Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Neuroimmunology Reports 2 (2022) 100089

Contents lists available at ScienceDirect

Neuroimmunology Reports

journal homepage: www.elsevier.com/locate/nerep

Acute hemorrhagic leukoencephalitis after administration of the first dose of ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine

Imran Rizvi, Ravindra Kumar Garg*, Priyanka Gupta, Hardeep Singh Malhotra, Neeraj Kumar, Ravi Uniyal, Shweta Pandey

Department of Neurology, King George's Medical University, Lucknow 226003, India

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
ChAdOx1 nCoV-19 vaccine
Vaccine

ABSTRACT

Background: Many central and peripheral nervous system complications, following COVID-19 vaccination, have been described. We report an unusual case of central demyelinating disorder, following the administration of the ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine.

Case-report: The 28-year female developed sudden onset headache followed by weakness of the left upper and lower limbs, and gait ataxia. Neurological symptoms developed two weeks after administration of the first dose of the ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine. Magnetic resonance imaging brain revealed T2/FLAIR hyperintense lesions involving bilateral subcortical white matter, splenium of the corpus callosum, and both cerebellar hemispheres. Few lesions showed blooming on gradient echo sequence suggestive of a hemorrhagic component. Post-contrast T1 images showed mild enhancement of demyelinating lesions. The patient was treated intravenously with methylprednisolone. After 12 weeks of follow-up, there was a substantial improvement in her symptoms. She became independent in all her activities of daily living.

Conclusion: In conclusion, this is an unusual case of acute hemorrhagic leukoencephalitis following ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccination.

Introduction

The global drive for vaccination against coronavirus disease 2019 (COVID-19) is going on at a rapid pace. In India, the vaccination drive is progressing well; as per WHO data, as of 29 November 2021 a total of 1240,157,719 vaccine doses have been administered. Currently, in India, three vaccines, Oxford University – AstraZeneca's Covishield vaccine (Serum Institute of India), Covaxin (Bharat Biotech), and Russian Sputnik V vaccine are available for administration. In the majority, ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine has been administered. Out of the total 1.3 billion COVID-19 vaccines doses administered, over 1.1 billion vaccine doses were of ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine (Statista Research Department, 2021; World Health Organization, 2021). COVISHIELD^{TM} (ChAdOx1 nCoV-19 SARS-CoV-2) vaccine is a chimpanzee adenovirus-based vaccine, developed by Oxford University and AstraZeneca, and manufactured in India by Serum Institute of India.

A wide range of severe neurological complications following COVID-19 vaccination has been reported. These complications include cerebral venous sinus thrombosis, Bell's palsy, acute transverse myelitis, acute disseminated encephalomyelitis, and acute demyelinating polyneuropathy (Garg and Paliwal, 2022). Reactivation of herpes zoster in many persons, following administration of mRNA vaccines, has also been recorded (Wan et al., 2022).

We report an unusual case, who developed an acute demyelinating disorder of the brain after receiving the first dose of ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine.

Case report

A 28-year female received her first dose of ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine on 3rd July 2021. She noticed mild local pain after intramuscular administration. Local reaction subsided on its own in 2–3 days. On 17th July 2021, she developed sudden onset severe holocranial headache, followed by weakness of the left upper and lower limbs. She noticed difficulty in gripping objects and doing fine movements with her left hand. She also had slippage of footwear from the left foot and she needed assistance for all her daily activities. The weakness was static for the next 3 days, and then the patient noticed an imbalance while walking. On examination, her general examination was normal. She was fully conscious and oriented. All her cranial nerves, including optic nerves, were normal. Power in the left upper and left lower limb by the Medical Research Council scale was 4/5; power on

* Corresponding author.
E-mail address: rkgarg@kgmcindia.edu (R.K. Garg).

https://doi.org/10.1016/j.nerep.2022.100089
Received 9 December 2021; Received in revised form 6 March 2022; Accepted 26 March 2022

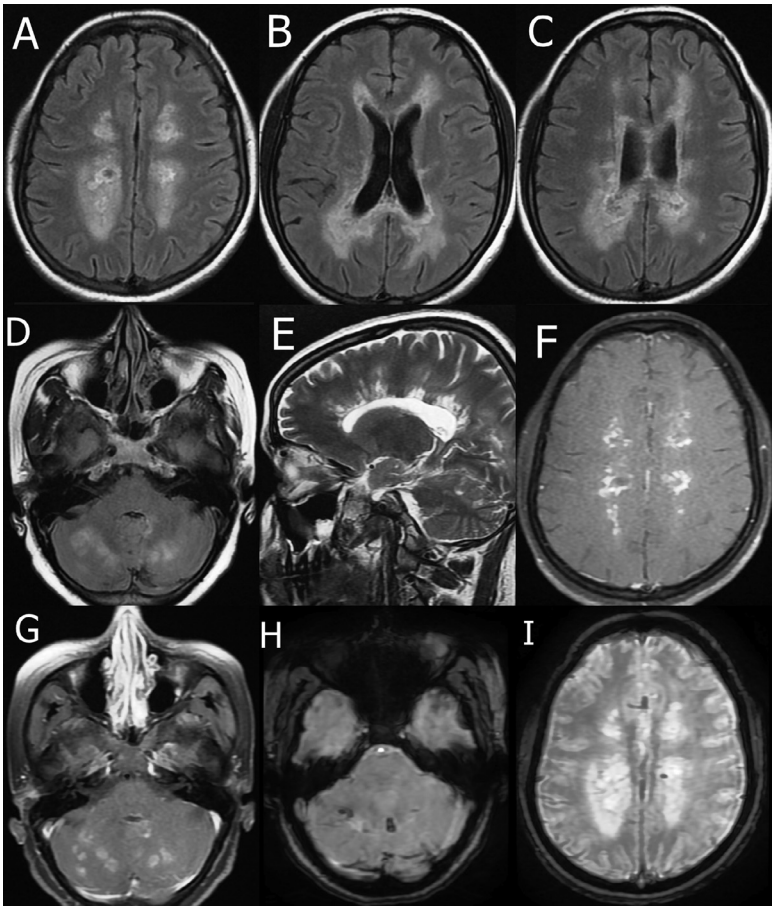

Fig. 1. MRI brain FLAIR sequence (A–D), showing hyper-intensities involving bilateral white matter (A), splenium of corpus callosum (B), periventricular white matter (C) and cerebellum (D). T2 sagittal image (E) showing hyper-intensities involving the periventricular white matter. Post contrast T1 images (F and G) showing contrast enhancement of lesions. GRE images (H and I) showing blooming in cerebellar lesions and periventricular lesions on left side.

the right side was 5/5. The Finger-nose test and the heel-shin test were bilaterally impaired. Tandem walking was not possible. Deep tendon reflexes on the left side were exaggerated. The plantar response on the left side was extensor.

Magnetic resonance imaging (MRI) of the brain demonstrated extensive T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities, involving bilateral subcortical white matter, splenium of the corpus callosum and cerebellar hemispheres. Few demyelinating lesions showed blooming on gradient echo sequence. After contrast administration, enhancement was seen in some lesions. (Fig. 1) Spinal MRI was normal. Cerebrospinal fluid (CSF) examination showed slightly increased protein level (68 mg/dl) with normal glucose level (46 mg/dl) and cell counts (<5 cells/mm^3). CSF virology, gram stain and culture did not reveal any abnormality. Anti-myelin oligodendrocyte glycoprotein and anti-aquaporin-4 antibodies in serum were absent.

MRI findings were consistent with the diagnosis of acute hemorrhagic leukoencephalitis (AHLE). The patient was treated with intravenous methylprednisolone (1000mg daily for 5 days). Following treatment, there was a significant improvement. At 12 weeks of follow-up, she was independent for all her activities of daily living.

Discussion

Acute disseminated encephalomyelitis (ADEM) is an inflammatory disease of the central nervous system that is characterized by widespread demyelination of the white matter of the brain and spinal cord. Classically, ADEM is generally incited by an infection or vaccination. ADEM is usually a monophasic illness, rarely patients can develop recurrent attacks (Bennetto and Scolding, 2004). AHLE is a rarer variant of ADEM, which is characterized by a hyper-acute course and evidence of micro or macro hemorrhages on brain imaging or brain pathology (Manzano et al., 2021; Kuperan et al., 2003). Diagnosis in our patient was consistent with AHLE as she had a very rapid course of illness. She had an episode of acute headache followed by rapidly evolving hemiparesis with gait and appendicular ataxia. Neuroimaging demonstrated white matter T2/FLAIR hyperintensities along with petechial hemorrhages within the demyelinating lesions.

Manzano et al. (2021) have systematically reviewed 46 cases of ADEM/ AHLE in patients with COVID-19 infection. ADEM was recorded in 31 patients and AHLE was diagnosed in 15 patients. Manzano et al. (2021) noted several differences between ADEM and AHLE following COVID-19 infection and ADEM and AHLE without a history of preceding COVID-19. Manzano et al. (2021) noted that the majority of reported cases of ADEM and AHLE following COVID-19 infection were adults. In the majority preceding COVID-19 infection was severe. On neuroimaging hemorrhagic changes within the demyelinating lesions were common. The outcome despite adequate immunotherapy was poor.

Many reports of CNS demyelination following COVID-19 vaccination are also now available. Ismail and Salama reviewed 32 cases of CNS demyelination following COVID-19 vaccination. ADEM was recorded in 5 patients with the age of affected patients ranging from 24 to 56 years. Common presenting clinical features were seizures, confusion, and headache. Anti-myelin oligodendrocyte glycoprotein and anti-aquaporin-4 antibodies could not be demonstrated in any of the patients. Demyelinating lesions of the spinal cord were noted only in one patient. Following immunotherapy, the prognosis is good and remarkable improvements were noted in all the patients. In two patients each, ADEM followed inactivated viral vaccine and mRNA-based vaccine. In one patient ADEM followed a viral-based vaccine (Kuperan et al., 2003). In our patient, the presenting features were focal neurological deficit with gait and appendicular ataxia (Ismail and Salama, 2022).

After an extensive search, we could find only two reports describing four patients with post-vaccinal CNS demyelination demonstrating hemorrhagic transformation of some lesions. Our patient had hemorrhagic demyelinating lesions of the brain. Permezel described a 63-year-old man, who 12 days after the first dose of the Oxford/AstraZeneca COVID-19 vaccine developed progressively deteriorating impaired consciousness. MRI revealed T2 and FLAIR hyperintensities in the periventricular and juxta-cortical regions of the cerebral white matter. The patient despite plasmapheresis died. postmortem histological examination of the brain and spinal cord revealed multiple areas of white matter demyelination along with hemorrhagic necrosis (Permezel et al., 2021). Ancau and colleagues described three patients of AHLE developing nine days after ChAdOx1 nCoV-19, COVID-19 vaccination. All these patients were promptly treated with intravenous methylprednisolone and plasma exchange. One patient succumbed to her illness and one of two surviving patients became vegetative. The third patient showed marginal improvement in sensory manifestations, however, paraparesis persisted even after six weeks of follow-up (Ancau et al., 2022).

We also reviewed the safety and efficacy data of the ChAdOx1 nCoV-19 vaccine. Voysey and colleagues analyzed a data set of four randomized controlled trials. In this analysis, a case of transverse myelitis was observed, occurring 14 days after ChAdOx1 nCoV-19 booster vaccination. In this particular case, an idiopathic, short segment, spinal cord demyelination was observed and a panel of experts ascribed this even to vaccine administration. There were two additional cases of post-vaccination transverse myelitis, 10 days and 68 days after the first dose. An independent panel of neurological experts considered them unrelated to the administration of the ChAdOx1 nCoV-19 COVID-19 vaccine. No case of post-vaccination ADEM or AHLE was recorded (Voysey et al., 2021). There are no data on the safety of administering the subsequent dose of ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccine to a person, who develops AHLE/ADEM following the first dose of the vaccine.

The phenomenon of molecular mimicry seems to be the most plausible pathogenetic mechanism responsible for COVID-19 vaccine-associated ADEM and AHLE. It has been hypothesized that antibodies generated against SARS-CoV-2 spike glycoprotein cross-react with antigens present on neuronal cells. Cross-reactivity between vaccine antigen and neuronal cells results in T and B-cell activation. The antigen presentation possibly initiates an immune-inflammatory reaction which in turn damages brain tissues (Chen et al., 27; Kanduc and Shoenfeld, 2020).

In conclusion, this is an unusual case of acute hemorrhagic leukoencephalitis following ChAdOx1 nCoV-19 SARS-CoV-2 (COVISHIELD^{TM}) vaccination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nerep.2022.100089.

References

Ancau, M., Liesche-Starnecker, F., Niederschweiberer, J., Krieg, S.M., Zimmer, C., Lingg, C., et al., 2022. Case series: acute hemorrhagic encephalomyelitis after SARS–CoV-2 vaccination. Front. Neurol. 12, 820049.

Bennetto, L., Scolding, N., 2004. Inflammatory/post-infectious encephalomyelitis. J. Neurol. Neurosurg. Psychiatry 75 (Suppl 1), i22–i28.

Chen, Y., Xu, Z., Wang, P., Li, X.M., Shuai, Z.W., Ye, D.Q., Pan, H.F., 2021. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology doi:10.1111/imm.13443, Dec 27Epub ahead of print.

Garg, R.K., Paliwal, V.K., 2022. Spectrum of neurological complications following COVID-19 vaccination. Neurol. Sci. 43, 3–40.

Ismail, I.I., Salama, S., 2022. A systematic review of cases of CNS demyelination following COVID-19 vaccination. J. Neuroimmunol. 362, 577765.

Kanduc, D., Shoenfeld, Y., 2020. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunol. Res. 68 (5), 310–313.

Kuperan, S., Ostrow, P., Landi, M.K., Bakshi, R., 2003. Acute hemorrhagic leukoencephalitis vs ADEM: FLAIR MRI and neuropathology findings. Neurology 60, 721–722.

Manzano, G.S., McEntire, C.R.S., Martinez-Lage, M., Mateen, F.J., Hutto, S.K., 2021. Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis following COVID-19: systematic review and meta-synthesis. Neurol. Neuroimmunol. Neuroinflamm. 8, e1080.

Permezel, F., Borojevic, B., Lau, S., de Boer, H.H., 2021. Acute disseminated encephalomyelitis (ADEM) following recent Oxford/AstraZeneca COVID-19 vaccination. Forensic Sci. Med. Pathol. 1–6. doi:10.1007/s12024-021-00440-7, Epub ahead of print.

Statista Research Department, 2021. Number of COVID-19 vaccine doses administered in India as of December 6, 2021, by type. Downloaded from https://www.statista.com/statistics/1248301/india-covid-19-vaccines-administered-by-vaccine-type/. Accessed on 08 December 2021.

Voysey, M., Clemens, S.A.C., Madhi, S.A., Weckx, L.Y., Folegatti, P.M., Aley, P.K., et al., 2021. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS–CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397, 99–111.

Wan, E.Y.F., Chui, C.S.L., Wang, Y., Ng, V.W.S., Yan, V.K.C., Lai, F.T.T., Li, X., et al., 2022. Herpes zoster related hospitalization after inactivated (CoronaVac) and mRNA (BNT162b2) SARS-CoV-2 vaccination: a self-controlled case series and nested case–control study. Lancet Reg. Health West. Pac. 21, 100393.

World Health Organization, 2021. WHO Coronavirus (COVID-19) Dashboard. The World Health Organization.