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LETTER TO THE EDITOR

# Acute haemorrhagic necrotizing encephalopathy in the setting of SARS-CoV-2 vaccination: a case report and literature review

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## Introduction

Globally, we are now in the position of having several highly effective vaccines targeting SARS CoV-2. Given the accelerated regulatory approval of SARS CoV-2 vaccines, it is imperative that the medical community remains vigilant towards vaccine-associated adverse effects. Here, we report a rare case of acute haemorrhagic necrotizing encephalopathy (ANE) 2 days after vaccination.

## Case report

A 75-year-old Caucasian female presented to the hospital with an altered level of consciousness and dysarthria. She had received her first dose of the ChAdOx1nCoV-1 vaccine 2 days prior and was also on a course of cefalexin for a presumed urinary tract infection (UTI).

Her past medical history included eosinophilic granulomatosis with polyangiitis (EGPA), hypertension, ischaemic heart disease, hypercholesterolaemia and monoclonal gammopathy of uncertain significance. Her regular medications were hydrochlorothiazide 25 mg daily, amlodipine 5 mg daily and simvastatin 10 mg daily.

Her EGPA had followed an unpredictable disease course since diagnosis 17 years prior, characterized by two significant flares in 2004 and 2016 affecting the lungs and genitourinary system requiring hospitalization. The patient was not known to have central nervous system (CNS) involvement. She had been on oral corticosteroids and azathioprine, but had ceased all immunotherapy 12 months prior to the current presentation.

On admission, she was afebrile with normal cardiovascular parameters. She was dysarthric with no other lateralizing neurological signs. Several hours later, she was witnessed to have two successive generalized tonic clonic seizures lasting 10 and 3 min, respectively. This resulted in a sustained drop in conscious state necessitating endotracheal intubation. She was commenced on broad-spectrum antimicrobial agents as empiric cover for possible infective encephalitis, together with levetiracetam as treatment for seizures. Computed tomography (CT) brain, CT angiogram, CT venogram and CT perfusion imaging were normal. Cerebrospinal fluid (CSF) cell counts were within normal limits with a markedly elevated CSF protein of 2.98 g/L (reference range 0.15–0.45 g/L). Electroencephalogram (EEG) showed diffuse slowing and frequent triphasic waves consistent with widespread cortical dysfunction. Cerebral magnetic resonance imaging (MRI) showed extensive bilateral and symmetrical T2 hyperintense abnormalities in the thalami and medial temporal lobes, along with scattered punctate foci of diffusion restriction and petechial haemorrhage. Repeat scan 4 days later showed progression of disease (Fig. 1). Testing of the patient's serum for SARS CoV-2 antibodies was negative. Extensive testing for other viral, autoimmune and paraneoplastic antibodies was unrevealing.

The clinical presentation and investigations were most consistent with ANE. She was treated with intravenous polyvalent immunoglobulins (2 g/kg over 5 days) and intravenous methylprednisolone 1 g/day for 4 days, followed by nasogastric prednisolone 1 mg/kg for 3 weeks. She made no observable recovery during the period of supportive therapy,

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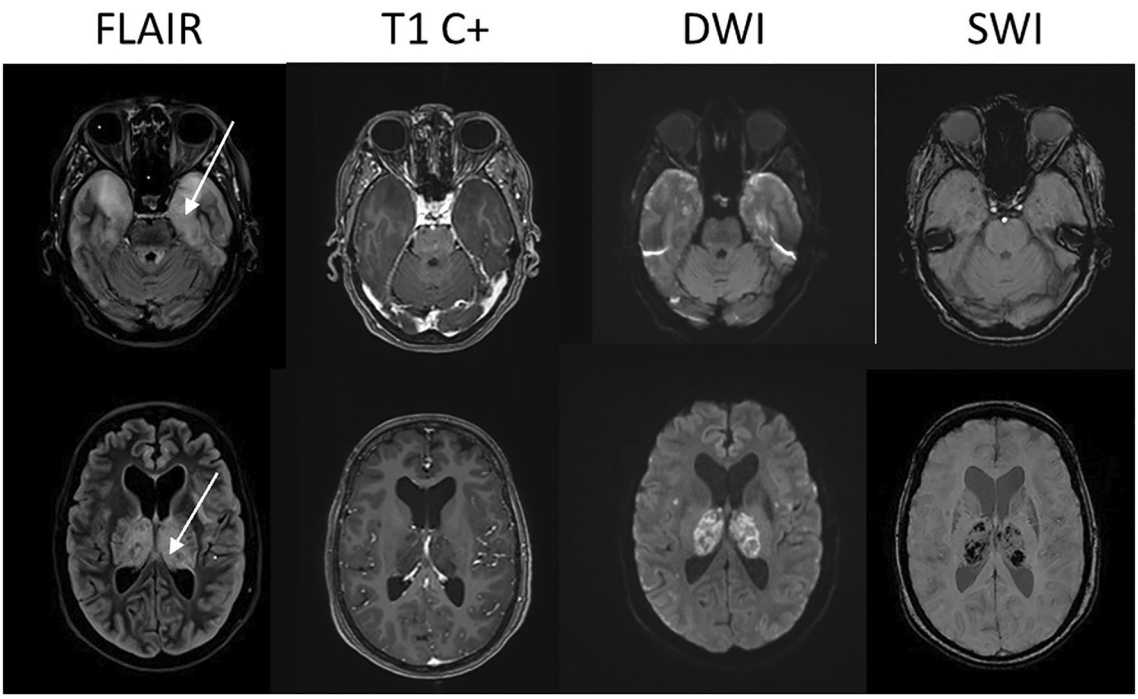


**Fig. 1** **A** Fluid-attenuated inversion recovery (FLAIR) sequence in MRI scan shows confluent hyperintensity within the bilateral thalami and medial temporal lobes (white arrows). **B** Contrast material-enhanced imaging shows irregular enhancement of the external capsules. **C** Diffusion weighted imaging (DWI) shows punctate foci of diffusion restriction. **D** Susceptibility-weighted images (SWI) show evidence of haemorrhage indicated by a hypointense signal

remaining GCS 3. The patient passed away 1 month after illness onset.

## Discussion

ANE is predominantly described in the paediatric population, temporally related to an immunological trigger, commonly viral infections. It presents 12–72 h after the trigger, manifesting with seizures, altered level of consciousness and vomiting.

Cerebral imaging shows symmetrical multifocal lesions with invariable thalamic involvement, often with haemorrhage [1]. In our patient, there was no evidence of a preceding viral infection. However, the onset of illness was temporally related to receiving the ChAdOx1nCoV-1 vaccine, implicating the vaccine as the most likely precipitant for ANE. ANE has been reported as a potential complication of SARS CoV-2 infection [1, 2]. To our knowledge, this is the first reported case of ChAdOx1nCoV-1 vaccine-associated ANE.

The main differential diagnosis of an aggressive recrudescence of systemic vasculitis was considered less likely given the acuity of the presentation, imaging findings and lack of other systemic features of vasculitis. Furthermore, the patient had no prior history of EGPA involving the CNS. Other differentials including infective and autoimmune encephalopathies were excluded based on the clinical picture and extensive investigations.

ANE is thought to occur secondary to intracranial cytokine storm which results in blood–brain barrier breakdown and subsequent immune-mediated insult to brain parenchyma [1, 2]. This is distinct from other more commonly encountered immune-mediated adverse events following vaccination such as Guillain–Barré syndrome and acute disseminated encephalomyelitis, which are believed to be due to molecular mimicry in individuals who are genetically susceptible [3].

While neurological complications after SARS CoV-2 infection are increasingly well understood, there is less information available on the neurological complications after SARS CoV-2 vaccination [4]. In an interim analysis of the ChAdOx1nCoV-1 vaccine in its phase 3 trial of 11,636 participants, only one case of transverse myelitis was considered vaccine related [5].

The rapid development of vaccines has provided hope that the COVID-19 pandemic will be brought under control within several years. However, prompt recognition and reporting of vaccine-associated clinical events by front-line clinicians offers the best hope of minimizing long-term disability for patients whilst also maintaining community trust.

**Author contributions** All authors contributed equally to the design, write-up and editing of this case report and literature review.

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**Availability of data and material** De-identified patient information can be provided on request.

**Code availability** Not applicable.

## Declarations

**Conflict of interest** Katherine Buzzard has received speaker's honoraria and/or educational support from Biogen, Sanofi Genzyme, Merck, Roche, Alexion and Teva and has served on medical advisory boards for Merck and Biogen.

**Ethical approval** Not applicable.

**Consent to participate** Included under supplementary files.

**Consent for publication** Included under supplementary files.

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