomiting, fever, dyspnea, chills, photophobia, cognitive impairment, blurred vision, Right side weakness | 12 CVST in: Transverse sinus, sigmoid sinus, straight sinus, superior sagittal sinus, internal jugular vein with 7 patients ICH and and 8 patients with non-CVST including thromboses including: portal vein thrombosis lower extremity deep vein thrombosis | Platelet count: Mean: 45.7 (Range:9-127) cells×10⁹/l PF4 IgG Assay: Done in 11 cases, all Positive d-Dimer: Positive in all patients | 4 patients were discharged to home. 3 patients died. Other: intensive care unit (ICU) care:3 non-ICU hospitalization:2 |
| 2  | Muir KL et al. [27] | 48 y/o F | Malaise and abdominal pain and then Headache | 14 days | CVST in the right transverse And straight sinuses. And ICH And splanchic -vein thrombosis | 13 CVST (CVST + ICH/SAH: 8) | Platelet count: Mean: 13 cells×10⁹/l PF4 IgG Assay: Positive d-Dimer: Positive | Critically ill | Discharged: 4 Died: 3 Critically ill:4 non-ICU hospitalization:2 |
| Total | | 13 F 6 Patients with Obesity One on OCP | | 9.2(Range: 6-14) | Headache most frequent presenting complain | | | |

Fig. 2. Possible mechanism of VITT after Viral Vector Vaccines. The free DNA in the vaccine could bind to PF4 and trigger platelet-activating immunoglobulin G (IgG) antibodies. This complex then binds to the platelet FcγRIIA receptors and causes platelet activation and formation of platelet microparticles. These microparticles initiate the formation of blood clots and inducing a prothrombotic cascade, which consequently decreases platelet count and causes thrombocytopenia. Moreover, the reticuloendothelial system, particularly the spleen, removes the antibody-coated platelets and aggravates thrombocytopenia. PF4: Platelet Factor 4, IgG: Immunoglobulin G. Created in BioRender.com by MN.
(ChAdOx1) or Johnson & Johnson (Ad26.COV2), CVST after VITT should be considered [42].

3.7. Recommended evaluations and laboratory workups

In patients with suspected CVST, computed tomography venogram (CTV) or magnetic resonance imaging venogram (MRV) are diagnostic tools with high accuracy rates [30]. For detecting the thrombosis in the other sites, appropriate imaging based on signs/symptoms should be obtained [42].

Laboratory workups should include; complete blood count (CBC) and peripheral blood smear, Fibrinogen and D-dimer levels, a prothrombin time (PT), partial thromboplastin time (PTT), and PF4-ELISA (HIT assay) [32].

If a patient presents with thrombosis and a normal platelet count post-AstraZeneca COVID (ChAdOx1) or Johnson & Johnson (Ad26.COV2) vaccination, early stages of VITT should be considered [42].

3.8. Treatment strategies

In suspected patients, the use of heparin should be avoided until VITT has been ruled out [42]. Close collaboration among vascular

\[\text{Consider CVST related to VITT}\]

- Avoid Heparin and platelet transfusion
- Collaboration among vascular neurologists, hematologists, and other consultants with expertise in managing systemic thrombosis. (with special attention to the possibility of thrombosis in the other sites such as portal vein if the patient has any relevant symptoms)
- IVIG (1 g/kg body weight) daily for 2 days after PF4 antibodies have been sent.
- Use of non-heparin anticoagulants for treatment of thrombosis

Fig. 3. Approach to the patients with CVST and VITT. CTV: computed tomography venography, MRV: Magnetic Resonance Venography, CBC: Complete Blood Count, INR: international normalized ratio, PTT: Partial Thromboplastin Time, PF4: Platelet Factor4, HIT: Heparin-induced thrombocytopenia.
neurologists, hematologists, and other consultants with relevant expertise is the cornerstone of managing VITT-associated systemic thrombosis and CVST [32]. Despite very limited data on treatment strategies, administration of intravenous immunoglobulin (IVIG) (1 g/kg body weight) daily for two days has been recommended after PF4 antibodies have been sent [32]. IVIG impedes antibody-mediated platelet clearance and may also down-regulate platelet activation by blocking platelet FcγRIIA receptors [40]. Some experts recommended using high-dose glucocorticoids, which may improve the platelet count within days [40]. Plasmapheresis could potentially be another treatment option that could temporarily reduce pathologic antibodies and correct coagulopathy [12]. Platelet transfusion should be avoided due to the risk of further antibody-mediated platelet activation and coagulopathy [12]. Use of non-heparin anticoagulants, including direct oral factor Xa inhibitors (Apixaban, Rivaroxaban), direct thrombin inhibitors (Argatroban, Bivalirudin), and Indirect (antithrombin-dependent factor) Xa inhibitors: Danaparoid, Fondaparinux, at therapeutic anticoagulant dosage might be considered [19]. In severe thrombocytopenia (i.e., <20,000 per mm3) or low fibrinogen levels, dosing strategy may require alteration [32]. In critically ill patients, parenteral agents with a short half-life are preferred [19,32]. Even in the presence of secondary ICH, anticoagulation should be used in CVST to prevent progressive thrombosis [32].

Once there is full platelet count recovery, and no other contraindications, direct oral anticoagulants or vitamin K antagonists have been suggested for subacute/chronic management [32] (Fig. 3).

3.9. Risks and benefits of vaccination

There is approximately 1 to 2% risk of mortality and several potential long-term sequelae in COVID-19 patients [4,43]. In patients with chronic underlying diseases or patients on particular medications, this rate might be even higher [44]. Conversely, Vaccination has a significant effect on the prevention of severe SARS-CoV-2 infection and ensuing complications [25] with an extremely low rate of severe complications. As initially estimated, the incidence of VITT is perhaps 1 case per 100,000 vaccine exposures [40]. Consequently, COVID-19 vaccination should be strongly encouraged given benefits outweigh its potential risks [40]. However, monitoring of the vaccines’ adverse effects is essential and should be performed by the health authorities.

4. Conclusion

Health care providers should be aware of clinical presentations, pathophysiology, diagnostic criteria, and management strategies of CVST associated with VITT post-COVID-19 vaccination. Despite being very rare, this phenomenon is serious and potentially fatal. Promote diagnosis and quick initiation of the appropriate treatment may help to provide patients with a better neurological outcome [22].

Declaration of Competing Interest

None.

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