CEREBRAL VENOUS THROMBOSIS AFTER COVID-19 VACCINATION. CASE REPORT.

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Abstract

Cerebral venous sinus thrombosis (CVST) is a rare complication in recipients of the adenovirus-vectored coronavirus disease 2019 (COVID-19) vaccine ChAdOx1 nCov-19 (Vaxzevria®; AstraZeneca®). So far, the majority of CVST cases after ChAdOx1 were women under 60 years old with predisposing prothrombotic risk factors presenting with thrombocytopenia in the context of vaccine-induced immune thrombotic thrombopenia (VITT) syndrome. Non-VITT CVST cases are extremely rare. In this report we present two CVST cases, one 59-year-old male and one 71-year-old female, with no previous risk factors or evidence of VITT syndrome that were successfully treated with low-molecular weight heparin. Clinical research findings on the matter and pathogenic mechanisms are briefly discussed. Although definite causality remains to be proven, clinicians should be suspicious of CVST in recipients of ChAdOx1 even in the absence of thrombocytopenia or prothrombotic risk factors.

Key words: cerebral venous sinus thrombosis; ChAdOx1; Vaxzevria®; vaccine-induced immune thrombotic thrombopenia

Introduction

Up to the end of August 2021, the cumulative number of COVID-19 cases reported globally was 216 million and the cumulative number of deaths was just under 4.5 million [1]. On 29th of January 2021, the European Medicines Agency (EMA) authorised use of Vaxzervia® (AZD1222, ChAdOx1 nCoV-19) throughout the European Union. The vaccine uses a modified simian adenovirus to deliver the SARS-COV-2 spike glycoprotein into human cells [2]. While the vaccine prevents severe course and death from COVID-19 and mainly causes minor adverse effects, rare cases of thrombosis have been reported, including cerebral venous sinus thrombosis (CVST) especially in women under 55 years old [3]. More specifically, among 281,264 people who received ChAdOx1 in Denmark and Norway an excess of 2.5 (0.9 to 5.2) CVST events per 100,000 vaccinations were found [4]. However, EMA concluded that the vaccine efficacy against COVID-19 infection outweighs the rare risk of blood clots' events [3].

Among CVST cases after ChAdOx1 vaccination (i.e. 169 cases per 34 million people up to April 4 2021), the majority was women (i.e. up to 77.8%) under 60 years old (i.e. 80%) diagnosed with the newly recognised vaccine-induced immune thrombotic thrombopenia (VITT) syndrome [5,6]. VITT clinically resembles autoimmune heparin-induced thrombocytopenia (HIT) and is caused by activating platelet factor 4 (PF4) antibodies on the platelet surface inducing thrombopenia along with organ-specific or disseminated thrombosis [7]. Definite diagnosis is based on recent vaccination history (i.e. 5-30 days before), clinical symptoms and signs of thrombosis, thrombocytopenia (i.e. <150,000/μL), increased blood D-dimers (>4000 μg/L) and positive PF4 antibodies [7,8]. Intravenous immunoglobulin and/or corticosteroids are the mainstay of VITT treatment. As in HIT, low-molecular weight heparin (LMWH) must be avoided except for fondaparinux. However, there are reports of non-VITT-related CVST cases [6,8]. In this case paper, we present two such cases with no previous thrombotic risk factors or diseases.

Cases

Case 1

A 59-year-old male patient was referred to the Neurological Department due to blurred vision since a few hours accompanied by right-sided progressive headache starting one week earlier. His medical history was unremarkable. He received the ChAdOx1 vaccine 15 days prior presentation. Vital signs were within normal limits. On neurological examination left homonymous hemianopsia was found. The remainder of the physical examination was unremarkable. The

patient had a computed tomography (CT) brain scan and angiography and magnetic resonance imaging (MRI) and MR venography (MRV). These revealed intraparenchymal brain haemorrhage in the right parieto-occipital region with surrounding oedema and thrombosis of right transverse and sigmoid cerebral sinuses (Fig.1). Nasal swab PCR was negative for COVID-19. Blood testing for autoimmune diseases (including PF4 antibodies), infections and thrombophilia were unremarkable. D-dimers and fibrinogen were within normal limits. The patient was diagnosed with cerebral sinuses venous thrombosis after ChAdOx1 vaccination, as no other obvious cause was found. The patient was firstly treated with intravenous mannitol for the cerebral oedema and therapeutic dose of enoxaparin. After a neurosurgical consultation, a non-invasive management was decided. The case was complicated with a lower respiratory infection successfully treated with intravenous ceftriaxone. At discharge the patient was still experiencing left hemianopsia with some improvement in his visual fields. A follow-up CT scan showed partial absorption of the hematoma.

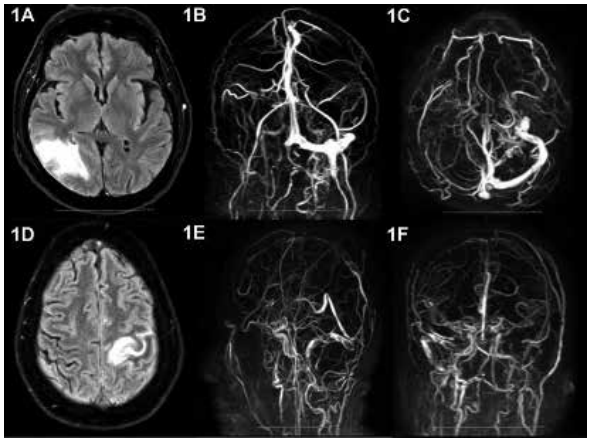
Case 2

A 71-year-old woman presented with right-sided weakness, and speech problems. Further questioning revealed a 10-day history of progressive headache which began few hours after the vaccination with ChAdOX1. Her medical history was unremarkable. Vital signs, on admission, were stable and within normal range. Neurological examination showed right-sided hemiparesis with hemisensory loss and aphasia. Fundoscopic exam was normal. Brain CT and MRI revealed a subarachnoid haemorrhage in the left parietal lobe with mild oedema. Brain MRV demonstrated occlusion of superior sagittal sinus, transverse sinus bilaterally and the left sigmoid sinus (Fig. 1). Nasal swab PCR was negative for COVID-19. Blood tests for autoimmune diseases (including PF4 antibodies), infections and thrombophilia were unremarkable. D-dimers were 8,923μg/L and fibrinogen was 5,96g/L. The patient was diagnosed with cerebral sinuses venous thrombosis after ChAdOx1 vaccination and therapeutic enoxaparin was initiated. After neurosurgical consultation, a non-invasive management was decided. At the 20th day the patient's neurological status was found markedly improved and she was discharged.

Discussion

In this case report we present two CVST cases after ChAdOx1 vaccine with no previous risk factors for thrombosis and no evidence of VITT syndrome. In one cohort study 37 cases of CVST after ChAdOx1 vaccination were reported, 11 of whom had low

Figure 1. Brain magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) of the case 1 and 2. Case 1: Axial FLAIR (1A) showing hyperacute in the right parieto-occipital region with surrounding oedema. Coronal (1B) and axial (1C) MRV showing thrombosis of the right transverse and sigmoid venous sinus. Case 2: Axial FLAIR (1D) showing subarachnoid hemorrhage with surrounding edema. Sagittal (1E) and coronal (1F) MRV showing thrombosis of the superior sagittal sinus, bilateral transverse sinuses and left sigmoid sinus



probability for VITT based on the VITT score [6]. In another more informative cohort of CVST patients in the UK, 25 non-VITT CVST cases (out of 95 CVST cases related to ChAdOx1 vaccine) were identified [8]. Researchers found that non-VITT cases had older age than VITT cases and CVST occurred even after the second dose of the vaccine in contrast to the VITT cases occurring only after the first dose. About 44% of non-VITT cases had no previous thrombotic venous risk factor, like in our cases, compared to 66% of VITT cases, but the difference was marginally non-significant. Also, non-VITT patients had higher fibrinogen blood levels and lower prothrombin time and activated partial thromboplastin time than VITT-cases. Non-VITT cases had fewer thrombosed veins, less venous infractions, and less cerebral hemorrhages than VITT-cases. Clinical features were similar among VITT and non-VITT CVST cases. However non-VITT cases showed a more favorable outcome compared to VITT cases, like the patients presented in this report [8].

In our first case D-dimers and fibrinogen were normal, while the second patient had increased D-dimers (i.e. over 4,000μg/L) with normal fibrinogen. This is accordance with previous research showing that D-dimers levels were suboptimal for including them in VITT criteria. In the same study a D-dimers level of >2000μg/L or fibrinogen <2g/L has been suggested for probable VITT-associated CVST [8]. On the other hand, normal D-dimers do not preclude

CVST [9]. Based on these suggestions, fibrinogen was more indicative than D-dimers for a non-VITT-related CVST in our patients.

Both of our cases were successfully treated with LMWH according to the published guidelines [9]. On the contrary, LMWHs are contraindicated in VITT syndrome [5], thus further substantiating the absence of VITT syndrome in our cases. Surgical and neurointerventional treatment is reserved only in selected cases, such as patients showing neurological deterioration or radiological signs of herniation or increased, uncontrollable intracranial pressure due to haemorrhagic or oedematous infarcts [9]. Our patients remained alert and clinically stable throughout their hospitalization.

The exact pathogenic mechanism explaining non-VITT-related thrombosis after ChAdOx-1 vaccination remains speculative. As in human adenoviruses infections, the ChAdOx1 simian adenovirus vector can potentially interact with human platelets and activate them [10]. Also the transcription of codon-optimized SARS-CoV-2 S proteins has been found to induce alternative splicing, producing truncated soluble S protein variants that could potentially bind to angiotensin-converting enzyme (ACE2) receptors on endothelial cells triggering thromboembolic events [10].

Although we cannot prove a direct causal relationship between previous ChAdOx1 and CVST in our cases, we could not identify any background thrombotic risk factor or disease. The absence of VITT in these cases outlines the need to keep health professionals vigilant for CVST diagnosis even in the absence of thrombocytopenia or increased D-dimers or previous thrombotic risk factors in patients presenting with symptoms like progressive headaches, or focal neurological signs up to 1 month after ChAdOx1.

Declarations of interest: None

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