Guideline

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European stroke organization interim expert opinion on cerebral venous thrombosis occurring after SARS-CoV-2 vaccination

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Abstract

Severe cases of cerebral venous thrombosis (CVT) with thrombocytopenia and anti-platelet factor 4 (PF4) antibodies occurring after adenoviral vector anti-SARS-CoV-2 vaccines have been recently reported. We aim to present a guidance document on the diagnosis and treatment of patients presenting with CVT after vaccination against SARS-CoV-2 infection. We reviewed the available evidence which consists on case reports, small case series, expert opinion and analogy with heparin-induced thrombocytopenia (HIT) management. Because of the low level of evidence, this is an interim document, based only on expert opinion consensus. In patients presenting with CVT after being vaccinated against SARS-CoV-2 infection, if there is thrombocytopenia a reliable HIT PF4 Antibody ELISA test should be performed, to confirm vaccine-induced immune thrombotic thrombocytopenia (VITT). In patients with CVT and thrombocytopenia, in whom VITT is suspected or confirmed, heparin (unfractionated or low molecular weight) should be avoided and non-heparin anticoagulants are preferred. If possible, platelet transfusions should be avoided. If the diagnosis of VITT is confirmed or suspected, early intravenous immunoglobulins are indicated. This expert opinion is supported by low quality evidence. It should be periodically updated, or changed to a formal guideline, as new and higher quality evidence is eventually produced. Because of their potential unfavourable clinical course, patients developing symptoms and signs suggestive of CVT after being vaccinated against SARS-CoV-2 virus should undergo urgent clinical and neuroimaging evaluation. In cases of suspected or confirmed VITT, non-heparin anticoagulants should be used, platelet transfusions avoided and intravenous immunoglobulin started early.

Keywords

Cerebral venous thrombosis, cerebral venous sinus thrombosis, SARS-CoV-2, COVID-19, vaccines, thrombocytopenia, HIT, VITT, anti-platelet antibodies, anticoagulants, immune-globulin

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Background

After the onset of mass vaccination of millions of persons with anti SARS-COV-2 vaccines, there were notifications of thrombotic events. Later on, case reports and case series of severe and often fatal cerebral venous thrombosis (CVT), occurring predominantly in young women, within 4–28 days of vaccination with the ChAdOx1 nCoV-19 vaccine produced by AstraZeneca (AZ) were published.[1–6] Many of these patients had also thrombocytopenia.[1–6]

The growing number and severity of those events led several countries to contraindicate the AZ vaccine in

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young and middle-aged adults, although the absolute risk of CVT was estimated to be low (5 per million vaccinated individuals).

In April 2021, a small number of similar cases were reported in temporal association with the Ad26.COV2.s Johnson & Johnson/Janssen (JJ) vaccine[7–9] (<1 per million vaccinated), leading the US authorities to halt temporarily the use of that vaccine.

A likely mechanism for these complications[1,6] was proposed in the following weeks, as several of these patients with CVT and thrombocytopenia tested positive for platelet factor 4 (PF4) antibodies, despite no previous treatment with heparin. Patients also tested positive on a platelet-activation assay in the presence of PF4 independent of heparin. This led to the conclusion that the thrombotic thrombocytopenia was probably mediated by platelet-activating antibodies against PF4, mimicking autoimmune heparin-induced thrombocytopenia (HIT).[1,6] This post-vaccine entity is currently named vaccine-induced immune thrombotic thrombocytopenia (VITT).

Purpose

Do neurologists and stroke physicians need a guidance document?

It is important that neurologists and stroke physicians, the specialists who usually care for patients with CVT, are informed and periodically updated on the diagnosis and treatment of patients presenting with CVT after vaccination against SARS-CoV-2. Documents from international and national regulatory agencies have discussed mainly the balance between benefits and harms, and whether to stop, restrict or continue the use of individual vaccines. Consensus and guidance documents from medical societies[10–13] have dedicated special attention to the diagnosis and treatment of VITT. We aim to adapt that guidance to neurological practice, with a focus on the specific management of CVT occurring shortly after anti-SARS-CoV-2 vaccination.

Method

Guideline statement or guidance document derived from expert consensus?

Because this is a new medical entity, with still few cases described, there is scarce knowledge on pathophysiological mechanism and limited experience on therapeutic management. The confidence in the effect of any specific intervention is very low and mostly based on indirect evidence. Available evidence comes from case reports, case series and analogy with HIT management. Consequently, writing of recommendations based on robust evidence is not possible. However, physicians must make clinical decisions and provide advice to patients and families. Therefore, the most sensible option is to produce interim documents, based on expert consensus and periodically update them as new evidence is produced.

Selection of the working group

Experts were selected among the authors of the ESO-EAN CVT guidelines 2017,[14] by the first author, who was the coordinator of the ESO-EAN CVT guidelines,[14] for their expertise and special interest on CVT following COVID-19 vaccination.

The experts stated no conflicts of interest, including intellectual conflicts of interest, related to their expert opinion.

The steps undertaken by the working group are summarised as follows:

1. A list of topics of clinical interest was produced and agreed by the working group members.
2. A systematic review of the PubMed database was conducted. The literature search was restricted to articles published in 2021, up to May 24th. Only English-language articles were included. Two authors independently screened titles and abstracts for eligibility (JMF and DAS). Second level selection or full text screening of these articles was performed independently by the same authors. Discrepancies or conflicts in selection or rejection of studies were then resolved by consensus. The working group members extracted the data for the selected articles.
3. Consensus process: The framework of the manuscript document and several draft versions of the manuscript were produced, circulated, reviewed and discussed by all the working group members and modified until a full consensus was reached.
4. Finally, the document was reviewed and approved by two external reviewers and members of the ESO Executive Committee.

Expert opinion

Description of CVT cases occurring after anti-SARS-CoV-2 vaccination

A table summarizing findings from the main case series of patients with diagnosis of CSVT after anti-SARS-CoV-2 vaccination that were published so far is provided as online-only supplemental material (Supplemental Table 1).

CVT was often severe, featuring focal deficits, seizures, mental status and alertness disturbances, brain

haemorrhagic lesions and intracranial hypertension with brain herniation

Who is at risk of CVT after anti-SARS-CoV-2 vaccination?

CVT associated with thrombocytopenia and with VITT has been described only after the AZ and the JJ vaccines.[1–9] Thrombocytopenia is usually severe

Almost all patients affected by CVT to date are young to middle-aged persons, predominantly women.

Persons with previous CVT, other venous or arterial thrombotic events or intracerebral haemorrhage, or those who have vascular risk factors or thrombophilia abnormalities, use estrogen progestins or have other risk factors for CVT do not appear to be at increased risk of CVT after anti-SARS-CoV-2 vaccination

The majority of CVT cases occurred after the first dose of AZ vaccine.

Diagnosis

What are the suspected symptoms/signs of CVT? Vaccinated persons should be informed that they might experience a transient headache on the days following vaccination. If the headache persists or is unusually severe, or if they have any other visual (visual blurring, decreased visual acuity, visual obscurations) or neurological symptoms (motor, sensory, language, level of consciousness, or cognitive deficits, or new seizures), they should seek urgent medical advice.

How many days after vaccination do those symptoms appear? Symptoms usually start within 30 days after vaccination.[1–9] Patients may start with headache 4 or more days after vaccination and suffer a neurological deterioration some days later. Other patients had a sudden severe clinical presentation from the onset.

How should CVT be confirmed/ruled out? Patients should be examined by a neurologist/stroke physician.

If there is a suspicion of CVT, CT with CT venography or MR with MR venography should be performed, as recommended.[14,15]

If CVT is confirmed, the patient should be urgently referred to a hospital with a stroke unit and/or a neurointensive care unit, capable of providing ICU care, endovascular treatment and decompressive surgery, if needed.

What could be the pathogenic mechanisms of CVT after vaccination against SARS-CoV-2? There are several possibilities for the occurrence of CVT after vaccination against SARS-CoV-2: 1) a fortuitous (chance) association of cryptogenic CVT and vaccination; 2) CVT related to other associated risk factors/associated conditions (e.g., contraceptives, genetic or acquired thrombophilia, ear/sinus infections, cancer, Behçet's disease, etc); 3) co-occurrence or recent SARS-CoV-2 infection[16–18]; 4) CVT as a thrombotic manifestation of VITT, as detailed above.[1,6]

What additional examinations and tests should be performed? Patients should have a physical examination to identify signs suggestive of other thrombotic events (e.g. limb deep vein thrombosis, splanchnic venous thrombosis, pulmonary embolism), or any type of bleeding.

Besides exclusion of COVID-19 infection and the recommended screening/investigation of the usual risk factors/associated conditions for CVT,[14,15] the following laboratorial examination should be also required in all suspected cases of VITT[11,12]:

- Complete blood count, blood cell film.
- Coagulation tests: D-dimers, fibrinogen, PT and aPTT.

If there is thrombocytopenia ($<150 \times 10^9$/L) or abnormal results of coagulation tests, a heparin-induced thrombocytopenia (HIT) PF4 Antibody ELISA test should be performed and, if possible, confirmed by functional tests.

Other causes of thrombocytopenia should be excluded, including pseudo-thrombocytopenia and other causes of immune thrombocytopenia.

How is VITT diagnosed/confirmed?

- CVT with thrombocytopenia ($<150 \times 10^9$/L) and a positive HIT ELISA test fulfil the criteria for possible VITT.
- Consultation with a haematologist/expert in thrombosis is recommended; the speciality dedicated to the diagnosis and management of VITT may vary from centre to centre/country to country.
- Rapid immunoassays widely used for the diagnosis of HIT are usually negative.[19]
- A positive HIT ELISA test may be confirmed by functional tests, if available.
- In some patients with VITT, HIT ELISA test may be negative, while functional tests (PF4-serotonin release assay) confirm VITT.[19]
- Check with your local/reference laboratory or with a haematology/thrombosis expert which functional tests are available and should be used, and what is the time lag in obtaining the results. If functional tests are not available, manage the case as recommended for VITT.[12]

Treatment

What antithrombotic medication should be used in the acute phase? In patients with CVT and thrombocytopenia ($<150 \times 109$/L), in whom VITT is suspected or confirmed, heparin (unfractionated or low molecular weight) should be avoided.

Use non-heparin anticoagulants such as argatroban, bivalirubin, danaparoid, fondaparinux, or direct oral anticoagulants, if platelets $> 50 \times 10^9$/L and there is no major or life-threatening systemic bleeding.[20–23]

The choice of the most appropriate non-heparin anticoagulant for the individual patient depends on the characteristics of the patient (including evidence of intracerebral haemorrhage, systemic bleeding, and platelet count), consideration of the specific properties of the medication (e.g., half-life, availability of antidote), and the experience of the treating physician.[20,21]

All other patients should be treated with unfractionated or low-molecular-weight heparin as recommended in the Guidelines for management of CVT.[14,15]

Should platelet transfusions be used or avoided? In CVT with thrombocytopenia ($<150 \times 10^9$/L), until the diagnosis of VITT is not excluded or if the diagnosis of VITT is confirmed, platelet transfusions should be avoided,[11,12] unless there is a major or life-threatening bleeding or the patient requires urgent surgery or an invasive diagnostic or therapeutic procedure, with high risk of bleeding.

Is immunotherapy necessary? Based on indirect evidence from HIT and apparent efficacy in several of the previously reported cases of VITT, in CVT with thrombocytopenia ($<150 \times 10^9$/L), if the diagnosis of VITT is confirmed or likely, early intravenous immunoglobulin is recommended (1000 mg/kg daily for 2 days).[12,20,21]

If there is no response to intravenous immunoglobulin, steroids and/or plasmapheresis are reasonable alternatives.[12]

What antithrombotic medication should be used in the post-acute phase, in patients with diagnosis of VITT? In CVT with confirmed VITT, vitamin K antagonists should only be started when the platelet count is stable and $>150 \times 10^9$/L).

Direct oral anticoagulants are an alternative.[24]

Other interventions in the management of CVT. All other interventions in the management of patients with CVT patients associated with anti-SARS-CoV-2 vaccination, including endovascular treatment and decompressive neurosurgery, should follow the Guidelines recommendations.[14,15]

How urgent is recognition and treatment of patients with CVT and suspected or confirmed VITT?. Urgent diagnosis of CVT and of VITT is mandatory to guide antithrombotic and immune treatment and to prevent or reverse progressive neurological deterioration and death

Prognosis

So far, case fatality (25–40%)[1–5,7–9] in the reported cases of CVT with VITT (Table is in supplemental material) has been higher than the mortality in large cohorts of patients with CVT from the pre-COVID-19 era (<5%).[25,26]

Future directions

New and higher quality evidence is likely to accumulate very soon, as new cases are diagnosed and larger case series are published. Larger non-selected prospective case-series and case-control studies with CVT diagnosed pre-COVID-19 pandemic are needed. Analysis of big data from pharmacovigilance databases and health-care networks diagnostic codes will also be useful. Analysis of the treatment strategies currently in use in patients who developing CVT after vaccination against SARS-CoV-2 infection will be informative in establishing the most appropriate management. As this expert opinion is supported by low quality evidence, it should be periodically updated, or upgraded to a formal guideline, as new and higher quality evidence is eventually produced.

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Contributorship

JMF coordinated the working group. JMF, DAS, JMC and IM performed the review of the available evidence. JMF drafted the manuscript. All authors revised critically the manuscript for important intellectual content and contributed to the editing and final approval.

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Supplemental material

Supplementary material for this article is available online.

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