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## Clinical Insights

## SARS-CoV-2 vaccine-induced cerebral venous thrombosis

Alfonso Ciccone\*

Department of Neurology with neurosurgical activity and stroke unit, ASST di Mantova, Mantova, Italy



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## VISUAL ABSTRACT

The nosological entity of the cerebral venous thrombosis caused by the SARS-CoV-2 vaccination differs from the common cerebral venous thrombosis in that it is due to immune thrombocytopenia triggered by vaccination. Cerebral venous thrombosis is one of several manifestations of this type of immune thrombocytopenia. Albeit many general aspects of management of cerebral venous thrombosis are similar, immune thrombocytopenia requires a specific therapeutic approach, which is not normally adopted for cerebral venous thrombosis due to other causes, therefore its early recognition is essential.

## What is a cerebral venous thrombosis?

Cerebral venous thrombosis (CVT) is a rare cause of stroke and intracranial hypertension syndrome. Compared to arterial stroke, CVT affects younger people, predominantly women, has a different risk factors profile, and a subtle and multiform clinical presentation. Risk factors include pregnancy and puerperium, oral contraceptives, inherited thrombophilia, malignancy, infections, obesity, diagnostic and treatment procedures. The wide spectrum of clinical presentations make the diagnosis difficult. The three main connected syndromes are isolated intracranial hypertension syndrome (headache with or without vomiting and papilloedema), focal syndrome (focal deficit such as paresis and aphasia, seizures or both), and encephalopathy (drowsiness, delirium, and consciousness disturbances up to coma)[1].

Non-invasive imaging studies, such as MR imaging with MR venography or CT with CT venography, should be used to confirm the diagnosis; MR with T2\*- weighted gradient recalled echo or susceptibility-weighted imaging, allow for the detection of intravenous thrombosis; non-contrast CT, instead, can be normal or have non-specific findings in most patients[2]. Therefore, clinical diagnostic suspicion must guide the correct neuroimaging investigations.

The main therapies for the acute phase are the anticoagulant treatment with either unfractionated intravenous heparin or subcutaneous low molecular weight heparin followed by oral anticoagulation[2] (vitamin K antagonists or dabigatran[3]), even when in presence of brain hemorrhage, and measures to reduce intracranial pressure[1,2].

Early recognition and improvement in CVT treatment has contributed to improve outcome and mortality, which declined below 5% in the last decades[4].

## Why a cerebral venous thrombosis after the SARS-CoV-2 vaccine?

The clinicians like myself, who had the chance of coming across a case of CVT following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, realized in the field that this condition is completely different from what we had experienced before. The first clinical aspect that stroked me at the initial observation in the emergency room was the result of the blood tests: the drop of platelet count and the high D-dimers level. While hematological diseases are known risk factor for CVT, these generally include conditions such as essential thrombocythemia, myeloproliferative malignancies, primary and secondary polycythemia, paroxysmal nocturnal hemoglobinuria[5], but not typically thrombocytopenia, which is more frequently linked to hemorrhagic than thrombotic complications. However, cases of CVT have been reported in the course of thrombocytopenia in systemic lupus [6] and of immune thrombocytopenia[7]. The coexistence of thrombosis with thrombocytopenia seems paradoxical[7], unless we explain the phenomenon by a mechanism of systemic platelet consumption and sequestration through agglutination triggered by the vaccine, which ultimately leads to systemic thrombosis. In fact, the reported cases had a median platelet count at diagnosis of 20,000–30,000 per cubic millimeter and almost invariably a high titer of antibodies to platelet factor 4

\* Corresponding author Alfonso Ciccone, Department of Neurosciences, ASST di Mantova, Strada Lago Paiolo 10, 46100 Mantova, Italy.  
 E-mail address: [alfonso.ciccone@asst-mantova.it](mailto:alfonso.ciccone@asst-mantova.it).

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(PF4)-polyanion complexes[8-10]. These issues led to speculation that the SARS-CoV-2 vaccine might determine CVT due to an autoimmune mechanism similar to the one of heparin-induced thrombocytopenia [11]. An alike syndrome heparin-induced thrombocytopenia was already described both after vaccination with other anti-viral vaccines, albeit without thrombosis[12], and after SARS-CoV-2 infection, where molecular mimicry between virus and platelet antigens was hypothesized[13,14]. Similarly, after vaccination, the antibodies produced against the spike proteins might cross-react with specific antigens expressed on the platelet surface, although this hypothesis has been questioned[15]. The reason why such a chain of events sporadically occurs after vaccination remains obscure. The peculiarities of CVT following SARS-CoV-2 vaccination have led to coining a specific term to indicate this syndrome: vaccine-induced immune thrombotic thrombocytopenia or VITT[15]. Of note, the term VITT refers to thrombotic thrombocytopenia as a systemic disease, not to specific organ diseases. However, CVT and splanchnic thrombosis are unusual in the course of heparin-induced thrombocytopenia where, nevertheless, antibodies to PF4 are present. The reason why these thrombotic manifestations occur in VITT, and not typically in heparin immune thrombocytopenia, remains to be established. The D-dimer test has good accuracy in the diagnosis of CVT[16]. D-dimer is the product of fibrin degradation and elevated D-dimers together with thrombocytopenia are highly suggestive of activation of systemic anticoagulation. Therefore, the finding of high D-dimers level may be useful to distinguish thrombocytopenia due to decreased platelet production from thrombocytopenia caused by systemic thrombosis.

The second remarkable aspect was the absence of the common risk factors for CVT. CVTs have many different causes and risk factors; most of the cases we face are women under oral contraceptive pill or hormonal replacement therapy[17]. The patient I visited was a healthy man in his fifties, with no prothrombotic risk factors. Most of the cases reported after the SARS-CoV-2 vaccination are women younger than 50 years of age but few of them were receiving oral contraceptives or hormonal replacement therapy[8-10]. Therefore, the trigger of the vaccine-induced immune thrombocytopenia is unknown and it appears to have nothing to do with common CVT risk factors.

The last unusual aspect I experienced in my patient with CVT after SARS-CoV-2 vaccination, was the catastrophic disease course: the subject died within 24 h from the first observation from a massive brain venous hemorrhagic infarction and with pulmonary embolism, despite treatment with low molecular heparin, steroids, platelet transfusion, and hemicraniectomy. The prognosis for CVT is generally good: the mortality with the current treatments is less than 5%[4], and approximately 75% of the affected subjects make a full recovery[5]. In contrast, almost 1 out of 2 patients with CVT as a manifestation of VITT, die within few days[8-10]. Death can occur both due to brain infarction, often hemorrhagic, caused directly by CVT, and due to extra cerebral thrombosis, such as pulmonary embolism, portal and splanchnic thrombosis[8-10]. These aspects underline the fact that we are faced with a systemic disease where thrombosis can be localized anywhere.

### Why look for the vaccine-induced immune thrombotic thrombocytopenia?

The occurrence of VITT is rare and is estimated on about 1 subject every 150,000 vaccinated, not far away from the CVT incidence in the general population. This explains why these complications were not seen in SARS-CoV-2 vaccine trials, which involved less than 30,000 subjects per arm.

Although most of the reported cases of VITT, for unknown reasons, are CVT, the possibility of arterial thrombosis in the brain or in other organs should not be excluded. Therefore, we should pay close attention to the frequent thrombo-embolic pathologies, such as stroke of arterial origin, where VITT can be masked by common risk factors for cerebrovascular pathologies. Indeed, the presence of other risk factors such as

atrial fibrillation, diabetes and atherosclerosis could prevent from searching on a much rarer, largely still unknown cause of thrombosis, such as VITT. The early recognition of VITT is fundamental for the consequent therapeutic choices, since these differ from the common CVT. Indeed, the early choice of a correct therapy should prevent the potentially catastrophic evolution of VITT. Early anticoagulant treatment in CVT is widely acknowledged and low-molecular-weight heparin is recommended in guidelines from the European Stroke Organization, although based on limited trial evidence[2]. On the contrary, in CVT linked to VITT low-molecular-weight heparin could possibly worsen the outcome. Likewise, platelet transfusion might be the wrong option because it could amplify the rate of immune thrombosis. Different scientific society published guidelines for the management of VITT, largely borrowed from the experience with heparin-induced thrombocytopenia [18-20]. Although there are some differences, these guidelines have in common the indication to avoid heparin in all its forms, including low-molecular-weight heparin, and avoid platelet transfusion. These therapies have instead been administered to most of the patients reported, including mine, when we were still unaware of VITT. High dosage intravenous immunoglobulins and possibly plasmapheresis, are probably effective.

### Conclusions

CVT after SARS-CoV-2 vaccination can be the first manifestation of a much more complex and life-threatening disorder, mimicking heparin-induced thrombocytopenia. CVT is not the only manifestation of vaccine-induced immune thrombotic thrombocytopenia, which can also occur with thrombosis in other sites. It is necessary to pay close attention to the most common thrombotic manifestations, such as stroke and myocardial infarction, among subjects with risk factors, because it cannot be excluded that some of these cases are adverse effects of the vaccine.

A headache, which is also a frequent symptom after vaccination, could be a manifestation of a CVT in a vaccine-induced immune thrombotic thrombocytopenia and a simple platelet count could help rule out this form. Conversely, a thrombocytopenia in patients with thrombotic manifestations of any kind within 4 weeks of vaccination (all cases reported so far have occurred within 24 days of vaccination [8-10]), should lead to a search for anti-FP4 antibodies.

A well-rounded awareness of these events' clinical and laboratory features plays a crucial role in the early identification of patients at their first clinical manifestation and helps undertake all preventions to avoid the dramatic consequences of immune thrombocytopenia. Although the indications on the treatment of vaccine-induced immune thrombotic thrombocytopenia are derived from studies on thrombocytopenia induced by heparin, the widespread knowledge of this possible severe adverse event of SARS-CoV-2 vaccination is already a good starting point.

### Declarations of interest

None.

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