Acta Neurologica Belgica (2024) 124:193–203
https://doi.org/10.1007/s13760-023-02373-0

ORIGINAL ARTICLE

Spectrum of various CNS inflammatory demyelination diseases following COVID-19 vaccinations

Manish Salunkhe[1] · Kamlesh Tayade[1] · Megha Priyadarshi[2] · Vinay Goel[3] · Isha Gulati[1] · Ajay Garg[3] · Rohit Bhatia[1] · M. V. Padma Srivastava[1]

Received: 15 January 2023 / Accepted: 21 August 2023 / Published online: 5 September 2023

Abstract

Background and purpose Although rare, neurological adverse events have been reported post-COVID-19 vaccination. This study reports 16 patients diagnosed with CNS inflammatory demyelinating diseases (CNS-IDD) within 6 weeks of COVID-19 vaccine administration.

Methodology A prospective observational study was conducted from June 2021 to May 2022. All patients were diagnosed according to the latest international guidelines with CNS-IDD within 6 weeks of COVID-19 vaccine exposure. Data regarding the demographic profile, clinical features, type of COVID-19 vaccination, radiological findings and occurrence of symptoms were noted and further analysed using descriptive statistics.

Results We reported 16 cases (median age 40 years) of CNS demyelination: fourteen occurred in temporal association with ChAdOx1-S vaccine and two in association with BBV152 vaccine. Median time duration of presenting symptoms after vaccination was 19 days (3–40 days). The most common presentation was myelitis (7/16 patients), followed by optic neuritis (6/16 patients). Demyelination events were reported after first and second dose in thirteen and five patients respectively, although two patients reported such events after both vaccine dosages. Myelin oligodendrocyte glycoprotein (MOG) IgG antibodies were positive in eight patients. Tumefactive demyelination was seen in four patients. Management included high-dose methylprednisolone, PLEX, IVIG or a combination of those, with a favourable outcome in the majority of cases.

Conclusion Although a rare event, awareness regarding potential demyelinating episodes post-COVID-19 vaccination can help in early diagnosis. The presence of increased MOG-IgG antibodies with temporal association in post-COVID vaccine patients raises a possibility of an immunogenic phenomenon leading to demyelinating disorders.

Keywords COVID-19 vaccine · ChAdOx1 nCoV-19 · CNS inflammatory demyelinating diseases · Myelin oligodendrocyte glycoprotein

✉ Rohit Bhatia
rohitbhatia71@yahoo.com

Manish Salunkhe
manishsalunkhe132@gmail.com

Kamlesh Tayade
drkamlesh21@gmail.com

Megha Priyadarshi
mpvision96@gmail.com

Vinay Goel
vinaygoel28@gmail.com

Isha Gulati
ishagulati4@gmail.com

Ajay Garg
drajaygarg@gmail.com

M. V. Padma Srivastava
vasanthapadma123@gmail.com

[1] Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

[2] Department of Infectious Diseases, All India Institute of Medical Sciences, New Delhi, India

[3] Department of Neuroradiology, All India Institute of Medical Sciences, New Delhi, India

Introduction

In December 2019, the world witnessed an emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2). As per the latest World Health Organization report, there were 611,421,786 confirmed cases on September 24, 2022, along with 6,512,438 deaths [1]. Apart from mortality, this pandemic had a devastating impact on the economy and social life globally.

The world's scientific community responded unprecedently and rapidly to this pandemic, by developing novel COVID-19 vaccines. Multiple randomized controlled trials observed that vaccines were the most effective tool to reduce mortality and morbidity during this pandemic [2–4]. There are four types of vaccines against COVID-19: nucleic acid (mRNA, DNA), protein-based (virus-like particle) vaccines, viral vector (replicating, non-replicating) and whole-virus (live attenuated, inactivated) vaccines [5]. Indian data as on September 24, 2022, reveal that a total of 1,02,61,06,833 of the Indian population have received at least the first dose, while 94,74,14,286 have completed the vaccination schedule of 2 doses and 20,08,20,471 have taken booster dose [6]. COVID-19 vaccines approved by the government of India are ChAdOx1-S (Recombinant, non-replicating adenovirus vector encoding the SARS-CoV-2 Spike glycoprotein) (Covishield/Vaxzervria, AstraZeneca), BBV152 (whole-virus inactivated) (Covaxin), Gam-COVID-Vac (recombinant replication-deficient adenovirus-based vaccine) (Sputnik V), RBD protein subunit COVID-19 vaccine (Corbevax) and SARS-CoV-2 rS (Recombinant spike protein nanoparticle vaccine) (Covovax) [6].

Neurological adverse events after immunization (AEFI) like cerebral venous sinus thrombosis, Bell's palsy and Guillain–Barré syndrome (GBS) have been reported in clinical trials and real-world settings post-COVID-19 vaccination [2, 7, 8]. Central nervous system inflammatory demyelinating diseases (CNS-IDD) were also reported in clinical trials. Two cases of transverse myelitis in the vaccine group were reported in the phase III trial ChAdOx1 vaccine [2]. However, prospective studies of CNS-IDD after COVID-19 vaccines are still lacking. We collected data from patients with CNS-IDD, suggestive of temporal associations with COVID-19 vaccination. We report 16 patients with different neurological manifestations of CNS-IDD within 6 weeks of COVID-19 vaccination.

Methodology

All patients were recruited prospectively at a tertiary care hospital in North India from June 2021 to May 2022. The following inclusion criteria were used: (1) evidence of CNS demyelination proved by clinical examination and radiological findings on magnetic resonance imaging (MRI); (2) recipient of COVID-19 vaccine, either first or second dose, within the past 6 weeks from the onset of symptoms; (3) no evidence of COVID-19 infection within the past 12 weeks from the onset of symptoms; and (4) no evidence of CNS demyelination within 12 months of the first attack. The aim of this study is to describe the characteristics of individuals who experience their first demyelinating episode post-COVID vaccination. We excluded patients diagnosed with CNS demyelination before receiving their first dose of vaccination. Patients were diagnosed as having MS according to the 2017 McDonald criteria, NMOSD was diagnosed according to the 2015 International Panel for NMO Diagnosis (IPND) criteria, and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) was diagnosed according to the recent international MOGAD panel criteria [9–11]. ADEM was diagnosed by the International Paediatric Multiple Sclerosis Study Group criteria for paediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2013 definitions [12]. Patients were diagnosed to have tumefactive demyelination if they had a lesion on the FLAIR sequence measuring > 2 cm [13].

Patients fulfilling inclusion criteria were studied for demographic profile, clinical features, type of COVID-19 vaccine exposure, duration between COVID-19 vaccination and symptom onset, investigations including cerebrospinal fluid (CSF) analysis, serum Aquaporin 4 IgG (AQP 4) antibodies, myelin oligodendrocyte glycoprotein (MOG) IgG antibodies, MRI of the brain and/or spine, and ancillary investigations to exclude alternative aetiologies: serum antinuclear antibodies (ANA) profile, C-reactive protein (CRP) antineutrophil cytoplasmic antibodies (ANCA), paraneoplastic antibodies and autoimmune encephalitis antibodies.

The institutional ethics committee approved this study, and written consent was taken from all participants.

Statistical analysis

Data were expressed as descriptive statistics, such as mean ± SD or median with the range for continuous variables and frequency, and percentage for categorical variables.

Table 1 Demographic and Laboratory details

Age (range)	40 years (16–66)
Female/male (%)	8/8 (50/50)
ChAdOx1 nCoV-19 vaccine (%)	14/16 (87.5)
BBV152 vaccine (%)	2/16 (12.5)
New onset central demyelinating disease	16/16
Disease onset after first dose (%)	13/16 (81.2)
Disease onset after second dose (%)	5/16 (31.2)
Median time duration of symptoms onset after vaccination (range)	18 days (3–40 days)
CSF study performed (%)	12/16 (75)
Median CSF cell count (range)	13 (0–200)
Raised CSF protein (> 45 mg/dl)	10/12 (83.33)
Median CSF protein levels (range)	66 mg/dl (28–468 mg/dl)
CSF OCB (%)	2/12 (16.66)
Serum MOG antibody positive (%)	8/16 (50)

CSF cerebral spinal fluid, *OCB* oligoclonal bands, *MOG* myelin oligodendrocyte glycoprotein

Results

We analysed a cohort of 16 patients (8 female and 8 male) who received COVID-19 vaccination and developed central demyelination. The majority of the patients were young with a median age was 40 years (range 16–66) (Table 1). All sixteen patients had new onset demyelination (Table 1). Clinically, the most common presentation was myelitis (7/16) or optic neuritis (6/16) (Table 2, Fig. 1). Three patients presented with hemiparesis and three patients presented with altered sensorium. One patient presented with signs of raised intracranial tension (Table 2).

In the present cohort, patients received ChAdOx1 nCoV-19 (14 patients) or BBV152 (2 patients). After the first dose of vaccination, 13/16 patients developed demyelinating event and 5/16 patients developed demyelinating events after the second dose of vaccine (Table 2). Two patients developed demyelinating events after both doses of vaccines. Median time duration of presenting symptoms after vaccination was 18 days (range 3–40 days) (Table 1).

MOG-IgG antibody was the most common antibody (8/16) detected in our cohort. One patient tested positive for ANA antibody (Table 2). None of the patients tested positive for AQP4 antibody, ANCA antibody, paraneoplastic or autoimmune encephalitis antibodies. We performed CSF studies on twelve patients. Median CSF white cell counts were 13 cells/µl (range 0–200 cells/µl). Oligoclonal bands (OCB) in CSF were detected in two patients. Ten patients (62.5%) had elevated CSF protein (> 45 mg/dl). Median CSF protein levels were 66 mg/dl (28–468 mg/dl) (Table 1).

Four patients had LETM on MRI (Fig. 1). Two patients had radiological findings consistent with multiple sclerosis. Tumefactive demyelinating lesions (TDL) were present in four patients (25%) (Fig. 2).

In the present cohort, two patients were diagnosed with RRMS (Fig. 3), eight patients were diagnosed with MOG antibody-associated disease (MOGAD), three patients were diagnosed as seronegative TDL, one patient had seronegative cortical encephalitis and one patient had seronegative multifocal central demyelination (Table 2).

All patients received injectable methylprednisolone and oral steroids during the acute event. Five patients received plasma exchange therapy due to inadequate response to steroids. Eight patients were started on azathioprine, three patients received rituximab, one patient received an injection of cyclophosphamide and one patient was started on mycophenolate mofetil (MMF) to prevent further disability. Two patients were not kept on any long-term immunomodulators. As none of the patient in our study relapsed till last follow-up, no patient was checked for positivity of MOG antibody (Table 3).

Discussion

Since the eighteenth century, vaccines have proved to be an effective solution in the prevention of infectious diseases. Rarely, however, vaccines may induce an unexpected inflammatory reaction by breaking the mechanism of self-tolerance, or the production of autoantibodies, causing evident autoimmune diseases [14].

A previous systematic literature review reported 71 cases of post-vaccination central demyelination. Influenza and human papillomavirus vaccines were the most common cause of central demyelination [14]. Neurological adverse events after COVID-19 vaccination are monitored by various regulatory authorities. Two cases of transverse myelitis were reported in the vaccine group in the phase III trial of the ChAdOx1 vaccine [2]. Vaccine adverse event reporting system (VAERS) has reported transverse myelitis and ADEM post-COVID-19 vaccine [15].

Myelitis was the most common presentation in our study. In the systematic review of 32 patients of CNS-IDD, transverse myelitis was most commonly reported following COVID-19 vaccinations [16]. In a study from southern India, transverse myelitis and optic neuritis were the most common presentations associated with ChAdOx1 vaccine [17]. In a recent systematic review, 17/32 cases were

Table 2 Examination and radiological findings of all patients

Cases	Age/gender	Duration between the dose and first neurological symptom	Type of vaccine/dosing	Examination finding	CSF findings	Serum antibody	Radiological findings
Case 1	53/M	15 days	ChAdOx1 nCoV-19/First dose	UMN Paraplegia and UMN bladder	Cells: 0 cells P: 72 mg/dl S: 133 mg/dl	MOG-IgG	Long segment intramedullary central (grey matter) T2 hyperintensity is noted in spinal cord from D1–D10 vertebral level
Case 2	66/F	22 days	ChAdOx1 nCoV-19/First dose	Signs of raised intracranial pressure—papilledema, lateral rectus palsy, headache, vomiting	Cells: 5 cells P: 50 mg/dl S: 133 mg/dl	None	Well-defined FLAIR hyperintense mass lesion involving subcortical, deep and periventricular white matter of left parietal and occipital lobe extending into splenium of corpus callosum on left side. Incomplete rim enhancement on post-contrast scan. Suggestive of tumefactive demyelination
Case 3	56/f	12 days	ChAdOx1 nCoV-19/First dose	Altered sensorium and right hemiparesis	Cells: 0 cells P: 50 mg/dl S: 133 mg/dl	None	B/L asymmetrical T2/FLAIR white matter hyperintensities are seen involving the Left fronto-parietal and temporo-occipital regions and right temporal and parieto-occipital regions with minimal mass effect, foci of blooming, patchy diffusion restriction and decreased NAA peak on MRS. Features s/o Tumefactive demyelination
Case 4	41/M	27 days	BBV152/second dose	Right upper limb weakness, slurring of speech	Cells: 0 cells P: 88 mg/dl S: 80 mg/dl	None	Multifocal variable sized FLAIR hyperintense lesions involving periventricular and subcortical white matter of bilateral cerebral hemisphere. On SWI multiple punctate and linear blooming foci were seen in subcortical white matter of bilateral cerebral hemisphere. Post-contrast studies showed multiple punctate, nodular and linear enhancing lesions in cerebral hemispheres

Table 2 (continued)

Cases	Age/gender	Duration between the dose and first neurological symptom	Type of vaccine/dosing	Examination finding	CSF findings	Serum antibody	Radiological findings
Case 5	34/F	19 days	ChAdOx1 nCoV-19/First dose	B/L progressive, painless subacute vision loss	Cells: 0 cells P: 51 mg/dl S: 71 mg/dl	MOG-IgG	Optic nerves Right > left intraneural hyperintensities
Case 6	58/M	9 Days	ChAdOx1 nCoV-19/First dose	UMN paraparesis and Bladder, decreased vision in right eye	NA	MOG-IgG	Long segment extensive myelitis in thoracic segment
Case 7	31/F	12 days and 30 days	ChAdOx1 nCoV-19/First dose and second dose	Tingling sensation and numbness in right upper limb (First Episode) Decreased vision in left eye (Second episode)	NA	None	MRI shows multiple FLAIR hyperintense lesions oriented perpendicular to the periventricular origin and involving calloso-septal interface. FLAIR hyperintensity is also seen along left optic nerve
Case 8	34/F	30 days	ChAdOx1 nCoV-19/Second dose	Decreased vision in right eye	None	MOG-IgG	Long segment FLAIR hyperintensity is seen involving intra-orbital and pre-chiasmatic segment of right optic nerve–optic neuritis
Case 9	21/F	20 days	ChAdOx1 nCoV-19/First dose	Signs of raised intracranial pressure—headache, vomiting and altered sensorium	Cells: 20 cells P: 114 mg/dl S: 137 mg/dl	None	FLAIR cortical hyperintensity in b/l frontal region
Case 10	45/M	20 days	ChAdOx1 nCoV-19/Second dose	Subacute progressive right hemiparesis	Cells: 5 cells P: 45 mg/dl S: 78 mg/dl	MOG-IgG, ANA	Well-defined confluent T2/FLAIR hyperintense and T1 hypointense lesion is seen in periventricular, deep and subcortical white matter of posterior part of left superior and middle frontal gyri, left precentral and post-central gyri with minimal mass effect and subtle diffusion restriction suggestive of tumefactive demyelination

Table 2 (continued)

Cases	Age/gender	Duration between the dose and first neurological symptom	Type of vaccine/dosing	Examination finding	CSF findings	Serum antibody	Radiological findings
Case 11	32/F	33 days	ChAdOx1 nCoV-19/First dose	Pins and needles like sensation in right lower limb and weakness in right lower limb	Cells: 130 cells P: 28 mg/dl S: 58 mg/dl	None	Multiple, eccentric, variably located T2 hyperintensities in cervical and lower dorsal spinal cord, with one showing contrast enhancement at C2-C3 segment. T2-FLAIR hyperintensities within in calloso-septal interface, centrum semiovale, subcortical white matter of bilateral frontal region, periventricular white matter of left anterior frontal region
Case 12	16/M	5 days and 3 days	BBV152/First and second dose	Sensory paraesthesia, urinary hesitancy and blurred vision in right eye	NA	MOG-IgG	FLAIR hyperintensity along intra-orbital segment of left optic nerve and multiple patchy eccentric T2 hyperintense lesions in cervical and thoracic cord
Case 13	54/M	17 days	ChAdOx1 nCoV-19/First dose	Decreased vision in both eyes (right > left)	Cells: 25 cells P: 59 mg/dl S: 155 mg/dl	MOG-IgG	Right eye optic peri-neuritis
Case 14	21/M	40 days	ChAdOx1 nCoV-19/First dose	Headache, altered sensorium. Paraplegia and urinary retention	Cells: 200 cells P: 468 mg/dl S: 48 mg/dl	MOG-IgG	Long segment extensive myelitis, extending from D3 to conus medullaris
Case 15	45/M	10 days	ChAdOx1 nCoV-19/First dose	Progressive subacute right hemiparesis	Cells: 178 cells P: 120 mg/dl S: 66 mg/dl	None	Well-defined multiple T2/FLAIR hyperintense lesions with relatively little mass effect and surrounding vasogenic oedema, disproportionate to the size of lesions in right frontal lobe and left occipito-parietal lobe. Suggestive of tumefactive demyelination
Case 16	39/M	24 days	ChAdOx1 nCoV-19/First dose	UMN quadriparesis and UMN bladder	Cells: 165 cells P: 160 mg/dl S: 53 mg/dl	None	Long segment extensive myelitis, extending from cervico-medullary junction to C5 segment and D4 segment to conus medullaris

FLAIR fluid-attenuated inversion recovery, *MRI* magnetic resonance imaging, *MRS* magnetic resonance spectroscopy, *NAA* N-acetylaspartate, *UMN* upper motor neuron, *CSF* cerebrospinal fluid, *P* protein, *S* sugar

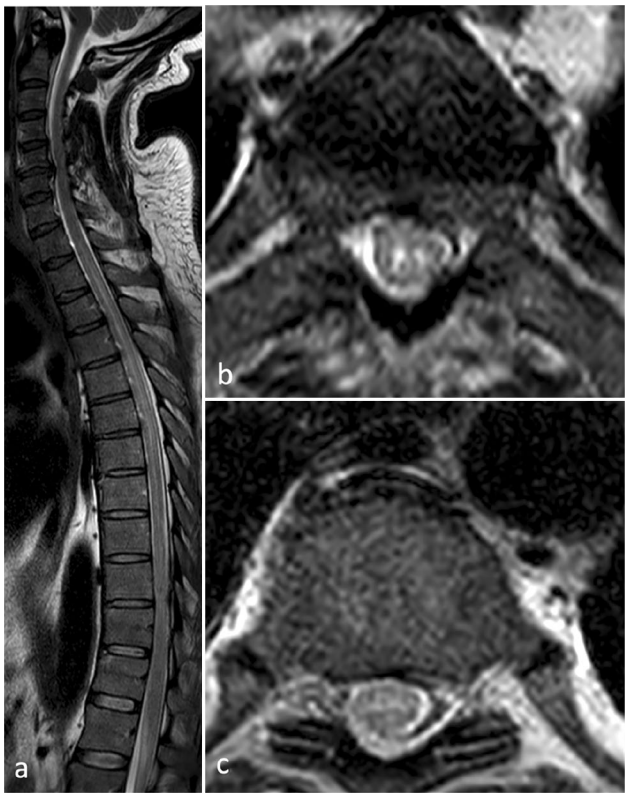

Fig. 1 MRI spine (**a**–**c**) shows long segment intramedullary central (grey matter) T2 hyperintensity is noted in spinal cord from D1–D10 vertebra level with mild cord expansion s/o longitudinally extensive transverse myelitis

reported after mRNA vaccination and 10/32 were reported after viral vector vaccines [16]. mRNA-based vaccines were the most common culprit in South Korea [18]. Female preponderance is usually seen in CNS-IDD, but in this cohort, we found equal cases in both gender.

The most common antibody detected in our cohort of post-vaccinal CNS-IDD was the MOG IgG antibody. Around 20% of cases of MOGAD are associated with infectious agents or vaccines [19]. Post-vaccine MOGAD has been explained with measles–rubella, Japanese encephalitis, diphtheria, pertussis and tetanus (DPT), influenza and polio vaccines [19, 20]. In a systematic review of post-COVID-19 vaccine MOGAD, 18/20 (90%) patients received the ChAdOx1 vaccine [21]. In our series, 7/8 MOGAD patients received the ChAdOx1 vaccine. None of the patients were evaluated for MOG IgG antibody in the follow-up. Previous studies suggest that MOGAD after COVID-19 vaccination is primarily a monophasic illness with a lack of persistent positive MOG antibody [17].

We reported two RRMS patients in our cohort. Apart from yellow fever vaccines, previous studies did not support the association between vaccination and multiple sclerosis relapses. However, relapses and new onset RRMS diagnosis have been observed previously [22]. In both case series, all patients had received mRNA COVID-19 vaccination [23]. Both RRMS patients received the ChAdOx1 vaccine.

The mechanism of CNS-IDD after COVID-19 vaccination is not clearly understood. Susceptibility of patients for autoimmune diseases, vaccine antigens and immune adjuvants used in the vaccine to enhance immune responses are the few factors speculated to have a role in the post-vaccination CNS-IDD [16]. Similarities between viral protein used in vaccine and self-antigens (i.e. myelin, oligodendrocyte specific protein) can trigger immune response (molecular mimicry) [24]. This inflammatory response caused by molecular mimicry can further increased by mechanisms like bystander activation and epitope spreading [25]. Bystander activation involves the activation of costimulatory pathways and cytokine release. In epitope spreading, antigen-specific immune response leads to tissue destruction. This releases endogenous epitopes, causing cytokine release and tissue damage [16]. Vaccine-related factors like type, route of administration and dose could possibly trigger of demyelination [24]. The occurrence of asymptomatic lesions and subclinical involvement has been reported in MS and MOGAD [26, 27]. It may be possible some of the patients in our cohort already had an underlying subclinical/asymptomatic demyelinating illness that was unmasked following the administration of COVID-19 vaccine.

ChAdOx1 vaccine viral vector vaccine using modified chimpanzee DNA adenovirus. This DNA later replicates in host DNA and produces viral spike protein which can elicit an immune response [5]. BBV152 is a whole-virus inactivated vaccine produced from the SARS-CoV-2 strain, in which the genetic material of the vaccine is destroyed but the antigen remains intact [28]. Vaccines deliver the SARS-CoV-2 antigen into dendritic cells (DC) using lipid adenoviral vectors in the case of the ChAdOx1 vaccine and the case of BBV152 by using the inactivated SARS-CoV-2 virus [5, 28].

ChAdOx1 vaccine triggers innate sensors like double-strand DNA sensor TLR9, and BBV152 vaccine activates TLR7/8 (IMDG) and the NLRP3 inflammasome. This results in the production of IL-12 drives naïve T-cells towards the pro-inflammatory Th1-biased response that generates strongly neutralizing antibodies and virus-specific CD8 effector T-cells to clear the infection. Antigen-specific memory B- and CD8 T-cells afford long-term protection [28, 29]. Researchers studied the cross-reactions between host and microbial proteins using the Protein Data Bank, showing that SARS-CoV-2 proteins possibly interact with proteins involved in axonal transport, neuronal transmission, synaptic vesicle trafficking, endocytosis, axonal transport and blood–brain barrier [29, 30].

Finally, the literature has reported more post-COVID-19 infection CNS-IDD cases than post-COVID-19 vaccines.

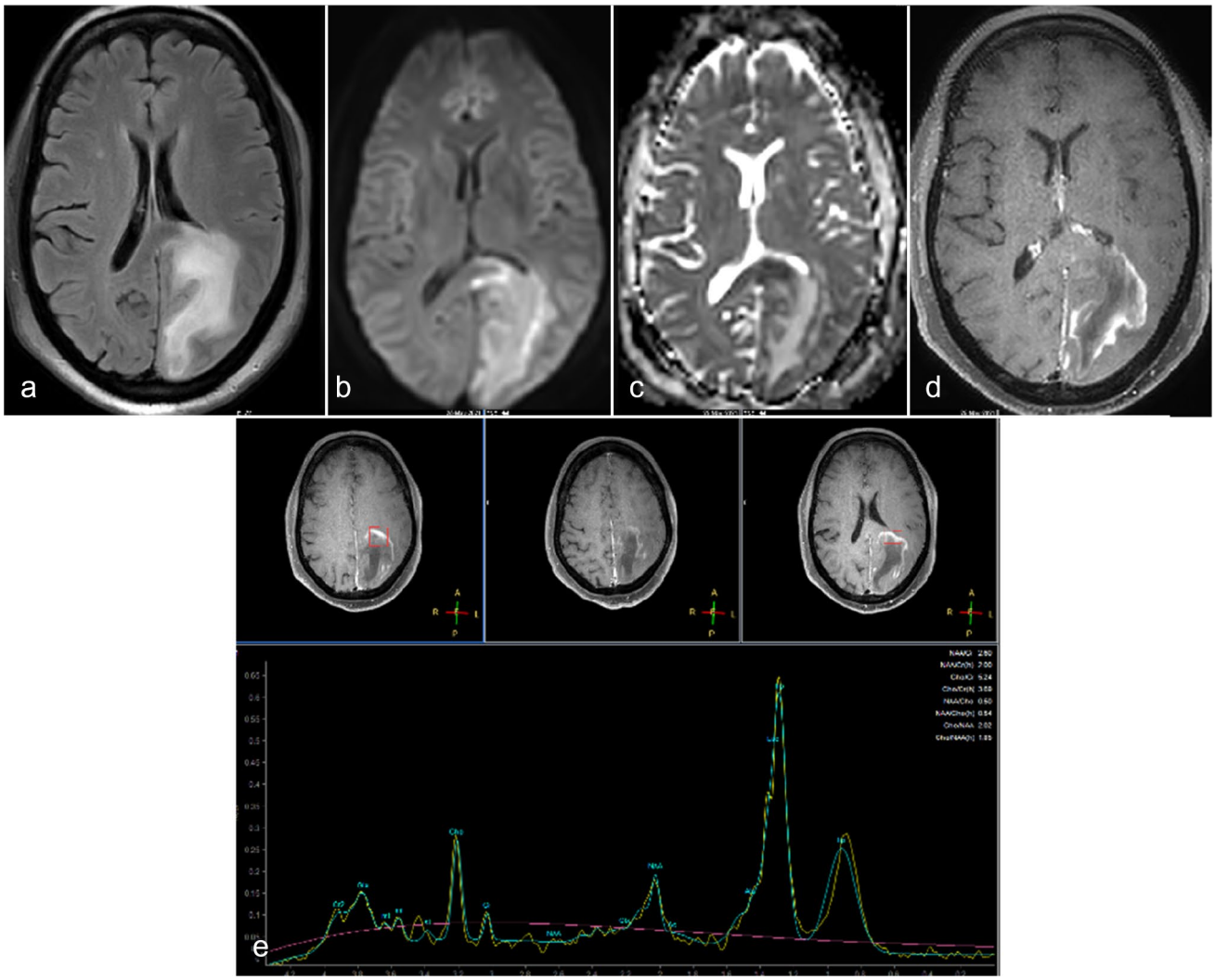

Fig. 2 MRI (**a**–**e**) images shows a well-defined FLAIR hyperintense mass lesion (**a**) involving subcortical, deep and periventricular white matter of left parietal and occipital lobe extending into splenium of corpus callosum on left side with peripheral diffusion restriction (**b** and **c**) and incomplete rim enhancement on post-contrast scan (**d**). MRS (**e**) shows large lipid–lactate peak from the peripheral enhancing edge of the lesion. Features are suggestive of tumefactive demyelination

This is in line with the available literature on various vaccines which suggest risk of demyelination to be substantially lower when compared to infections [16]. Population-based studies from Europe showed no increased risk of neuroimmunological events post-COVID-19 vaccination like transverse myelitis, meningitis and encephalomyelitis. However, people with COVID-19 infections have a higher risk of transverse myelitis or encephalomyelitis [31, 32]. A systematic review by Ostovan et al. showed that apart from a lower incidence of transverse myelitis associated with COVID-19 vaccines, the intensity of post-vaccine myelitis was lesser than myelitis post-COVID-19 infection [33]. Thus, although the risk of CNS-IDD post-vaccines is there, the benefits of vaccination overshadow the possible risk of CNS inflammation.

The risk of vaccine-related CNS-IDD is low, even in patients with known autoimmune CNS diseases [34]. Retrospective studies have shown that vaccines BNT162b2-Pfizer-BioNTech and mRNA-1273-Moderna benefit from vaccination and outweigh the risk of vaccine-related CNS-IDD reactivations [34–36]. In the study of 26 AQP4-IgG + NMOSD and 30 MOGAD patients, one patient had a relapse within 4 weeks of vaccination [34]. Seven out of 324 (2.2%) patients with multiple sclerosis reported relapse within two months post-BNT162b2-Pfizer-BioNTech vaccination [36].

This study has limitations. Establishing causality between COVID-19 vaccines and CNS-IDD may be uncertain as this is a case series. We did not report the rate of CNS-IDD post-COVID-19 infection in the community. We did not compare

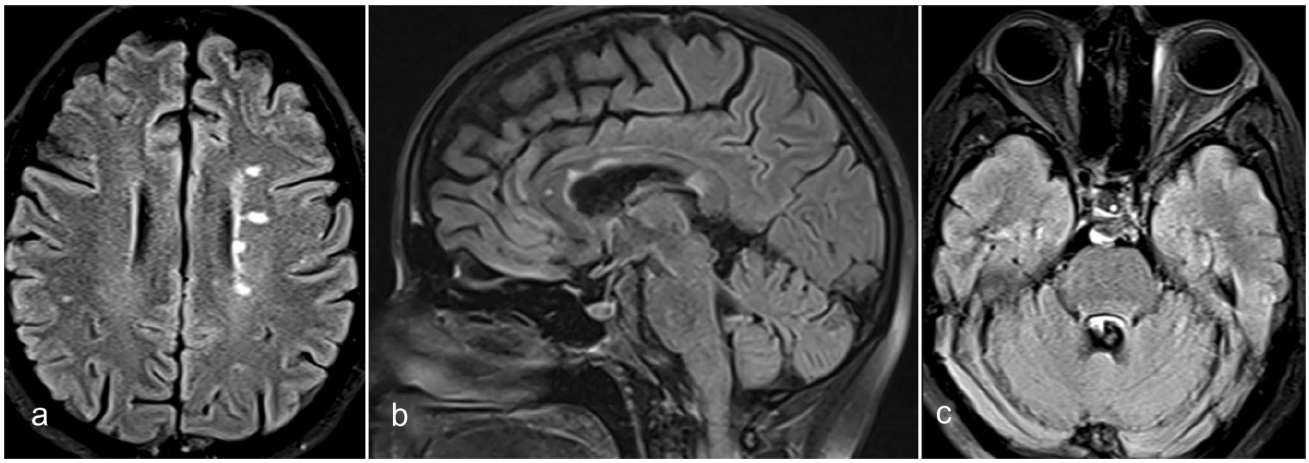

Fig. 3 MRI images (**a**–**c**) shows multiple FLAIR hyperintense lesions oriented perpendicular to the periventricular origin (**a**) and involving calloso-septal interface (**b**). FLAIR hyperintensity is also seen along left optic nerve (**c**). These imaging features are in favour of demyelination disease (multiple sclerosis)

Table 3 Treatment details and clinical outcome of all patients

	Initial treatment	Plasmapheresis/IVIg	Steroid sparing agent	Nadir EDSS	Last follow-up EDSS	Final diagnosis
Case 1	IVMP for five days	Plasmapheresis	Azathioprine	EDSS 8	EDSS 1	MOGAD LETM
Case 2	IVMP for five days	None	None	EDSS 6	EDSS 1	Seronegative TDL
Case 3	IVMP for five days	None	None	EDSS 7.5	EDSS 6.5	Seronegative TDL
Case 4	IVMP for five days	None	Injection cyclophosphamide	EDSS 1.5	EDSS 0	Multifocal CNS demyelination
Case 5	IVMP for five days	Plasmapheresis	Azathioprine	EDSS 5	EDSS 5	MOGAD optic neuritis
Case 6	IVMP for five days	None	Azathioprine	EDSS 6.5	EDSS 6.5	MOGAD optic neuritis and myelitis
Case 7	IVMP for five days	None	Dimethyl fumarate	EDSS 1	EDSS 0	RRMS
Case 8	IVMP for five days	None	Azathioprine	EDSS 5.5	EDSS 0	MOGAD optic neuritis
Case 9	IVMP five days	Plasmapheresis	None	EDSS 2	EDSS 0	Autoimmune meningoencephalitis
Case 10	IVMP five days	None	Rituximab	EDSS 6	EDSS 1	MOGAD-TDL
Case 11	IVMP five days	None	Dimethyl fumarate	EDSS 6	EDSS 0	RRMS
Case 12	IVMP five days	Plasmapheresis	Azathioprine	EDSS 2	EDSS 1	MOGAD opticomyelopathy
Case 13	IVMP five days	None	Azathioprine	EDSS 5.5	EDSS 1	MOGAD optic neuritis
Case 14	IVMP five days	Plasmapheresis	Rituximab	EDSS 7.5	EDSS 1	MOGAD Myelitis and meningoencephalitis
Case 15	IVMP five days	None	Azathioprine	EDSS 4	EDSS 1	Seronegative TDL
Case 16	IVMP five days	IVIG	Azathioprine	EDSS 7.5	EDSS 7.5	Seronegative Myelitis

IVMP intravenous methyl prednisolone, *IVIG* intravenous immunoglobulin, *EDSS* expanded disability status scale, *TDL* tumefactive demyelination, *RRMS* relapsing remitting multiple sclerosis, *LETM* longitudinally extensive transverse myelitis

probable CNS-IDD cases with controls, i.e. diagnosed with one of the CNS-IDD and were not vaccinated within 6 weeks of the demyelination.

Conclusion

We describe the temporal association between COVID-19 vaccines and CNS-IDD. Differences between episodes of demyelination after a particular type of vaccine, temporally

associated demyelination events and the presence of MOG-IgG antibody in a significant proportion of patients could increase the likelihood of immunogenic phenomenon post-vaccination in the particular patient. Long-term post-marketing surveillance and large prospective controlled studies are required to establish a possible causal relationship between the COVID-19 vaccine, CNS-IDD and safety of individual vaccines.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-023-02373-0.

Funding Nil.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. WHO (World Health Organization). https://covid19.who.int/
2. Voysey M, Clemens SAC, Madhi SA 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. https://doi.org/10.1016/S0140-6736(20)32661-1
3. Ella R, Reddy S, Jogdand H et al (2021) Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis 21:950–961. https://doi.org/10.1016/S1473-3099(21)00070-0
4. Anderson EJ, Rouphael NG, Widge AT et al (2020) Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 383:2427–2438. https://doi.org/10.1056/nejmoa2028436
5. Kyriakidis NC, López-Cortés A, González EV et al (2021) SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines. https://doi.org/10.1038/s41541-021-00292-w
6. CoWIN. https://www.cowin.gov.in/. Accessed 15 Dec 2022
7. Garg RK, Paliwal VK (2022) Spectrum of neurological complications following COVID-19 vaccination. Springer International Publishing
8. Maramattom BV, Lotlikar RS, Sukumaran S (2022) Central nervous system adverse events after ChAdOx1 vaccination. Neurol Sci 43:3503–3507. https://doi.org/10.1007/s10072-022-06000-3
9. Thompson AJ, Banwell BL, Barkhof F et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162–173. https://doi.org/10.1016/S1474-4422(17)30470-2
10. Wingerchuk DM, Banwell B, Bennett JL et al (2015) International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85:177–189. https://doi.org/10.1212/WNL.0000000000001729
11. Banwell B, Bennett JL, Marignier R et al (2023) Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: international MOGAD panel proposed criteria. Lancet Neurol 22:268–282. https://doi.org/10.1016/S1474-4422(22)00431-8
12. Krupp LB, Tardieu M, Amato MP et al (2013) International pediatric multiple sclerosis study group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler J 19:1261–1267. https://doi.org/10.1177/1352458513484547
13. Hardy TA (2019) Pseudotumoral demyelinating lesions: diagnostic approach and long-term outcome. Curr Opin Neurol 32:467–474. https://doi.org/10.1097/WCO.0000000000000683
14. Karussis D, Petrou P (2014) The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. Autoimmun Rev 13:215–224. https://doi.org/10.1016/j.autrev.2013.10.003
15. Goss AL, Samudralwar RD, Das RR, Nath A (2021) ANA investigates: neurological complications of COVID-19 vaccines. Ann Neurol 89:856–857. https://doi.org/10.1002/ana.26065
16. Ismail II, Salama S (2022) A systematic review of cases of CNS demyelination following COVID-19 vaccination. J Neuroimmunol 362:577765. https://doi.org/10.1016/j.jneuroim.2021.577765
17. Netravathi M, Dhamija K, Gupta M et al (2020) 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
18. Kim KH, Kim SH, Park NY et al (2022) Onset of various CNS inflammatory demyelination diseases following COVID-19 vaccinations. Mult Scler Relat Disord 68:104141. https://doi.org/10.1016/j.msard.2022.104141
19. Jarius S, Ruprecht K, Kleiter I et al (2016) MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 13:1–45. https://doi.org/10.1186/s12974-016-0718-0
20. Otiv M, Botre A, Shah P (2022) Measles–rubella vaccine–associated MOG-antibody positive acute demyelinating encephalomyelitis with optic neuritis in a child. Ther Adv Vaccines Immunother 10:251513552211150. https://doi.org/10.1177/25151355221115016
21. Jarius S, Bieber N, Haas J, Wildemann B (2022) MOG encephalomyelitis after vaccination against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2): case report and comprehensive review of the literature. J Neurol 269:5198–5212. https://doi.org/10.1007/s00415-022-11194-9
22. Khayat-Khoei M, Bhattacharyya S, Katz J et al (2022) COVID-19 mRNA vaccination leading to CNS inflammation: a case series. J Neurol 269:1093–1106. https://doi.org/10.1007/s00415-021-10780-7
23. Toljan K, Amin M, Kunchok A, Ontaneda D (2022) New diagnosis of multiple sclerosis in the setting of mRNA COVID-19 vaccine exposure. J Neuroimmunol 362:577785. https://doi.org/10.1016/j.jneuroim.2021.577785
24. Yamakawa M, Kuno T, Mikami T et al (2020) 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. J Neurol Sci 150:1–9
25. Kaulen LD, Doubrovinskaia S, Mooshage C et al (2022) Neurological autoimmune diseases following vaccinations against SARS-CoV-2: a case series. Eur J Neurol 29:555–563. https://doi.org/10.1111/ene.15147
26. Salunkhe M, Gupta P, Singh RK et al (2023) Clinical and radiological spectrum of anti-myelin oligodendrocyte glycoprotein (MOG) antibody encephalitis: single-center observational study. Neurol Sci. https://doi.org/10.1007/s10072-023-06686-z

27. Valencia-Sanchez C, Guo Y, Krecke KN et al (2022) Cerebral cortical encephalitis in MOGAD. Ann Neurol. https://doi.org/10.1002/ana.26549
28. Dotiwala F, Upadhyay AK (2022) A comprehensive review of BBV152 vaccine development, effectiveness, safety, challenges, and prospects. Front Immunol. https://doi.org/10.3389/fimmu.2022.940715
29. Matsumoto Y, Ohyama A, Kubota T et al (2022) MOG antibody-associated disorders following SARS-CoV-2 vaccination: a case report and literature review. Front Neurol 13:1–6. https://doi.org/10.3389/fneur.2022.845755
30. Yapici-Eser H, Koroglu YE, Oztop-Cakmak O et al (2021) Neuropsychiatric symptoms of COVID-19 explained by SARS-CoV-2 proteins' mimicry of human protein interactions. Front Hum Neurosci 15:1–16. https://doi.org/10.3389/fnhum.2021.656313
31. Li X, Raventós B, Roel E et al (2022) Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis. The BMJ. https://doi.org/10.1136/bmj-2021-068373
32. Patone M, Handunnetthi L, Saatci D et al (2021) Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med 27:2144–2153. https://doi.org/10.1038/s41591-021-01556-7
33. Ostovan VR, Sahraian MA, Karazhian N et al (2022) Clinical characteristics, radiological features and prognostic factors of transverse myelitis following COVID-19 vaccination: a systematic review. Mult Scler Relat Disord 66:104032. https://doi.org/10.1016/j.msard.2022.104032
34. Nmosd I (2022) Risk of disease relapse following COVID-19 vaccination in patients with AQP4-IgG-positive NMOSD and MOGAD. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2021.103424
35. Dinoto A, Gastaldi M, Iorio R et al (2022) Safety profile of SARS-CoV-2 vaccination in patients with antibody-mediated CNS disorders. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2022.103827
36. Crossette-Thambiah C, Pericleous C, Asmar N et al (2022) Clinical and biological features of cerebral venous sinus thrombosis following ChAdOx1 nCov-19 vaccination. J Neurol Neurosurg Psychiatry 93:445–448. https://doi.org/10.1136/jnnp-2021-327340