Cerebral venous sinus thrombosis after ChAdOx1 nCov-19 vaccination with a misleading first cerebral MRI scan

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SUMMARY
Vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) have recently been described as rare complications following vaccination against SARS-CoV-2 with vector vaccines. We report a case of a young woman who presented with VITT and cerebral CVST 7 days after vaccination with ChAdOx1 nCov-19 (AstraZeneca). While the initial MRI was considered void of pathological findings, MRI 3 days later revealed extensive CVST of the transversal and sigmoidal sinus with intracerebral haemorrhage. Diagnostic tests including a platelet-factor-4-induced platelet activation assay confirmed the diagnosis of VITT. Treatment with intravenous immunoglobulins and argatroban resulted in a normalization of platelet counts and remission of CVST.

BACKGROUND
Active vaccination against SARS-CoV-2 is currently one of the most important measures to contain the COVID-19 pandemic. With increasing numbers of ChAdOx1 nCov-19 (AstraZeneca) vaccinations, adverse events such as thrombotic thrombocytopenia and cerebral venous sinus thrombosis (CVST) were observed as very rare complications. Vaccine-induced thrombotic thrombocytopenia (VITT) mediated by platelet-activating antibodies against platelet factor 4 (PF4) was observed and considered causative for such vascular events. Here, we report a case of VITT causing a CVST in an otherwise healthy young woman following ChAdOx1 nCov-19 vaccination and highlight particular laboratory and imaging features which may advise clinical decision making in the next weeks.

CASE PRESENTATION
A young woman in the early 30s presented to our emergency department with an isolated headache (Numerical Rating Scale (NRS) score=8), progressive thrombocytopenia of 37 000/µL and an increased D-dimer concentration of 12 859 µg/L fibrinogen equivalent unit (FEU) (reference range: <500 µg/L FEU). The screening test for heparin-induced thrombocytopenia (HIT) was positive (particle gel agglutination immunnoassay for antibodies against PF4/heparin, polyvalent, i.e., not specific for IgG antibodies; ID-PaGIA Heparin/PF4 Antibody Test, DiaMed). The PCR test for SARS-CoV-2 from a nasopharyngeal swab was negative. On clinical examination, the patient presented with a discrete gait ataxia and reported progressive amnestic difficulties as well as discrete amnesic aphasia. A new MRI scan revealed CVST of the left transverse and sigmoidal sinus with a left-temporal and left-cerebellar intracerebral haemorrhage (figure 1B-2). The results of the heparin-induced platelet activation assay (HIPA) and the platelet-factor-4-induced platelet activation assay (PIPA, a modified HIPA test) showed strong IgG-receptor-mediated platelet activation in both the presence and absence of heparin confirming the diagnosis of VITT. In addition, a hypercoagulable state work-up showed no relevant findings.

INVESTIGATIONS
Three days later, the patient was referred to our department with persisting headaches (NRS score=8), progressive thrombocytopenia of 37 000/µL and an increased D-dimer concentration of 12 859 µg/L fibrinogen equivalent unit (FEU) (reference range: <500 µg/L FEU). The screening test for heparin-induced thrombocytopenia (HIT) was positive (particle gel agglutination immunnoassay for antibodies against PF4/heparin, polyvalent, i.e., not specific for IgG antibodies; ID-PaGIA Heparin/PF4 Antibody Test, DiaMed). The PCR test for SARS-CoV-2 from a nasopharyngeal swab was negative. On clinical examination, the patient presented with a discrete gait ataxia and reported progressive amnestic difficulties as well as discrete amnesic aphasia. A new MRI scan revealed CVST of the left transverse and sigmoidal sinus with a left-temporal and left-cerebellar intracerebral haemorrhage (figure 1B-2). The results of the heparin-induced platelet activation assay (HIPA) and the platelet-factor-4-induced platelet activation assay (PIPA, a modified HIPA test) showed strong IgG-receptor-mediated platelet activation in both the presence and absence of heparin confirming the diagnosis of VITT. In addition, a hypercoagulable state work-up showed no relevant findings.
and sinus transversus. (B-coronal T1w sequence of the cerebellum, temporal lobe
Headache intensity is shown in black according to the
presentation in our hospital was provided by the generalist.

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OUTCOME AND FOLLOW-UP
Under continuous anticoagulation with argatroban, the patient improved with regressive headache but persistent
minimal gait ataxia, amnestic deficits as well as discrete amnestic aphasia. A follow-up MRI scan showed persisting
CVST but regressive cerebellar haemorrhage with a slightly
progressive temporal perifocal oedema (figure 1B-3). Subsequently, the platelet count increased in the following days
(figure 1A).

DISCUSSION
Consistent with the initial description of VITT following
ChAdOx1 nCov-19 vaccination,1 2 we report on a young
woman with unremarkable medical history suffering from
CVST. The delay between vaccination and symptom onset
was 7 days, which is in the range of 5–16 days reported for
VITT. A positive PIPA confirmed the diagnosis.

Following positive HIT screening test, treatment of
CVST was started with argatroban. Because of contin-
uous clinical improvement, this treatment was continued
before switching the patient to anticoagulation with dabig-
(tran (Pradaxa) on day 8 after hospitalisation. According
to current recommendations,3 we treated the patient with
intravenous immunoglobulins for 2 days. Subsequently,
the platelet count increased continuously.

Although our patient suffered from headache and mild
thrombocytopenia at first presentation, the initial MRI scan
was without any clear pathological finding. The follow-up
MRI scan, however, revealed an extensive CVST. There is an
ongoing debate about the appropriate imaging modality for
detecting CVST. In a recent meta-analysis,4 CT and MRI had
similar diagnostic performance. Retrospectively, we noted
small irregularities at the bottom of the left transverse sinus
in the contrast-enhanced T1w image (figure 1B-1). In view of
the clinical course, this warrants a high sensitivity also for
(small) abnormalities in cerebral veins and sinuses in these
patients. The clinical challenge of managing such patients
and the importance of high vigilance are also supported by a
similar patient who also deteriorated at second presentation
to the hospital in a recent case series.5

Given the high number of patients presenting to emer-
gency departments with headache or other unspecific
symptoms following vaccination with ChAdOx1 nCov-19
or other vector vaccines for SARS-CoV-2, our case adva-
eciates to give high priority to patients with signs of throm-
boctopenia and/or elevated D-
formed if clinical
suspicion persists. Progression of thrombocytopenia
should be monitored, while a platelet substitution is not
recommended as it could further aggravate thrombosis
and thrombocytopenia.3 Although our HIT test was posi-
tive, it is important to note that commercially available
tests are not sufficient to exclude/confirm VITT so far
and literature should be screened regularly for avail-
ability of new tests/recommendations3 in this rapidly
evolving field. Given the high number of vaccinations

TREATMENT
The patient was admitted to our stroke unit; antiocoagu-
lation with argatroban (Argatra) was initiated immedi-
ately; and intravenous immunoglobulin therapy (1 g/kg
body weight/day for 2 days) was applied for treatment of
suspected VITT.

Figure 1  A time course of clinical characteristics and
labatory results following vaccination. Platelet count
is depicted in red. The value of day 9 prior to second
presentation in our hospital was provided by the generalist.
Headache intensity is shown in black according to the
Numerical Rating Scale. (B) Serial cerebral MRI scans. Upper
row: axial T2* sequence of the infratentorial brain; lower row:
coronal T1w sequence of the cerebellum, temporal lobe
and sinus transversus. (B-1) MRI scan at first presentation
in our emergency department with thrombocytopenia and
headache. At first look, the MRI scan was without any clear
pathological finding. The follow-up MRI scan showed persisting
CVST and intracerebral haemorrhage (asterisks). (B-2) First follow-up MRI 3 days later revealed a CVST of
the left transverse and sigmoidal sinus (red arrows) with a
left-temporal and left cerebellar intracerebral haemorrhage
(asterisks). (B-3) Most recent follow-up MRI showing a
Persistence of CVST and intracerebral haemorrhage with a
slightly progressive perifocal oedema. Volume of cerebellar
haemorrhage slightly decreased. CVST, cerebral venous
sinus thrombosis; ER, emergency room; HIPA, heparin-
induced platelet activation assay; HIT, heparin-induced
thrombocytopenia; IVIG, intravenous immunoglobulin; PIPA,
platelet-factor-4-induced platelet activation assay.
with ChAdOx1 nCov-19, the occurrence of VITT and subsequent CVST has to be considered a very rare complication: according to a recent European Medicines Agency report as of 4 April 2021, 34 million people have been vaccinated with ChAdOx1 nCov-19 (Vaxzevria, formerly COVID-19 Vaccine, AstraZeneca), and 169 cases of CVST and 53 cases of splanchnic vein thrombosis were recorded by EudraVigilance.3 Our case report intends to raise awareness in emergency departments and to provide a diagnostic and therapeutic work-up for this rare complication of vector vaccines against SARS-CoV-2.

**Learning points**

- High priority should be given to patients presenting with headaches following ChAdOx1 nCov-19 vaccination.
- Screening for thrombocytopenia and/or elevated D-dimer is mandatory in such patients.
- Initial cerebral MRI scans can be normal—if clinical suspicion for sinus vein thrombosis persists, a repeated MRI scan should be performed in patients following ChAdOx1 nCov-19 vaccination.
- Current commercially available heparin-induced thrombocytopenia screening tests are not sufficient to diagnose vaccine-induced thrombotic thrombocytopenia.

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