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COVID-19 vaccine associated demyelination & its association with MOG antibody

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ABSTRACT

Background: ChAdOx1-S (Covishield™/Vaxxervia, AstraZeneca) and BBV152 (Covaxin) SARS-CoV-2 vaccines are proven to be safe and effective, but rare complications have been reported.

Objective: To describe reports of central nervous system (CNS) demyelination following ChAdOx1-S and BBV152 vaccinations.

Methods & Results: We report 29 (17 female; mean 38 years) cases of CNS demyelination; twenty-seven occurred in temporal association with ChAdOx1-S vaccine; two in association with BBV152 vaccine. Eleven patients had presentation with myelitis, six patients developed optic neuritis, five had acute demyelinating encephalomyelitis, three presented with brainstem demyelination, and four had multifocal involvement. Myelin oligodendrocyte glycoprotein (MOG) antibodies were positive in ten patients. One patient with ADEM and tumefactive demyelinating lesions died after a prolonged intensive care unit stay and superimposed infection. As compared to the control group (87); the postvaccinial cases were found to have a significantly higher mean age, presence of encephalopathy (p value:0.0007), CSF pleocytosis (p value: 0.0094) and raised CSF protein (p value: 0.0062).

Conclusions: It is difficult to establish a causal relationship between vaccination and neurological adverse events such as demyelination. The temporal association with the vaccination and the presence of MOG antibodies raises the possibility of an immunogenic process triggered by the vaccine in susceptible individuals.

1. Introduction

COVID-19, caused by novel beta-coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the biggest health concern worldwide. The world is striving to combat the pandemic with the available medical facilities and recently developed vaccines. As of December 21 2021, 828,519,766 (59.18%) of the Indian population have received at least the first dose, while 554,958,415 (39.64%) have completed full vaccination of one of the three vaccines: ChAdOx1-S (Covishield™/Vaxxervia, AstraZeneca), BBV152 (Covaxin) and Gam-COVID-Vac (Sputnik V) (https://www.cowin.gov.in/) Though these were proven to be safe and effective in randomised controlled trials (Voysey et al., al.,2021; https://www.bharatbiotech.com; Logunov et al., al.,2021) very rare, but significant adverse events following

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; CNS, Central Nervous System; MOG, Myelin Oligodendrocyte Glycoprotein; ADEM, Acute Disseminated Encephalomyelitis; CSF, Cerebrospinal Fluid; COVID-19, Coronavirus Disease 2019; AE/EF, Adverse Events Following Immunization; CVST, Cerebral Venous Sinus Thrombosis; VITT, Vaccine Induced Thrombotic Thrombocytopenia; GBS, Guillain-Barre Syndrome; ON, Optic Neuritis; ATM, Acute Transverse Myelitis; NMO, Neuromyelitis Optica; MRI, Magnetic Resonance Imaging; VEP, Visual Evoked Potential; BAER, Brainstem Auditory Evoked Response; SSEP, Somatosensory Evoked Potential; ANA, Antinuclear Antibody; CRP, C-Reactive Protein.

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immunisation (AEFI) have been detected in post-market release sur-
veillance. amongst neurological complications, the association with
ChAdOx1-S vaccine has been confirmed for cerebral venous sinus
thrombosis (CVST) due to vaccine-induced thrombotic thrombocyto-
penia (VITT) (Alam W., 2021); however, isolated reports of Guillain
Barre Syndrome (GBS) (Maramattom et al., 2021; Waheed et al.,
2021) and central nervous system (CNS) demyelination have been
published. We have recently observed CNS demyelination ranging from
optic neuritis (ON), acute transverse myelitis (ATM), Acute demyelin-
ating encephalomyelitis (ADEM) and brainstem demyelination in the
immediate post-vaccination period. Hereby, we report on 29 patients
with different neurological manifestations of CNS demyelination pre-
senting within six weeks of vaccination against SARS-CoV-2 reported
from a tertiary university hospital from India over a period from May to
December 2021.

2. Patients and methods

All patients were evaluated prospectively at neurological emergency
and outpatient services at a tertiary-care university hospital in south
India from 15th May 2021 to 8th December 2021. The capture and
reporting of the patients’ data are covered by the institutional ethics
approval already in place for the Multiple Sclerosis and Allied Demye-
lination Registry maintained at the institute. The inclusion criteria
comprised: a) receipt of a SARS-CoV-2 vaccine, either first or second
dose, within the past 42 days (according to World Health Organization
Global Advisory Committee on Vaccine safety- WHO GACVS(http:
//vaccine-safety-training.org/frequency-and-severity.html)) b) No
recent history of COVID-19 infection within the past 3 months; and c)
Evidence of CNS demyelination based on clinical and radiological fea-
tures. The exclusion criterion was presence of other precipitating factors
besides SARS-CoV-2 vaccine as a cause for demyelination in the last
3 months. Patients fulfilling these criteria had the following data captured:
demographic, clinical features as evaluated by a consultant neurologist, the type of COVID-19 vaccine, investigations including hemogram, biochemical parameters, CSF (cerebrospinal fluid) analysis, serum and/or CSF neuromyelitis optica (NMO) antibodies, myelin oligodendrocyte glycoprotein (MOG) antibodies (testing done with IgG1), magnetic resonance imaging (MRI) of the brain and/or
spine, evoked potentials (visual evoked potentials (VEP), brainstem
auditory evoked response (BAER), somatosensory evoked potential
(SEEP)) and ancillary investigations to exclude alternative aetiologies:
serum autoimmune antibodies (ANA) profile, C-reactive protein (CRP),
and antineutrophil cytoplasmic antibodies (ANCA). Two separate au-
thors (NM, BS) applied the criteria for labelling causality in neurological
AEFI independently as mentioned previously (Butler et al., 2021).
The authors were blinded with respect to assessment of causality of
vaccines for demyelination.

2.1. Statistical analysis

Data were expressed as descriptive statistics, such as Mean ± SD for
continuous variables, frequency and percentage for categorical vari-
ables. The data was normally distributed for analysis. For quantitative
variables- independent samples t-test were used and for proportions
variables chi square test employed and a p value < 0.05 considered
statistically significant.

3. Results

One hundred sixteen patients with CNS demyelination were assessed
during the study period, of whom 29 (Table 1) met the inclusion criteria
for postvaccinial demyelination and the rest were taken as controls
(supplementary table) as either they were already diagnosed with one of
the disorders with CNS demyelination or were not vaccinated within six
weeks of the demyelination. The 29 post-vaccination demyelination
patients were predominantly young females (17 females, 12 males with
mean age of 37.86±12.34 years), and majority of them (n = 17,58.6%)
hailed from Karnataka district. The most common clinical presentations
were paraparesis with sensory disturbances and sphincter dysfunction in
eleven patients (37.9%), blurred vision in six (20.7%), features of
disseminated encephalomyelitis in five (17.2%), multifocal involvement
in four (13.9%) and brainstem involvement in three (10.3%) patients.
Only one patient (Patient 7) had history of SARS-CoV-2 infection, nine
months prior to vaccination.

Twenty-seven patients received ChAdOx1-S vaccine, while two were
vaccinated with BBV152. Most patients (n = 22, 75.9%) developed the
symptoms after the first vaccination dose and none of them had prior
history of demyelination. The timing of presentation for neurological
symptoms after vaccine exposure ranged from 1 to 42 days. The patients
presented at a mean of 16.3 days after vaccination with majority of them
(45%) presenting in the second week (6–14 days) of vaccine exposure.
Based on the criteria by Butler et al. (Butler et al., 2021) for causality
assessment in neurological AEFI, all our cases were judged to have a
probable causality label. This is in view of temporal association of
symptoms occurring within six weeks of administration of COVID-19
vaccination without an alternative reason.

The most prevalent antibody in our series of probable postvaccinial
cases was Myelin oligodendrocyte glycoprotein (MOG) antibody. The
method employed for MOG testing at our centre is a cell-based immu-
noassay using transfected cell lines with full length human MOG for in
vitro determination of IgG antibodies against this antigen. Our labora-
tory assessment of MOG antibody included its semiquantitative esti-
mation based on assessment of intensity on immunofixation. Ten of our
patients (34.5%) were positive for this antibody, out of which four of
them presented with ON, three with ADEM, two had longitudinally
extensive myelitis (LETM) and one presented with simultaneous ON and
myelitis. Two patients were diagnosed with aquaporin 4 positive
NMOSD (Neuromyelitis Optica Spectrum Disorder) in this postvaccinial
period while one patient was diagnosed with Mc Donald’s definite MS.
Rest of the patients were seronegative for both AQP4 as well as MOG
antibodies. The patients were also worked up for other secondary causes
demylination. ANA profile showed antibody positivity in four pa-
tients; the antibodies were anti proliferating cell nuclear antigen (PCNA)
(2 patients) and anti Jo-1 (antihistidyl transfer RNA [t-RNA] synthetase
(1 patient) and U1RNP/U1 Ribonucleoprotein) (1 patient). Paraneo-
plastic profile was done in one patient, and it was positive for anti-
recoverin antibody with no evidence of malignancy on computed to-
mography of the chest and abdomen. CSF examination was performed
in 26 patients. The CSF white cell count ranged from 0 to 720 cells/µl (0–5
cells/µl in ten patients; normal range); 5–50 cells/µl in nine patients; ≥
51 cells/µl in six patients; excluded traumatic CSF of Patient 16). Thir-
ten patients had normal CSF protein (15–45 mg/dl); the mean protein
of those with an elevated result was 82.04 mg/dl (excluded traumatic
CSF of Patient 16). Imaging (Fig. 1) showed involvement of optic nerves
in all patients presenting with optic neuritis. T2-Flair hyperintensities
affecting the brain parenchyma and spinal cord were observed in seven
and four patients respectively. There were ten patients showing lesions
both in brain as well as spinal areas.

28 out of 29 patients received intravenous methylprednisolone fol-
lowed by oral steroids. Plasmapheresis was used in fifteen (51.72%)
patients in view of either inadequate improvement with steroids or
contraindications to their use such as presence of infected bed sore(pa-
tient 25). Furthermore one patient received intravenous immunoglo-
bulin and five each received mycophenolate mofetil and rituximab due
to persistent disabilities and incomplete recovery with steroids and plas-
mapheresis. Significant improvement was seen in most (96.5%) of the
patients with medical management over 4-week period. One patient of
ADEM (Patient 3) with tumefactive demyelinating lesions remained
critically ill, requiring invasive ventilation, and died after a prolonged
intensive care unit stay and superimposed infection (she could not be
treated with rituximab or other immunosuppressants in view of
Table 1
Clinical Characteristics of 29 Patients with Central Nervous System Demyelination following SARS-CoV-2 Vaccination.

| No | Age (years) | Gender | Presenting Complaints | Total Duration of Illness | Type of Vaccine/ Dosing | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis |
|----|-------------|--------|-----------------------|--------------------------|-------------------------|----------------------------------------------------------|---------------------|--------------|-----------|-----------|
| 1. | 29/F        |        | Headache, Rt eye blurring of vision | 15 days                 | ChAdOx1 nCoV-19 / 1st dose | 11 days Rt: eye RAPD, VA – Rt: hand movement close to face; Lt - 6/6 | CSF: 0 cells, P:18 mg/dl Serum and CSF OCB absent ANA, ANCA, RA factor, CRP -negative Serum MOG- positive VEP: Rt - absent waveform, Lt – normal MRI brain: T2 /FLAIR hyperintensity of long intraorbital segment of Rt optic nerve with contrast enhancement | Inj. MP 1 gm x 5 days 1 cycle of LVPP T. Prednisolone 40 mg OD followed by tapering doses | MOG-antibody –associated Rt Optic neuritis |
| 2. | 26/F        |        | Bl calf pain, backache, Bl LL weakness & decreased sensation below D6 level | 11 days                 | BBV152 / 1st dose | 11 days Quadriaparesis with paradoxical breathing, Power- Bilateral upper limb between MRC grade 2-3, lower limb MRC grade 0, decreased sensation below D6, DTRs 2+ in upper limb, absent in lower limb, plantars equivocal | CSF: 207 cells-polymorphic predominant, P: 95.8 mg/dl, G: 50 mg/dl, ANA profile- PCNA strongly positive; CRP – positive ANCA, RA factor-negative Serum NMO-MOG - negative SSEP absent waveforms, MRI: Long segment T2/FLAIR hyperintensity from C2-L1 with post contrast enhancement, axial section showing H-shaped involvement | Inj. MP 1 gm x 5 days 5 cycles of LVPP T. Prednisolone 40 mg OD followed by tapering doses | Acute Transverse myelitis - LETM |
| 3. | 54/F        |        | Progressive quadriaparesis followed by altered sensorium | 1 month 12 days | ChAdOx1 nCoV-19 / 1st dose | 14 days Drowsy, not opening eyes, bl UL flexion posturing, quadriaparesis with 2/5 power in UL and 0/5 power in LL. | CSF: 8 cells-lymphocytic predominant, P:77 mg/dl, G:98 mg/dl ANA, ANCA, CRP -negative Serum NMO-MOG- negative MRI brain: T2/FLAIR hyperintensities in the corpus callosum, bl periventricular and subcortical white matter, infratentorial region with patchy contrast enhancement | Inj. MP 1 gm x 5 days 5 cycles of LVPP T. Prednisolone 40 mg OD followed by tapering doses | ADEM |
| 4. | 44/M        |        | Imbalance on walking, hiccups, vomiting, urinary retention, double vision | 12 days                 | ChAdOx1 nCoV-19 / 1st dose | 7 days Lt VA: 6/9, Rt – 6/6. spastic quadriaparesis, bilateral cerebellar signs in UL. | CSF: 130 cells-lymphocytic predominant, P: 38 mg/dl, G: 63 mg/dl, ANA, ANCA -negative Serum and CSF MOG- Strongly positive, MRI: T2 hyperintensities in the cervical and dorsal cord and conus cordis | Inj. MP 1 gm x 5 days 5 cycles of LVPP T. Prednisolone 40 mg OD | MOG-antibody –associated – LETM |
| 5. | 50/F        |        | Bl feet paraesthesias with LL weakness. | 3 weeks                 | ChAdOx1 nCoV-19 / 1st dose | 28 days Bl finger extensor weakness, Lt LL decreased distal vibration sense with spasticity in Bl LL | CSF: 2 cells-lymphocytic predominant, P:28 mg/dl, G:87 mg/dl ANA profile- PCNA weakly positive ANCA -negative, Serum NMO-MOG -negative, NCS –normal MRI Spine: focal cervical syrinx (C7-T1), demyelination across C6 | LV MP-5 days T. Prednisolone 40 mg OD T. Amitriptyline 25 mg OD | Acute Transverse myelitis |
| 6. | 39/M        |        |                | 20 days                 |                          | 14 days RT eye-RAPD, Rt VA: Finger counting at 2 | CSF: 0 cells, P:18 mg/dl Serum and CSF OCB absent ANA, ANCA, RA factor, CRP -negative Serum MOG- positive VEP: Rt - absent waveform, Lt – normal MRI brain: T2 /FLAIR hyperintensity of long intraorbital segment of Rt optic nerve with contrast enhancement | Inj. MP 1 gm x 5 days T. | (continued on next page)
| No | Age (years) / Gender | Presenting Complaints | Total Duration of Illness | Type of Vaccine/Dosing | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| 7. | 54/M | Left eye blurring of vision | 3 weeks | ChAdOx1 nCoV-19 / 1st dose | 14 days | VA: Bl 6/12, Lt eye RAPD present, Rt eye-normal pupillary reaction. | MOG-positive, VEP- bl prolonged (Right-132 ms, left-115 ms) MRI: T2/FLAIR hyperintensity of long intranarial segment of Rt optic nerve with contrast enhancement | Prednisolone 40 mg OD | MOG associated optic neuritis |
| 8. | 34/M | Rt eye blurring of vision | 2 weeks | ChAdOx1 nCoV-19 / 1st dose | 1 day | Rt eye- non reactive pupil, VA-perception of light present, Lt eye VA – 6 /18 | MOG-antibody– associated Rt Optic neuritis |
| 9. | 35/F | Progressive paraparesis followed by altered sensorium | 8 days | ChAdOx1 nCoV-19 / 1st dose | 9 days | Conscious, confused, VA: Bl 6/9, Bl LI paraparesis with power 1/5, DTR- 3+ in upper limb, 2+ in lower limb, plantars- left extensor, right equivocal | MOG-antibody –associated ADEM |
| 10. | 20/F | Double vision | 2 weeks | ChAdOx1 nCoV-19 / 1st dose | 3 days | VA: Bl 6/6, Rt eye adduction restriction, Lt eye restriction in all gazes, fundus normal | MOG-antibody –associated ADEM |
| 11. | 31/M | Bladder disturbances followed by progressive numbness of whole body and LL weakness | 5 days | ChAdOx1 nCoV-19 / 1st dose | 14 days | Lower limb spasticity, paraparesis with power 1/5, decreased sensations by 70% below LI, plantars extensor, UL DTRs-3+ and LL 2+ | MOG-antibody –associated ADEM |

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| No. | Age (years) / Gender | Presenting Complaints | Total Duration of Illness | Type of Vaccine / Dosing | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis |
|-----|----------------------|-----------------------|--------------------------|--------------------------|----------------------------------------------------------|----------------------|---------------|------------|-----------|
| 12. | 20/F                 | Rt UL paraesthesias followed by paraparesis & altered sensorium | 2 days                   | BBV152 / 1st dose        | 1 day                                                   | VA: BI 6/6. LL proximal weakness (3/5), distal 4/5, DTRs 3+, Rt LL ~50% decreased sensation, Plantars Equivocal | FLAIR hyperintensity with subtle enhancement CSF: 8 cells - lymphocytic predominant P:24.9 mg/dl, G:61 mg/dl ANA profile, ANCA, VDRL, RA factor, CRP -negative Serum and CSF NMO-MOG negative, CSF OCB - Positive VEP, BERA, SSEP- normal MRI: few juxtacortical and short segment cervical T2/FLAIR hyperintensity at CS level with suble enhancement | Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD 5 cycles of LVPP | ADEM       |
| 13. | 45/F                 | Bilateral (Rt followed by Lt) eye blurring of vision | 6 weeks                  | ChAdOx1 nCoV-19 / 1st dose | 21 days                                                  | VA: Rt 6/12, Lt hand movement perception, Lt RAPD present, Rt eye- normal pupillary reaction, Lt upper limb spasticity and extensor plantar | CSF: 2 cells - lymphocytic predominant, P: 52.3 mg/dl G: 95 mg/dl CSF OCB- positive ANA profile, ANCA, RA factor, CRP- negative Serum MOG panel - strongly positive VEP: BI waveform absent, BERA AND SSEP- Normal MRI brain and spine-T2/FLAIR short segment hyperintensity with enhancement of bilateral optic nerves, Rt optic nerve tortuous CSF: 105 cells - lymphocytic predominant, P: 28.12 mg/dl G: 70.4 mg/dl Serum MOG - strongly positive MRI brain: T2/FLAIR hyperintensity in Bl fronto parietal region, no other focal deficits | Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD 3 cycles of LVPP | MOG associated optic neuritis |
| 14. | 33/F                 | Fever, vomiting followed by altered sensorium and persistent paraesthesias below mid thoracic level | 4 weeks                  | ChAdOx1 nCoV-19 / 1st dose | 14 days                                                  | VA: Rt 6/12, Lt 6/9, Bl normal papillary reaction, no other focal deficits | MRI brain: T2/FLAIR hyperintensity in Bl fronto parietal region, no enhancement CSF: 6 cells - lymphocytic predominant, P: 54.2 mg/dl G: 77 mg/dl ANA, ANCA, VDRL, RA factor, CRP- negative ACE: 31.4 U/L Paraneoplastic panel: Anti – recoverin 2+ VEP-prolonged Bl 123 ms, BERA, SSEP -normal Serum NMO MOG - negative MRI brain and spine: T2/FLAIR hyperintensity at Bl subcortical, periventricular deep white matter, intula, cerebellar hemispheres, brainstem, short segment expansile T2 hyperintensities are | Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD | MOG-associated ADEM |
| 15. | 53/F                 | Bl LL numbness, tingling paraesthesias & urinary disturbances | 12 days                  | ChAdOx1 nCoV-19 / 2nd dose | 1 day                                                   | Tone and Power normal, Touch and pain sensation reduced by 75% below T4, Vibration sense reduced upto T4, plantars Bl equivocal, DTRs-UL 2+ and LL 3+ | MRI brain: T2/FLAIR hyperintensity at Bl subcortical, periventricular deep white matter, intula, cerebellar hemispheres, brainstem, short segment expansile T2 hyperintensities are | Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD | Acute Transverse myelitis – LETM |

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| No | Age / Gender | Presenting Complaints                                      | Total Duration of Illness | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis           |
|----|--------------|-----------------------------------------------------------|---------------------------|---------------------------------------------------------|---------------------|---------------|-----------|---------------------|
| 16 | 38/M         | Giddiness, double vision, imbalance while walking, right eye blurring of vision followed by headache | 20 days                  | 6 days                                                  | VA: Rt 6/9, Lt 6/6, Bl normal pupillary reaction, Bl gaze evoked horizontal and torsional nystagmus, DTRs: 3+, plantars Bl extensor. | CSF: 6 CELLS; P: 67.8 mg/dl, G: 81 mg/dl ANA, ANCA, VDRL, RA factor, CRP-negative ACE: 20.7 U/L, VEP-prolonged, BERA, SSEP-normal Serum NMO-MOG-negative MRI brain and spine: T2/FLAIR hyperintensity in left MCP, right corona radiate with no contrast enhancement CSF: 4 cells – 50% lymphocytes, P:26.8 mg/dl, G:108 mg/dl, OCBs-positive ANA profile and ANCA-negative Serum NMO-MOG-negative, VEP-Bl not recordable, BERA and SSEP-Normal MRI brain: subcortical hyperintense foci in Bl cerebral hemispheres MRI Optic nerves: Right–Left intraneuronal hyperintensities in intraorbital segments | Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD | CNS demyelination |
| 17 | 30/M         | Sequential blurring of vision in both eyes                | 11 days                  | 14 days                                                 | VA: Bl eye-absent perception of light, Lt eye-2/60 Fundi: Bl Disc oedema | CSF: 4 cells – 50% lymphocytes, P:26.8 mg/dl, G:108 mg/dl, OCBs-positive ANA profile and ANCA-negative Serum NMO-MOG-negative, VEP-Bl not recordable, BERA and SSEP-Normal MRI brain: subcortical hyperintense foci in Bl cerebral hemispheres MRI Optic nerves: Right–Left intraneuronal hyperintensities in intraorbital segments | Inj. MP 1 gm x 5 days 5 cycles of LVPP | Rituframab | Bilateral optic neuritis |
| 18 | 30/F         | Paraesthesias over both palms followed by development of girdle like sensation over waist and electric shock like sensation on flexion of neck | 90 days                  | 15 days                                                 | VA: 6/6 Bl, Cranial nerves and motor examination-normal Sensory examination-40% decreased sensation to touch over both palms, Romberg’s-negative | CSF: 4 cells, P:36 mg/dl, G: 60 mg/dl, OCBs-positive CRP-positive, ESR-68 mm/hr ANA, ANCA, VDRL, RA factor-negative, Vitamin B12, homocysteine-normal, ACE: 24.2 U/L Evoked potentials-normal Serum NMO-MOG-negative MRI brain and spine: single focus of T2/FLAIR hyperintensity in selenium of corpus callosum, short segment hyperintensity in cervical cord along C3. | Inj. MP 1 gm x 5 days 3 cycles of LVPP T. MMF (1.5 gm/day) | ATM - Cervical cord demyelination |
| 19 | 36/M         | Bl LL tingling and paraesthesias followed by development of motor weakness and urinary disturbances | 20 days                  | 32 days                                                 | VA: Rt (aphakia): PL present, left: 6/9. Cranial nerves: normal Upper limbs: motor and sensory examination-normal Lower limbs: hypotonia, power: hip joint: Bl 1/5, Knee joint: Bl 0/5, Ankle joint: Bl 1/5, DTRs absent in lower limbs, Sensory level at D4 | CSF: 720 cells – 80% lymphocytes P: 144.4 mg/dl, G: 50 mg/dl ANA, ANCA, VDRL, RA factor, CRP-negative, ACE: 60.9 U/L Serum NMO-MOG-negative Serum MOG-Strengthened positive MRI brain: hyperintensities along bilateral trigeminal nerves in pons MRI spine: long segment spinal cord involvement from obex till conus CRP- clear, P: 27.7 mg/dl, G: 62 mg/dl ANA, ANCA, VDRL, RA | Inj. MP 1 gm x 7 days 5 cycles of LVPP | MOG associated LETM |
| 20 | 27/F         | Ill-defined pain followed by weakness in left             | 26 days                  | 8 days                                                  | VA: 6/6 Bl, Cranial nerves normal Motor examination- | CSF: 720 cells – 80% lymphocytes P: 144.4 mg/dl, G: 50 mg/dl ANA, ANCA, VDRL, RA factor, CRP-negative, ACE: 60.9 U/L Serum NMO-MOG-negative Serum MOG-Strengthened positive MRI brain: hyperintensities along bilateral trigeminal nerves in pons MRI spine: long segment spinal cord involvement from obex till conus CRP- clear, P: 27.7 mg/dl, G: 62 mg/dl ANA, ANCA, VDRL, RA | Inj. MP 1 gm x 5 days T. | CNS demyelination |

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### Table 1 (continued)

| No | Age (years) | Presenting Complaints | Total Duration of Illness | Type of Vaccine/Dosing | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis |
|----|-------------|-----------------------|--------------------------|------------------------|--------------------------------------------------------|---------------------|--------------|-----------|-----------|
| 21 | 60/M        | Acute onset tingling paraesthesias and motor weakness in left upper and lower limb, followed by behavioural and memory disturbances | 34 days | ChAdOx1 nCoV-19 / 2nd dose | 14 days | MMSE-27/30 Cranial nerves-VA:R-6/6, L-6/9, nystagmus present Motor system-Power: normal, DTRs-brisk | grade I spasticity in left upper limb, mild pronator drift, DTRs brisk. Sensory examination-normal | factor, CRP-negative, ACE-normal EPs- Normal Serum NMO and MOG-negative MRI brain: multifocal discrete hyperintense T2/flair lesions in Bl periventricular white matter with few lesions showing peripheral diffusion restriction and contrast enhancement. MRI spine-normal CSF: 9 cells – 90% lymphocytes, P:66.3 mg/dl, G:132 mg/dl, OCBs-negative ANA, ANCA,B12, Homocysteine, VDRL-negative, ACE-normal Serum NMO and MOG-negative, VEP-normal MRI brain: multiple focal lesions in right pons, midbrain, medial temporal lobes, splenium of corpus callosum, high parietal lobes with tumefaction and peripheral enhancement. | Prednisolone 40 mg OD | ADEM |
| 22 | 23/F        | Burning paraesthesias in right palm associated with numbness and motor weakness followed by burning sensation in right foot over next 7 days | 41 days | ChAdOx1 nCoV-19 / 2nd dose | 7 days | VA-6/6 Bl Cranial nerves-normal Motor system-normal Sensory system-decreased vibration along distal right upper and lower limb joints | VA-6/18 Bl Cranial, motor and sensory examination-normal | CRP: 23 mg/dl ANA-negative Serum NMO and MOG-negative CSF-OCB-negative MRI brain T2/flair hyperintensities adjacent to right frontal horn, ependymal margins of bilateral lateral ventricles MRI spine-short segment hyperintensities at C2-C3,C5,D4 | Inj MP 1 gm x 5 days T. Prednisolone 40 mg OD T. MMF (1 gm) | Cervical cord myelopathy |
| 23 | 40/M        | Blurring of vision from left eye followed by acute urinary retention and right eye vision loss | 77 days | ChAdOx1 nCoV-19 / 1st dose | 10 days | VA-6/6 Bl Cranial nerves-normal Motor system-Tone and power normal in upper limbs LL-hypotonia, grade-0 power with hyporeflexia, plantars mute | VA-6/6 Bl Cranial nerves-normal Motor system-Tone and power normal in upper limbs LL-hypotonia, grade-0 power with hyporeflexia, plantars mute | MRI brain: T2 Hyperintensities in pons, bilateral thalami, right frontal cortex MRI spine-longitudinally extensive myelitis from C4-D3 | Inj MP 1 gm x 5 days T. Prednisolone 60 mg OD T. MMF (2 gm) | MOG associated Opticomyelopathy |
| 24 | 45/M        | H/o fever accompanied by urinary retention and difficulty in walking progressing to altered sensorium | 5 days | ChAdOx1 nCoV-19 / 1st dose | 10 days | VA-6/6 Bl Cranial nerves-normal Motor system-Tone and power normal in upper limbs LL-hypotonia, grade-0 power with hyporeflexia, plantars mute | VA-6/6 Bl Cranial nerves-normal Motor system-Tone and power normal in upper limbs LL-hypotonia, grade-0 power with hyporeflexia, plantars mute | CSF: 44 cells – 44% lymphocytes, P:90.9 mg/dl, G:68 mg/dl, rabies CSF PCR-Negative VEP-1.41,R-1.29, BERA-normal, N20-normal, P37–40 (mildly prolonged), ANA-U1RNP-1+, C-ANCA-, Serum MOG- strongly positive S. NMO–Negative MRI | INJ MP 5 days, LVPP 3 CYCLES TAB WYSOLONE 40 MG TAB MMF 1.5 GM | MOG-ADEM |

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Table 1 (continued)

| No | Age (years) / Gender | Presenting Complaints | Total Duration of Illness | Type of Vaccine/ Dosing | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis |
|----|----------------------|-----------------------|--------------------------|------------------------|--------------------------------------------------------|---------------------|--------------|-----------|-----------|
| 25 | 34/F                 | H/o recurrent vomiting and hiccups progressing to imbalance while walking | 60 days | ChAdOx1 nCoV- 19 / 2nd dose | 36 days | Cranial nerves: Right gaze evoked nystagmus, rest normal Motor examination: Tone and power normal, DTRs brisk BL Sensory examination: pseudobulbaris Left: Right., Romberg’s positive, Tandem gait impaired | CSF: 32 cells – 100% lymphocytes, P-49.2 mg/dl, G:74 mg/dl ANA,ANCA,VDRL-negative, Serum NMO and MOG-negative MRI brain: T2 Hyperintensities in cervicomedullary junction, right frontal subcortical region MRI spine-cervical cord II C2-C5,also in dorsal cord | I/V MP-5 days LVPP-4 cycles Tab Wysolone 40 mg Inj Rituximab | Area postrema syndrome - Aquaporin 4 positive NMO |
| 26 | 31/M                 | H/o progressive upper and lower limb tingling f/b difficulty in walking, urinary urgency, and constipation | 17 days | ChAdOx1 nCoV- 19 / 1st dose | 42 days | Cranial nerves-normal UL motor examination-normal, LL power-4/5,brisk DTRs, extensor plantars Sensory level at T4 | CSF: 15-15.3 mg/dl, – 63 mg/dl,OCB Negative ESR-46 mm/hr Serum NMO-weakly positive Serum MOG-negative ANA-Ro-52 1+, ANCA-negative MRI brain:T2 hyperintensity in dorsal aspect of medulla | LVPP-3 cycles | Tab Wysolone 40 mg Inj Rituximab | Of brain and spine-hyperintensities in brainstem, cervicodorsal cord and supratentorial regions with central cord swelling |
| 27 | 52/F                 | H/o progressive slurring of speech with right upper limb and lower limb weakness, followed by appearance of swallowing difficulty | 51 days | ChAdOx1 nCoV- 19 / 1st dose | 35 days | Spastic anarthria+ Gaze restricted left+: right Right facial weakness Motor examination-hypotonic right upper and lower limb with 0/5 power, left sided power-5/5,BL DTRs brisk and plantars extensor | CSF: 17 CELLS,P-40.5 mg/dl,G:56 mg/dl ESR-18,CRP-POSITIVE ANA,ANCA-Negative, VDRL-Negative. S. NMO and MOG-Negative MRI brain: Tumefactive demyelination in left frontal hemisphere with insular involvement along with left more than right midbrain involvement | L/V MP-5 days LVPP-4 cycles Tab Wysolone 40 mg Inj Rituximab | ATM - acute transverse myelitis |
| 28 | 65/F                 | H/o urinary retention followed by numbness and weakness of both hands and blurring of vision of right eye | 30 days | ChAdOx1 nCoV- 19 / 1st dose | 42 days | V/A-R- hand movements close to face,L-6/18 UL: motor examination normal LL: Power-0/5 DTRs absent in LL Sensory level:T6 | CSF: 4 CELLS,P-23 mg/dl,G:111 mg/dl,CSF- OCB+, ANA-, ANCA-,CRP-13 mg/ | LVPP – 3 cycles | L/V MP-5 days Tab Wysolone 40 mg Tab MMF 1.5 gm | LETM - Aquaporin 4 positive NMO |
| 29 | 20/F                 | H/o tingling in tips of right hand followed by progressive | 24 days | ChAdOx1 nCoV- 19 / 2nd dose | 39 days | V/A-6/6 BL Motor examination: Tone increased in right upper limb and lower | CSF: 4 CELLS,P-23 mg/dl,G:111 mg/dl,CSF- OCB+, ANA-, ANCA-,CRP-13 mg/ | L/V MP-5 days | Tab Wysolone 40 mg Inj Rituximab | Cervical myelopathy - MS |

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Intravenous immunoglobulin; ADEM: Acute disseminated encephalomyelitis; M: male; NCS: nerve conduction studies; APLA: Antiphospholipid antibodies; ms: milligrams per decilitres; G: glucose; ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; RA: rheumatoid factor; CRP: C-reactive protein; ACE: angiotensin-converting enzyme; BD: twice daily; MS: Multiple Sclerosis.

Abbreviations: No: number; F: female; Rt: right; RAPD: Relative afferent pupillary defect; VA: visual acuity; Lt: left; CSF: cerebrospinal fluid; P: protein; mg/dl= milligrams per decilitres; G: glucose; ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; RA: rheumatoid factor; CRP: C-reactive protein; ACE: angiotensin-converting enzyme; BD: twice daily; MS: Multiple Sclerosis.

Table 1 (continued)

| No | Age (years) / Gender | Presenting Complaints | Total Duration of Illness | Type of Vaccine/ Dosing | Duration between the dose and first neurological symptom | Examination finding | Investigations | Treatment | Diagnosis |
|----|----------------------|-----------------------|--------------------------|-------------------------|----------------------------------------------------------|---------------------|--------------|-----------|-----------|
|    |                      |                       |                          |                         |                                                                         | limb Power - 5/5 in all 4 limbs |                        | dl,EBV-IGG + S.NMO and MOG-Negative | MRI brain: hyperintensities in BL juxtacortical, subcortical, periventricular white matter, anterior temporal lobes as well as infratentorial regions including pons, MCP and medulla MRI Spine: short segment lesions in cervical and dorsal spine |
| 12 |                      |                       |                          |                         |                                                                         | normal Plantar right extensor and left flexor Sensory system- Pain and touch decreased by 10 percent in right upper and lower limb JPS normal Vibration normal Romberg positive Gait ataxic |
| 2  |                      |                       |                          |                         |                                                                         | motor weakness |
| 3  |                      |                       |                          |                         |                                                                         | cerebellar signs |
| 4  |                      |                       |                          |                         |                                                                         | sensory deficit |
| 5  |                      |                       |                          |                         |                                                                         | ataxia |
| 6  |                      |                       |                          |                         |                                                                         | persistent sepsis |
| 7  |                      |                       |                          |                         |                                                                         | inadequate improvement with immunomodulation and the superimposed infection may have contributed to the severe illness and fatality in this patient. Two patients received a second ChAdOx1-S vaccine dose while taking 20 mg of oral prednisone and did not show neurological worsening. One patient received an alternative BBV152 vaccination after an original ChAdOx1-S vaccine dose without any adverse events. Majority of patients in the control group had the diagnosis of MS (48 out of 87;55.1%) followed by Aquaporin-4-positive NMOSD (11 out of 87;12.6%). Ten patients in the control group were positive for antibody against MOG, out of which one developed the neurological symptoms during the period of active COVID infection. A total of 22 patients in the control group had a history of prior COVID infection, five of whom reported worsening/new neurological symptoms within 90 days of the infection, one patient was detected to be asymptomatic positive after she presented with a neurological relapse, and another one had onset of neurological symptoms during the period of active COVID infection (found to be positive for MOG antibody). 44 patients in the control group reported to be vaccinated against COVID-19. A history of worsening/relapse was present in three patients each within 6 weeks and 6–12 weeks of vaccination and in another six patients beyond the three-month period (supplementary table). As compared to the control group, the postvaccinal cases were found to have a significantly higher mean age (37.86 years of cases as compared to 30.82 years in controls). The difference in clinical features was remarkable for the presence of encephalopathy features in the postvaccinal group (20.7% in postvaccinal group vs 2.3% in the control group) (p value:0.0007). The type of vaccine received did not influence the incidence of neurological adverse effects observed when matched for the control population. Further on, we observed that a higher proportion of postvaccinal cases had CSF pleocytosis (60% in postvaccinal group and 31.1% in the control group) (p value: 0.0094) and raised CSF protein (48% in postvaccinal group and 18.7% in the control group) (p value: 0.0062) as compared to controls. The proportion of patients with MOG antibody positivity were also higher in the postvaccinal group (Table 2). | 4. Discussion We report on 29 cases of CNS demyelinating occurring within six weeks of administration of SARS-CoV-2 vaccine; 27 of them occurred in temporal association with ChAdOx1-S vaccine, while two of them were in association with BBV152 vaccine. Each patient was investigated extensively to rule out other causes of demyelination. Ten (34.5%) of them were found to be positive for MOG antibodies. The association of MOG antibodies with COVID-19 vaccines has not been reported previously, though there are reports of MOG associated myelitis and optic neuritis with COVID-19 infection (Zhou et al., 2020; https://www.aao.org/editors-choice/covid-19-linked-to-mog-antibody-associated-optic-n). Post vaccination MOG positivity has been reported with other vaccines such as tetanus, measles, Japanese encephalitis and rubella vaccines (Azumagawa et al., 2016; Kumar et al., 2020). However in these reports there were other associated inciting factors as well that could have precipitated MOG positive status like Chlamydia pneumoniae subclinical infection and pregnancy. Most MOG-associated demyelination has been reported without any preceding event/illness though a handsome proportion has also been found to be associated with post-infectious demyelinating following Epstein-Barr virus, herpes simplex virus and Borrelia infections (Wynford-Thomas et al., 2019) or following vaccination (Kumar et al., 2020). The role of MOG antibodies in these conditions is not clear, whether they are pathogenic or represents an epiphenomenon. The other antibodies found in this cohort were PCNA antibodies in two of our patients, and anti JO-1 and U1RNP each positive in other two patients. The association of these antibodies following vaccination has not been reported in literature. Antibodies against PCNA are normally found in sera from patients with chronic Hepatitis B (HBV) and Hepatitis C (HCV) infection(Hsu et al., 2006). Anti Jo-1 positive status is commonly seen post-vaccination (Vleugels RA and Callen JP., 2009) (Toplak N. and Avin T., 2015).Anti-U1 RNP has been previously observed likewise with influenza vaccination as well. Whether seropositivity for these extractable nuclear antigens represents a heightened immune response in already susceptible individuals, or are contributory towards the disease pathogenesis, is a question that needs addressed in larger experimental studies. |
Most of our postvaccinial patients responded to steroids while nearly half of them required additional rescue therapy in the form of plasmapheresis in view of inadequate improvement. This cohort had a single (3.4%) mortality in a patient with tumefactive demyelination, who did not respond to immunotherapy and subsequently died due to sepsis.

Post-vaccination acute demyelinating encephalomyelitis accounts for 5–10% of all cases of post-vaccine serious neurological events (Huynh et al., 2008). The overall incidence of post-vaccination ADEM is estimated to be with higher risk following immunization against measles. Other common causes of post-vaccination ADEM include vaccines against the varicella zoster, rubella, hepatitis A and B, influenza viruses (Huynh et al., 2008). Apart from ADEM, optic neuritis has also been reported most commonly in association with vaccines (Karussis D and Petrou P., 2014) such as measles, rubella, hepatitis A and B, influenza, pneumococcal vaccine, BCG. Post vaccination myelitis has been previously reported in literature with influenza, pneumococcal, measles, rubella, Japanese encephalitis, and others. In this study, we have found all these three types of demyelination and 34.5% of them had associated positive MOG antibodies.

The exact pathophysiological mechanism in post-vaccine demyelination is not clearly identified. In combating the COVID-19 pandemic many different types of vaccines have been developed with varying mechanisms of action. Four major vaccine mechanisms have been explored against COVID-19 virus: DNA-based vaccines, mRNA-based vaccines, protein-based vaccines, and inactivated virus. We had 27 out of 29 patients who had received ChAdOX1-S vaccine in the postvaccine cohort. ChAdOX1-S is a recombinant vaccine developed by AstraZeneca and the University of Oxford which utilises non-replicating viral vector in form of replication deficient simian adenovirus containing genes for full length structural spike protein of SARS-CoV2 (Mascellino et al., 2021). While BBV152 vaccine is a whole virion inactivated Vero cell vaccine which is developed in collaboration with Indian Council of Medical Research (ICMR)-National Institute of Virology (NIV). The virus in this vaccine has been inactivated using beta-propiolactone (Ella et al., 2021). Hence, ChAdOX1-S and BBV152 vaccine either use a modified Chimpanzee virus or inactivated whole SARS-CoV2 virion itself to generate a protective immune response, by offering a sufficient antigenic stimulus that can drive the host B and T cell responses without causing the disease (Mascellino et al., 2021). The prevalent mRNA vaccines (Pfizer and Moderna, amongst others) employ the utilization of mRNA sequence from the SARS-CoV2 virus that is able to code for the spike protein of the virus and hence build an immunogenic response in the vaccine recipients. In a recent systematic review, postvaccinial demyelinating events were reported with all of the approved COVID-19 vaccines, though the highest number of demyelinating events were reported with mRNA vaccines followed by viral vector and inactivated vaccines (Ismail II and Salama S., 2022). Pathogenetically, whether this immune response gets aberrant or autoreactive, or some other factors are potentially causative for the autoimmune demyelination is a subject of considerable interest. Immune adjuvants included in the vaccine preparations that aim to enhance the immune responses have been incriminated as one of the main mechanism. This phenomenon has been described as ‘autoimmune or inflammatory syndrome induced by adjuvants (ASIA).’ The other concept responsible for the

**Fig 1.** A-E: MRI brain axial images of patient 3: shows T1 hypo to isointense (A), T2/FLAIR (B,C) hyperintensity lesion in bilateral frontoparietal parasagittal region. Diffusion images (D) shows restriction at periphery, same region showing T1 post contrast (E) patchy as well as open ring enhancement suggestive of tumefactive demyelination. F,G,H: MRI Brain axial images of patient 1: T2 FLAIR (F) sequence showing right optic nerve hyperintensity throughout the intraorbital segment with anterior-most portion showing diffusion restriction (G). The intraorbital segment shows T1 post contrast enhancement (H). I,J: MRI Brain axial images of patient 16: T2 Flair hyperintense (I) left middle cerebellar peduncle lesion with diffusion restriction (J). K, L: MRI brain (K) and spine (L) of patient 16: T2/FLAIR hyperintense lesions in bilateral anterior temporal poles (right more than left), occipital juxtacortical white matter. Spinal cord showing T2 hyperintense short segment lesion at C6 cervical cord. M,N: MRI spine (M, N) of patient 2: T1 isointense and T2 hyperintense (M) long segment hyperintensity extending from C2 to lower dorsal cord with no post contrast enhancement. Axial section (N) at C3 level showing central cord T2 hyperintensity – H Pattern.
immunopathogenesis is molecular mimicry-based on shared structural similarities due to shared amino acid sequences or similar conformational structures between the vaccine and self-antigen (Karussis D and Petrou P., 2014; Schattner A., 2005). The pathogenesis for MOG associated post-vaccine demyelination is postulated to be similar molecular mimicry mechanism, stimulation of autoreactive T-cell clones, enhanced antigen expression and possible epitope spread (Wyntford-Thomas et al., 2019). 

The COVID-19 pandemic has led us to witness various neurological manifestations of the virus. The pathogenesis resulting in various neurological manifestations can be due to a variety of mechanisms, such as immune mediated, hypoxic injury, coagulation abnormalities and direct invasion by virus (Zhao et al., 2020; Solomon et al., 2020; Song et al., 2021). There are many studies reporting COVID-19 associated demyelination (Artemiadis et al., 2021; Garg et al., 2021; Khandelwal et al., 2021; Moreno-Escobar et al., 2021; Zanin et al., 2021). Likewise, the development phase of our vaccine armamentarium was attributed to underlying multiple sclerosis in one patient from China following SARS-CoV-2 (Vero Cells, Beijing Institute of Biological Products Co., Ltd., Beijing, China) vaccination and longitudinally extensive transverse myelitis (LETM) following ChAdOx1-S, AstraZeneca vaccine from Germany (Pagenkopf C and Südmeyer M., 2021). Our study is the largest series of CNS demyelination in temporal association with COVID-19 vaccine and exclusion of alternative aetiologies.

Vaccination in India began on January 16, 2021; initially vaccines were administered to all health care workers. The vaccination program then expanded to cover front line workers (police, paramilitary forces, sanitation workers, and disaster management volunteers) since February 2021. The next phase, since March 2021, included citizens above the age of 60 years and people above the age of 45 with comorbidities. Adults above 18 years of age were provided vaccination after third week of June 2021. From June 18 to July 17, 4.53 million doses were administered daily, the highest for any 30-day period since the vaccination drive started (https://www.thehindu.com/data/data-covid-19-vaccination-rate-improved-in-all-states-between-june-july-2021/article35509004.ece). The stepwise rollout in people of different backgrounds and ages, and fluctuations in numbers vaccinated, may hamper accuracy of our basic incidence calculation, as may the potential for cases to not have been reported, but at one case per 10 million population per year, these serious potential side effects appear very rare in comparison to the beneficial effects of the vaccine in combating the pandemic.

There are some limitations in our study. Since this was a chart review of the control population, we cannot flawlessly estimate the occurrence of COVID-19 infection in our population. We also did not have data for COVID antibody testing prior to vaccination in the cases presenting with postvaccinal demyelination. Another limitation of our study is the lack of facility of quantitative assessment of MOG antibody titres at our centre, though the semiquantitative assessment was still possible, thus categorising results into positive and strongly positive samples.

5. Conclusion

In conclusion, while it is difficult to establish a causal relationship between vaccination and neurological adverse events such as demyelination, neurologists and physicians should be aware of this potential rare adverse event. The temporal association with the vaccination, the disproportionate number of patients affected following different vaccine brands, and the presence of MOG antibodies in a substantial proportion of these individuals raises the possibility of an immunogenic process triggered by the vaccine in susceptible individuals. However, these rare occurrences, with very low incidence, and so we urge this information not to be misquoted as it would result in vaccine hesitancy and subject to misinformation by the social media.

Availability of data and material

The anonymised data of each patient are available with unique alphanumeric code, that will be shared if required by the authors.

Author contributions

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Table 2
Comparison of Demographic, Clinical and Laboratory Parameters amongst The Postvaccinal Demyelination Cases And Control Population During The Same Period.

| Age (mean±SD) | Gender, females (%) | Optic nerve involvement at presentation | Encephalopathy features | Patients vaccinated with ChAdOx1 NCov-19 | CSF pleocytosis | Raised CSF protein | CSF oligoclonal bands | ANA positivity | CRP positivity | MOG positivity | Aquaporin-4 positivity |
|--------------|---------------------|----------------------------------------|-------------------------|----------------------------------------|-----------------|---------------------|---------------------|----------------|----------------|----------------|---------------------|
| 37.86±12.34  | 15 (38.6%)          | 21 (44.9%)                             | 6 (20.3%)               | 27 (93.1%)                            | 19 (19.1%)      | 12 (25.5%)          | 6 (60%)              | 6 (60%)        | 7 (70%)       | 10 (20.7%)     | 2 (20.7%)           |
| 38.02±11.81  | 61 (70.1%)          | 21 (44.9%)                             | 2 (2.3%)                | 34 out of 44 vaccinated (77.3%)        |                  | 19 out of 61 (31.1%)|                      |                |              |                |                     |
|              | 0.0069              | 0.2553                                 | 0.4641                  | 0.0007                                 | 0.0766          | 0.0494              | 0.0623              |                |              |                |                     |

Abbreviations: N: Number; SD: Standard deviation; CSF: Cerebrospinal fluid; ANA: Antinuclear antibody; CRP: C-Reactive Protein; MOG: Myelin Oligodendrocyte Glycoprotein.
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Mahadevan A: Study concept, design, Data acquisition
Tom Solomon: Study concept, design, Data acquisition and analysis
Bhagtheshwar Singh: Study concept, design, Data acquisition and analysis

All authors: Drafting large portions of the manuscript, figures. All authors have critically reviewed and approved the manuscript.

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Declaration of Competing Interest
None

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2. Patients for making us understand the illness better

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