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BRIEF COMMUNICATION

Central nervous system adverse events after ChAdOx1 vaccination

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Abstract

Introduction Post-ChAdOx1 vaccine (AZD1222) adverse events following immunization (AEFI) are uncommon. Recently described neurological events include thrombocytopenia with thrombosis syndrome (TTS) with cerebral venous thrombosis and Guillain-Barré syndrome. There are very few AEFI reports following COVID vaccination from India, because of underreporting or other factors. A few cases of acute transverse myelitis (ATM) and post-vaccinal encephalitis have also been reported.

Materials and methods Over 11 months, in 2 districts of Kerala, India, 8.19 million people were vaccinated with the ChAdOx1 vaccine.

Results During this period, we encountered five cases of autoimmune central nervous system (CNS) AEFI following ChAdOX1 (Oxford/AstraZeneca, Covishield™) vaccination. These included three cases of acute disseminated encephalomyelitis (ADEM), one case of opsoclonus myoclonus ataxia syndrome (OMAS), and one case of limbic encephalitis. The calculated crude incidence of post-ChAdOX1 autoimmune CNS AEFI was approximately 0.24 cases per million for encephalitis and 0.36 per million for ADEM. This was compared to the crude annual incidence of community-acquired ADEM worldwide (3.2–4 per million) and the crude annual incidence of community-acquired encephalitis in India (8.35–10 per million).

Conclusion There was no increase in the incidence of post-vaccination CNS AEFI (ADEM or encephalitis) as compared to the community incidence of ADEM or encephalitis. While this emphasizes the safety of ChAdOX1 nCoV-19 vaccination for COVID-19, it is important to recognize these post-vaccination autoimmune syndromes early to initiate immunosuppressive therapy.

Keywords ChAdOX1 nCoV-19 vaccination and encephalitis · Post-vaccination neurological events · ChAdOX1 nCoV-19 vaccination and myelitis

Sir,

Adverse events following immunization (AEFI) with the adenovector viral (AVV) ChAdOx1 vaccine (AZD1222) (AstraZeneca) are rare and include the thrombocytopenia with thrombosis syndrome (TTS) and Guillain-Barré syndrome [1, 2]. Only one series of post-vaccinal encephalitis after ChAdOx1 vaccination has been reported [3].

We report a series of seronegative autoimmune central nervous system (CNS) AEFI following ChAdOx1 (AstraZeneca) vaccination. CSFA acute encephalitis panel, serum paraneoplastic antibodies, serum, and CSF autoimmune encephalitis panel, NMDA and VGKC antibodies (Eurommun AG, immunofluorescence (IFA) assay) were performed in all cases.

Case 1

A 64-year-old man presented with 2 days' history of fever and drowsiness 10 days after the first dose of ChAdOX1 vaccination. MRI brain showed features of limbic encephalitis and middle cerebellar peduncle hyperintensities (Fig. 1,

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panels A and B). CSF showed lymphocytic pleocytosis. Elevated systemic inflammatory markers were noted (ESR, CRP, d-dimer, ferritin). Post-vaccination seronegative limbic encephalitis was considered, and IV methylprednisolone 1 g/day × 5 days and plasmapheresis were initiated. Eight weeks after vaccination, 1 g rituximab was administered, and he was discharged without deficits.

Case 2

A 65-year-old man developed behavioral changes 10 days after the 2nd dose of ChAdOX1 vaccination. Over the next 3 weeks, he developed jerky movements. Examination revealed an opsoclonus myoclonus ataxia syndrome (OMAS). CSF showed mild pleocytosis (TC 10 cells). A diagnosis of post-vaccination OMAS was considered, and he was started on IVIg and IVMP 1 g/day × 5 days, with remarkable improvement.

Case 3

A 64-year-old man started developing ascending paresthesias in the legs which progressed up to an epigastric band-like sensation, leg stiffness, and hand paresthesias. These started 20 days after the 2nd dose of ChAdOX1 vaccine. On examination, he had a brisk jaw jerk, spastic quadriparesis with grade 3/5 power in the upper limbs, grade 0/5 power in the lower limbs, and loss of posterior column sensations till the T6 level. MRI showed multifocal cord hyperintensities and bilateral hemispheric corticospinal tract hyperintensities (Fig. 1, panel C). He improved to grade 4/5 motor strength in the upper and lower limbs after 5 days of IVIg and IVMP. Post-vaccination acute disseminated encephalomyelitis (ADEM) was considered. At 1 month, he was administered rituximab 1 g IV and continued to improve. A repeat MRI at 1 month showed stabilization of the lesions and no new contrast enhancement.

Case 4

A 46-year-old man presented with urinary complaints, progressive lower limb weakness (grade 0/5 MRC score), and numbness 4 days after his first dose of ChAdOX1 vaccination. MRI brain and spine showed extensive supratentorial, infratentorial, and long segment spinal cord hyperintensities (Fig. 1, panel D). Thrombocytopenia and increased LDH were noted (Table 1). He received a 2nd course of IVMP followed by plasma exchange, after which he improved significantly and was able to ambulate independently. Post-vaccination ADEM was considered.

Case 5

A 42-year-old woman started developing severe daily headache and photophobia, 5 days after the 1st dose of ChAdOX1 vaccination. On examination, she had papilledema. The CSF opening pressure was elevated, but other parameters were normal (Table 1). As a contrast MRI showed leptomeningeal enhancement, a seronegative autoimmune meningeal process was suspected and oral steroids were administered for 15 days. She recovered

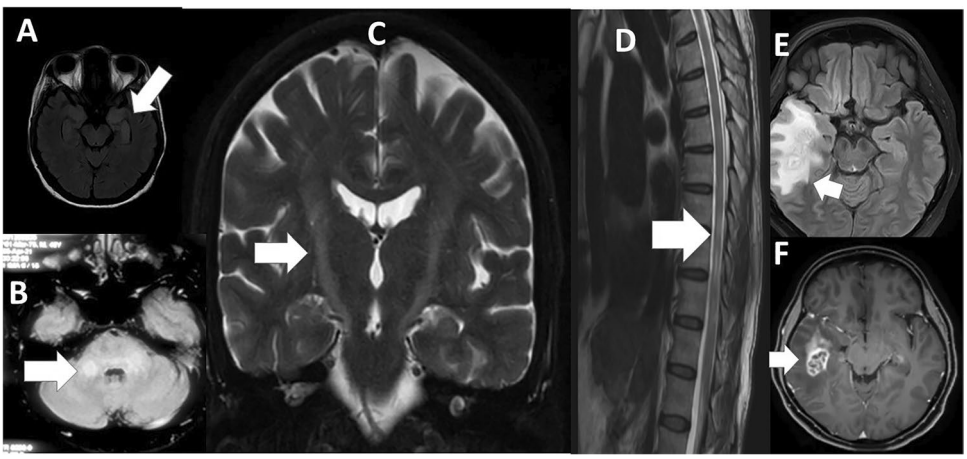

Fig. 1 **A** FLAIR hyperintensities in the mesial temporal lobe. **B** FLAIR hyperintensities in both middle cerebellar peduncles (left > right). **C** T2-weighted MRI hyperintensities extending from the perirolandic cortex along the corona radiata, via the corticospinal tracts. **D** T2-weighted sagittal spine MRI images showing a D9–10 short segment linear hyperintensity. **E**, **F** Axial FLAIR and post-contrast T1-weighted images showing right temporal lobe edema and an irregular contrast enhancing lesion (white arrows)

Table 1 Clinical and laboratory parameters of our cases

Age (yrs), sex	Time to onset after ChAdOx1-vaccination	Clinical signs and symptoms, final Dx	Laboratory parameters (peak)	Imaging	Treatment	Outcome and length of stay, level of diagnostic certainty (Brighton criteria)
1. 64/male	10 days after first dose	Headache, altered sensorium, fever Glomerulonephritis, subsegmental pulmonary embolism Limbic encephalitis	SARS-CoV-2 RT PCR negative Anti-SARS-CoV-2 spike protein IgG antibody positive CSF-25 cells/mm^3 (40 mg/dl) and normal glucose Serum & CSF autoimmune encephalitis/paraneoplastic panel/NMO, MOG/viral encephalitis: negative	CT chest; normal MRI brain: hyperintensities in bilateral medial temporal lobe and head and proximal body of hippocampus (L > R) CT thorax: subsegmental embolism	IV methylprednisolone, plasma exchange, rituximab	Discharged after 2 months, mRS 1 Level 2
2. 65/male	10 days after 2nd dose	Behavioral changes, opsoclonus myoclonus ataxia syndrome (OMAS)	NMDA/VKGC/NMO, MOG/paraneoplastic panel negative CSF: TC 10 cells. Protein 65 mg/dl	MRI brain/spine: normal Whole-body PET/CT normal	IVIg 2 g/kg IVMP 1 g/day × 5 days	mRS 1 Level 2
3. 46/male	5 days after first dose	Fever, urinary complaints Progressive paraparesis Acute disseminated encephalomyelitis (ADEM)	SARS-CoV-2 RT PCR negative Anti-SARS-CoV-2 spike protein IgG antibody CSF63 cells/mm^3 Protein (52 mg/dl), sugar (93 mg/dl) CSF encephalitis panel: negative Serum NMO and MOG: negative ANCA negative	MRI spine: longitudinally extensive transverse myelitis MRI brain: T2, FLAIR hyperintensities in bilateral middle cerebellar peduncle (left > right), pontine tegmentum, right paramedian medulla, and left thalamocapsular region CT thorax/abdomen: normal	IV methylprednisolone, plasma exchange	Recovered, mRS 1 Level 2
4. 64/male	20 days after 2nd dose	Progressive paresthesia of legs, followed by upper limbs, spastic paraparesis ADEM	NMDA/VKGC/NMO, MOG/paraneoplastic panel negative CSF normal	MRI brain and spine: bilateral corticospinal tract hyperintensities Dorsal cord hyperintensity at D8–9 Whole-body PET/CT normal	IVIg 2 g/kg IVMP 1 g/day × 3 days Rituximab 1 g IV	mRS 1 Level 2

Table 1 (continued)

Age (yrs), sex	Time to onset after ChAdOx1-vaccination	Clinical signs and symptoms, final Dx	Laboratory parameters (peak)	Imaging	Treatment	Outcome and length of stay, level of diagnostic certainty (Brighton criteria)
5. 42/female	5 days after 1st dose	Persistent daily headache, papilledema	CSF: opening pressure 32 cm H_2O CSF parameters normal Serum & CSF autoimmune encephalitis/NMO, MOG/viral encephalitis panel: negative Brain biopsy: suggestive of tumefactive demyelination	MRI: initial MRI: leptomeningeal and sulcal enhancement 25 days later: large right temporal irregular enhancing lesion with significant perilesional edema	Decompression of lesion Excisional biopsy Oral prednisolone 40 mg/day × 15 days	mRS 1

MRC Medical Research Council, *TC* total WBC count, *ALC* absolute lymphocyte count, *SIRS* systemic inflammatory response syndrome, *mRS* modified Rankin score

and steroids were stopped. Two days later, her headache recurred. An MRI on day 25 showed a large irregular right temporal lobe enhancing lesion (Fig. 1, panels E and F). Brain biopsy was suggestive of tumefactive demyelination. Her headache remitted spontaneously after the excision biopsy.

We describe seronegative autoimmune CNS AEFI following ChAdOX1 vaccination, which included post-vaccination encephalitis (PVE) and post-vaccination ADEM (PV-ADEM). One of our cases satisfied a level 1 Brighton criterion level 1, and four other cases reached level 2 of diagnostic certainty for post-vaccination AEFI [4].

Our cases occurred within 20 days (range 5–20 days) after vaccination. All patients showed a response to immunosuppressive therapy or spontaneous resolution, and 80% had imaging findings suggestive of inflammatory CNS demyelination. As of November 19, 2021, over 1.15 billion doses of ChAdOx1 had been administered in India [5]. In two districts of Kerala, where our cases were detected, over 9.1 million doses had been administered, of which more than 90% were the ChAdOx1 vaccine (8.19 million).

To understand the impact of these AEFI, the incidence of community-acquired encephalitis (CAE) and community-acquired ADEM (c-ADEM) can be compared with that of PVE and PV-ADEM. The crude annual incidence of CAE in India is 8.35–10 per million, and the worldwide crude annual incidence of c-ADEM is 3.2–4 per million (Indian data is lacking) [6].

Comparatively, the incidence of PVE is estimated at 0.4–0.8 per million doses after ChAdOX1 vaccination and 0.2 per million with the mRNA vaccine (BNT162b2) [3, 7]. Our population showed a calculated crude incidence of PVE of ~ 0.24 cases per million (2 cases per 8.19 million vaccinees), similar to that for mRNA vaccines.

PV-ADEM has not yet been reported; however, our cohort had a calculated crude incidence of 0.36 cases per million (3 cases per 8.19 million vaccinees).

The incidence of post-vaccination CNS AEFI (PVE and PV-ADEM) was 10–20-fold less than the incidence of CAE and c-ADEM. While this emphasizes the safety of ChAdOX1 vaccination, it is important to recognize these syndromes early, to initiate appropriate immunosuppressive therapy. Delayed recognition of these CNS AEFI may lead to a futile search for other etiologies and increased morbidity.

Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

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