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Spectrum of Neurological Adverse Events Following COVID-19 Vaccination: An Observational Study From a Tertiary Care Centre of Eastern India

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Keywords: post -vaccination neurological complications; Guillain-Barré syndrome; central nervous system demyelination; vascular events

Article

Spectrum of Neurological Adverse Events Following COVID-19 Vaccination: An Observational Study from a Tertiary Care Centre of Eastern India

Running Title: Spectrum of Post COVID-19 Vaccination Neurological Adverse Events

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Abstract: Background: As the world tends to recover from the crisis created by the COVID-19 pandemic, vaccines have served as one of the most valuable tools of combat and large-scale immunization has helped to tide over the catastrophe. However, several reports of post -vaccination neurological complications around the globe have surfaced up in recent literature. This study was conducted with an aim to describe the spectrum of neurological ailments requiring hospitalization following COVID-19 vaccination. Methods: An ambispective observational study was carried out from March 2021 to February 2022 at a tertiary care institute with 25 patients who satisfied the inclusion criteria of a new onset neurological illness requiring hospitalization within 4 days to 42 days of vaccination. The patients were duly followed upto months after discharge. Results: The median age of the sample was 36 years and the median latency of onset of neurological events was 14 days. Guillain-Barré syndrome was documented in 11 patients; majority were acute motor axonal neuropathy (45.45%) followed by acute inflammatory demyelinating polyradiculoneuropathy (36.36%) and acute motor sensory axonal neuropathy (18.18%). Central nervous system demyelination was reported in 9 patients; two patients had acute disseminated encephalomyelitis, 2 patients were diagnosed with myelin oligodendrocyte glycoprotein antibody-associated disease, one patient with aquaporin-4 positive neuromyelitis optica spectrum disorder , and the rest were labelled as seronegative central nervous system demyelination. Vascular events were noted in 5 patients comprising of 2 cases each of cerebral venous sinus thrombosis and intracerebral hemorrhage and a case of Moyamoya angiopathy. All patients were conservatively managed and had a complete to partial recovery suggestive of a favorable outcome after 3 months. Conclusion: The pathomechanisms of post -vaccination neurological complications is yet to be elucidatedand any causal association attributable to vaccination warrants further research. Compared to the enormity of the vaccinated population, the adverse effects are miniscule to hinder and discourage vaccination.

Keywords: post -vaccination neurological complications; Guillain-Barré Syndrome; central nervous system demyelination; vascular events

Introduction

The raging COVID-19 pandemic, which has claimed innumerable lives globally has been effectively curbed since the advent and implementation of large-scale vaccination. As the world

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tends to recover from economic and social crisis, governing authorities across the world have taken an ardent initiative to develop vaccines on an urgent basis and immunize their population. Subsequent emergency use authorizations were granted to many vaccines by some countries. ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)-COVISHIELD, manufactured by SERUM Institute of India and COVAXIN, manufactured by Bharat Biotech, developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV) are the two vaccines which have been used in India for mass immunization. Implementation of large-scale vaccination has resulted in decreased transmission, less severity and decreased rate of hospitalization of COVID-19 patients; however, a diverse spectrum of neurological adverse events have been reported following vaccination.[1] Therefore, despite the undeniable role of vaccination in order to mitigate this pandemic, long-term effects of vaccination is yet to be unveiled. The authors hereby present a spectrum of neurological complications encountered over a year in a tertiary care centre of Eastern India following COVID-19 vaccination.

Methodology

An ambispective observational study was carried out in our institute from March 2021 to February 2022 after obtaining permission from institutional ethical committee (IPGME&R/IEC/2022/401). The patients who were admitted in our neurology ward who satisfied the inclusion criteria of a new onset neurological illness requiring hospitalization within 4 days to 42 days of vaccination were included in this study. The study excluded patients with definite attributable factors leading to similar illness and patients with pre-morbid neurological ailments. A detailed history was followed by a thorough clinical examination and appropriate diagnostic procedures (if required) to complete a detailed assessment in these patients. these patients. Viral serology (HIV I&II, HbsAg, anti HCV) was done in all patients. A nerve conduction velocity (NCV) test was done in patients with Guillain-Barré syndrome (GBS) followed by a cerebrospinal fluid (CSF) assay after day 7 of the onset of illness. In patients with central nervous system (CNS) demyelination, 3T MRI brain, orbit and spine was performed followed by CSF assay and a visually evoked potential (VEP). Serum antinuclear antibodies (ANA), extractable nuclear antigen (ENA) profile, antineutrophilic cytoplasmic antibody (ANCA), angiotensin converting enzyme (ACE), anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, anti-aquaporin-4 antibodies and other suitable investigations were performed to detect any primary/secondary demyelinating etiology. For vascular events, 3T MRI brain with contrast Magnetic resonance venogram and Magnetic resonance angiogram of intracranial vessels were performed as per requirement. Non-contrast computed tomography brain was performed in intracerebral hemorrhage and coagulation profile, vasculitis profile was worked up as per requirement. The patients were duly followed up 3 months after discharge. The data was subsequently analyzed and the results were compared with existing literature. Since adverse reactions following COVID-19 vaccinations are diverse and intriguing, we looked up the literature available on Medline, Pubmed and other databases using MeSH terms like 'COVID-19 vaccine' ' Covid 19 vaccine' or 'neurological adverse reactions' for information and review.

Results

Over a period of one year, 25 patients who fulfilled the inclusion criteria were enrolled for the study. The median age of the sample was 36 years and majority of them were males (64%). The latency for neurological events varied from 4 days to 32 days, the median latency being 14 days. The demographic and clinical profile has been tabulated in Table 1.

Table 1. Comprehensive profile of the patients with post vaccination neurological adverse events; CSF- Cerebrospinal fluid, MRI- Magnetic resonance imaging, NCCT- Non-contrast computed tomography, NAD- No abnormality detected, DWI- Diffusion weighted imaging GBS- Guillain-Barre Syndrome, AMAN- Acute motor axonal neuropathy, AMSAN- Acute motor and sensory axonal neuropathy, AIDP- Acute inflammatory demyelinating polyradiculoneuropathy, NCV- nerve conduction velocity, CMAP- Compound muscle action potential, SNAPs- Sensory nerve action potentials, IvIg- Intravenous immunoglobulin, LETM- longitudinally extensive transverse myelitis, ON- optic neuritis, VEP- visual evoked potential, OCB-oligoclonal band, NMO-neuromyelitis optica, MOG- myelin oligodendrocyte glycoprotein, CVST- Cerebral venous sinus thrombosis, ICH- intracerebral hemorrhage, MRV- Magnetic resonance venogram, MRA- Magnetic resonance angiogram, ICA- internal carotid artery, LMWH- Low molecular weight heparin.

Age (Years)/gender	Vaccine received	Latency of onset of disease from vaccination	Diagnosis	Neuroimaging (MRI)	CSF analysis	Ancillary investigations	Treatment received	Outcome at 3 months
Guillain-Barre Syndrome								
23/M (Case 1)	COVISHIELD 1st dose	26 days	GBS (AMAN)	Cervical spine: normal	Albuminocytological dissociation	NCS: Reduced CMAP in all 4 limbs	IvIg	Complete recovery
48/M (Case 2)	Covaxin 1st dose	10 days	GBS (AMSAN)	Cervical spine: degenerative disc changes	Albuminocytological dissociation	NCS: Reduced CMAP and absent SNAPs in all 4 limbs	IvIg	Partial recovery
21/M (Case 3)	COVISHIELD 1st dose	12 days	GBS (AIDP)	Cervical spine: normal	Albuminocytological dissociation	NCS: Prolonged distal latencies with reduced velocities of both lower limbs	IvIg	Complete recovery
27/F (Case 4)	COVISHIELD 2nd dose	7 days	GBS (AMAN)	Cervical spine: normal	Albuminocytological dissociation	NCS: Reduced CMAP in all 4 limbs	IvIg	Partial recovery
64/F (Case 5)	COVISHIELD 1st dose	32 days	GBS (AIDP)	Cervical spine: degenerative disc changes	Albuminocytological dissociation	NCS: Prolonged distal latencies with reduced velocities of all 4 limbs	Conservative management	Complete recovery
45/M (Case 6)	COVISHIELD 1st dose	11 days	GBS (AMAN)	Cervical spine: normal	Albuminocytological dissociation	NCS: Reduced CMAP in all 4 limbs	IvIg	Complete recovery
33/M (Case 7)	COVISHIELD 1st dose	14 days	GBS (AMSAN)	Cervical spine: normal	Albuminocytological dissociation	NCS: Reduced CMAP and absent SNAPs in all 4 limbs	IvIg	Complete recovery
41/M (Case 8)	COVISHIELD 1st dose	18 days	GBS (AIDP)	Cervical spine: normal	Albuminocytological dissociation	NCS: Prolonged distal latencies with reduced velocities of both lower limbs	IvIg	Partial recovery

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34/F (Case 9)	COVISHIELD 1st dose	18 days	GBS (AMAN)	Cervical spine: normal	Albuminocytological dissociation	NCS: Reduced CMAP in all 4 limbs	IvIg	Complete recovery
22/M (Case 10)	COVISHIELD 1st dose	16 days	GBS (AMAN)	Cervical spine: normal	Albuminocytological dissociation	NCS: Reduced CMAP in all 4 limbs	IvIg	Partial recovery
59/M (Case 11)	COVISHIELD 1st dose	30 days	GBS (AIDP)	Not done	Albuminocytological dissociation	NCS: Prolonged distal latencies with reduced velocities of both lower limbs	Conservative management	Complete Recovery
Central Nervous System Demyelination								
21/M (Case 1)	COVISHIELD 1st dose	14 days	CNS demyelination (LETM+ bilateral ON)	**Orbit:** T2 hyperintensity in retrobulbar and canalicular segments of right optic nerve with post contrast enhancement **Brain:** T2 hyperintensity in thalami, PLIC, left perisylvian cortex, lower pons **Spinal cord:** T2 hyperintensity with central cord involvement D3-D9	Lymphocytic pleocytosis (62 cells/cumm), protein-40mg/dl Glucose-70mg/dl	**Serum MOG antibodies: positive** Serum NMO antibodies: Negative VEP: Bilateral retino-optic pathway dysfunction (right>left)	Intravenous pulse methylprednisolone followed by oral prednisolone taper Followed by Tab Mycophenolate mofetil	Partial recovery

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33/F (Case 2)	COVISHIELD 1st dose	15 days	CNS demyelination (ADEM)	**Brain:** T2 FLAIR hyperintense lesions in periventricular white matter of genu and splenium of corpus callosum, PLIC, left SCP with varying contrast enhancement **Spinal cord:** short segment eccentric T2 hyperintense foci at C2-C3, D2-D4, D8-D9 **Orbit:** NAD	Cell: 10/cumm, lymphocytes Protein-36 mg/dl Glucose-61mg/dl	VEP: NAD CSF IgG index, OCB: Negative Serum MOG, NMO: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper	Partial recovery
31/M (Case 3)	COVISHIELD 1st dose	7 days	CNS demyelination	**Brain:** T2 hyperintense lesions in inferior medulla with extension upto C1 vertebra, with post contrast enhancement **Orbit and spinal cord:** NAD	Cell-8/cumm, lymphocytes Protein-49mg/dl Glucose-75mg/dl	VEP: NAD CSF OCB, IgG index: negative Serum NMO/MOG antibodies: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper	Partial recovery

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27/F (Case 4)	COVISHIELD 1st dose	11 days	CNS demyelination (ADEM)	**Brain:** T2/T2FLAIR hyperintense fluffy bihemispheric variable sized lesions involving the cortex, bilateral periventricular white matter with forceps major with heterogenous contrast enhancement **Orbit: NAD** **Spinal cord:** heterogenous patchy T2 hyperintensity at C2-C4.	Cell-23/cumm, lymphocytes Protein-70mg/dl, glucose-59mg/dl	VEP: NAD CSF OCB, IgG index: negative Serum NMO/MOG antibodies: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper	Complete recovery
42/M (Case 5)	COVISHIELD 1st dose	21 days	CNS demyelination (bilateral ON)	**Brain:** NAD **Orbit:** T2 hyperintensity in right>left optic nerve with post contrast enhancement **Spinal cord:** NAD	Cell-4/cumm, lymphoctes Protein-26mg/dl Glucose-55mg/dl	VEP: Bilateral retino-optic pathway dysfunction CSF OCB, IgG index: negative Serum NMO antibodies: negative **Serum MOG antibodies: Positive**	Intravenous pulse methylprednisolone followed by oral prednisolone taper Followed by Tab Mycophenolate mofetil	Partial recovery

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23/F (Case 6)	COVISHIELD 1st dose	18 days	CNS demyelination (cerebellar ataxia and bilateral ON)	**Brain:** T2 hyperintense lesion in left cerebellar hemisphere abutting the fourth ventricle and a T2 hyperintense lesion in high parietal lobe without any contrast enhancement **Orbit and spine:** NAD	Cell- 35/cumm, lymphocytes Protein- 39mg/dl Glucose- 62mg/dl	VEP: Bilateral retino-optic pathway dysfunction (left>right) CSF OCB, IgG index: negative Serum NMO/MOG antibodies: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper	Complete recovery
28/M (Case 7)	COVISHIELD 2nd dose	7 days	CNS demyelination (area postrema syndrome)	**Brain:** T2 FLAIR hyperintensity in dorsal medulla with extension upto left ICP with post contrast enhancement **Orbit and spinal cord:** NAD	Cell- acellular Protein-34mg/dl Glucose-58mg/dl	VEP: NAD CSF OCB, IgG index: negative Serum NMO/MOG antibodies: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper	Complete recovery
24/F (Case 8)	COVISHIELD 1st dose	15 days	CNS demyelination (LETM)	**Brain:** NAD **Spinal cord:** central cord T2 hyperintensities at C3-C4 to D2-D3 levels, D5-D6 to D9-D10 levels. **Orbit:** NAD	Cell-35/cumm (lymphocytes) Protein-67 mg/dl Glucose-74 mg/dl	VEP: bilateral retino-optic pathway dysfunction CSF OCB, IgG index: negative **Serum NMO antibodies: positive** Serum MOG antibodies: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper Planned for Inj. Rituximab	Complete recovery
22/F (Case 9)	COVISHIELD 1st dose	25 days	CNS demyelination	**Brain:** T2FLAIR hyperintense lesions in dorsal pons, middle cerebellar peduncle **Spinal cord:** NAD **Orbit:** NAD	Cell- 10/cumm (lymphocytes) Protein- 82mg/dl Glucose- 56 mg/dl	VEP: NAD CSF OCB, IgG index: negative Serum NMO/MOG antibodies: negative	Intravenous pulse methylprednisolone followed by oral prednisolone taper	Partial recovery
Vascular events								

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52/M (Case 1)	COVISHIELD 1st dose	5 days	CVST	**Brain:** sulcal bleed with superior sagittal sinus occlusion in MRV (contrast)	N/A	Anti-PF4 antibodies: negative Platelet count: 2.5 lakh/cumm Prothrombotic panel: negative	Inj. LMWH followed by Apixaban	Complete recovery
51/M (Case 2)	COVISHIELD 1st dose	6 days	CVST	**Brain:** NAD Venogram (contrast): thrombosis in superior sagittal sinus and transverse sinus with extensive venous collaterals	N/A	Anti-PF4 antibodies: negative Platelet count: 1.5 lakh/cumm Prothrombotic panel: negative	Inj. LMWH followed by Warfarin	Complete recovery
35/M (Case 3)	COVISHIELD 1st dose	8 days	ICH	**NCCT Brain:** right thalamic bleed	N/A	CT Angiography of intracerebral vessels: Negative PT/INR/aPTT: WNL	Conservative management	Complete recovery
69/M (Case 4)	COVISHIELD 1st dose	11 days	ICH	**NCCT Brain:** right high parietal lobar bleed	N/A	CT Angiography of intracerebral vessels: Negative PT/INR/aPTT: WNL	Conservative management	Complete recovery
49/F (Case 5)	COVISHIELD 1st dose	4 days	MoyaMoya angiopathy	**MRI Brain:** multiple T2 hyperintensities in deep frontoparietal white matter, DWI restriction in bilateral centrum semiovale (left>right)	N/A	MRA of intracranial vessels: Bilateral supraclinoid terminal ICA occlusion suggestive of Moya-Moya angiopathy Vasculitis and connective tissue disease profile- negative, lipid profile- NAD	Conservative management	Partial recovery

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Guillain-Barré syndrome (GBS)

In this study, eleven patients with GBS were documented fulfilling level 1 or 2 of diagnostic certainty as per Brighton criteria.[2] The median age of presentation was 34 years and the latency of onset of GBS after vaccination ranged from 7 days to 32 days (median latency of onset - 16 days). After electrophysiological studies, the patients were categorized into acute motor axonal neuropathy (AMAN), acute demyelinating polyradiculoneuropathy (AIDP), acute motor and sensory axonal neuropathy (AMSAN). Majority of the patients were diagnosed as AMAN (45.45%), followed by AIDP (36.36%) and AMSAN (18.18%). Ten patients had history of COVISHIELD vaccination while one had been vaccinated with Covaxin. In this study , GBS was reportedly common after first dose of vaccination in all patients barring one patient, who had reported the same after the second dose. The median CSF albumin was 72.45 mg/dl. The clinical profile and outcome of these GBS patients has been displayed in Table 2. Among the eleven patients, only three patients had lower motor neuron (LMN) facial palsy and none of them reported any bulbar dysfunction. Dysautonomia was recorded in only two patients. The Erasmus Guillain-Barré Respiratory insufficiency score (EGRIS) ranged from 2 to 5; however, none of the patients required invasive ventilation. All patients were treated with intravenous immunoglobulin except two patients who had spontaneous improvement and was heading towards an uneventful recovery. All of the patients were discharged with a median mRC sum score of 42 and a follow up after 3 months revealed partial recovery in four patients and complete recovery in the rest.

Table 2. Clinical profile and outcome of patients admitted with Guillain-Barre Syndrome (GBS) . MRC- Medical Research Council, EGRIS- Erasmus GB Respiratory insufficiency score, LMN- lower motor neuron, AMAN- Acute motor axonal neuropathy, AMSAN- Acute motor and sensory axonal neuropathy, AIDP- Acute inflammatory demyelinating polyradiculoneuropathy.

GB variant	Case	MRC sum score on admission	Cranial nerve involvement/bulbar dysfunction	Dysautonomia	Invasive ventilation	EGRIS	Outcome	MRC sum score on discharge
AMAN	1	32	Nil	Present	No	2	Discharged	38
	2	28	Nil	Absent	No	3	Discharged	42
	3	42	Nil	Absent	No	2	Discharged	48
	4	32	Nil	Absent	No	2	Discharged	36
	5	18	Nil	Absent	No	5	Discharged	32
AIDP	1	36	Bilateral LMN facial palsy	Absent	No	3	Discharged	48
	2	38	Unilateral LMN facial palsy	Absent	No	5	Discharged	48
	3	32	Bilateral facial palsy with left lateral rectus paresis	Absent	No	5	Discharged	42
	4	42	Nil	Absent	No	3	Discharged	52
AMSAN	1	28	Nil	Present	No	3	Discharged	36
	2	45	Nil	Absent	No	2	Discharged	56

Central nervous system (CNS) demyelination

Nine patients with CNS demyelination were documented in this series. The median age of presentation was 27 years and the latency of onset varied from 7 to 25 days (median- 15 days).

ADEM

Among the nine patients, acute disseminated encephalomyelitis (ADEM) was reported in two patients, both of them had history of taking the first dose of COVISHIELD vaccination. The latency of onset of symptoms from vaccination ranged from 11 days to 15 days. One patient with ADEM

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presented with an encephalopathy followed by sequential neurodeficits in the form of cerebellar ataxia and upper motor neuron type paraparesis. Brain imaging with contrast revealed T2 FLAIR hyperintense foci in both grey and white matter with heterogenous contrast enhancement. Spinal imaging with contrast showed short segmental, eccentric T2 hyperintense foci at cervico-dorsal vertebral levels with heterogenous contrast enhancement. Another patient diagnosed with ADEM presented with focal to bilateral tonic clonic seizures followed by encephalopathy. Brain imaging with contrast revealed cortical and deep white matter poorly demarcated fluffy lesions, although orbital and spinal imaging were unremarkable. Primary and secondary causes of demyelination were negated by suitable investigations in these two cases. Both patients were treated with pulse intravenous methylprednisolone (1000mg/day) for 5 days followed by oral prednisolone (1mg/kg) in a tapering dose.. A follow-up visit after 3 months documented partial recovery with physical rehabilitation in the first patient and complete recovery in the second.

Myelin oligodendrocyte glycoprotein antibody disease (MOGAD)

Two cases of MOGAD have been documented in this series with history of first dose of COVISHIELD vaccination 14 and 21 days prior to onset of neurological symptoms. One patient (Case 1, Central nervous system demyelination, Table 1) presented with a subacute onset bilateral dimness of vision with color desaturation followed by upper motor neuron type (UMN) paraparesis and subsequent acute painful retention of urine within a span of 7 days. His visual acuity on admission was 6/60 in right eye and 6/36 in the left; fundoscopy was suggestive of bilateral papillitis. Orbital imaging with contrast showed T2 hyperintensity in retrobulbar and canalicular segments of right optic nerve with post-contrast enhancement; spinal imaging with contrast showed central cord T2 hyperintensities without contrast enhancement from D3-D9 suggestive of longitudinally extensive transverse myelitis (LETM); corresponding brain imaging with contrast revealed non-enhancing T2 hyperintensities in deep grey, white matter and brainstem. Lymphocytic pleocytosis was detected in CSF assay and visual evoked potentials (VEP) revealed bilateral retino-optic pathway dysfunction (right>left). Another patient presented (Case 5, Central nervous system demyelination, Table 1) with bilateral sequential optic neuritis (visual acuity- only perception of light in right eye, 6/60 in left) in absence of any other neurodeficit. Orbital imaging with contrast revealed post-contrast enhancement of right>left optic nerve while brain and spinal imaging were unremarkable. Serum MOG antibodies (live cell-based assay) turned out to be positive in both these patients and they were diagnosed with MOGAD as per international consensus and recommendations on diagnosis of MOGAD.[3] Both of these patients were started on oral prednisolone 1mg/kg on tapering dosage after a pulse intravenous methylprednisolone (1000mg/day) for 5 days. Subsequently, mycophenolate mofetil was added as a steroid sparing agent. Follow-up after 3 months revealed visual acuity of 6/18 in both eyes and improvement of paraparesis with physical rehabilitation in the first patient and a partial recovery with a visual acuity of 6/36 in both eyes in the second patient.

Neuromyelitis optica spectrum (NMO) disorder

A 24-year-old female (Case 8, Central nervous system demyelination, Table 1) presented with a subacute onset UMN paraparesis with features suggestive of UMN bladder in absence of any other neurodeficit. Spinal imaging with contrast revealed T2 hyperintense central cord lesions at C3-C4 to D2-D3 levels, D5-D6 to D9-D10 levels suggestive of LETM; brain and orbital imaging were non-contributory. Serum aquaporin-4 antibodies (live cell-based assay) turned out to be positive. She was initiated on oral prednisolone on a tapering dose following a pulse methylprednisolone course, and subsequent five cycles of plasmapheresis before adding rituximab as a steroid sparing agent. Her neurodeficit had a dramatic improvement after plasmapheresis and she had an uneventful recovery after 3 months.

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Seronegative CNS demyelination

A 31-year-old male (Case 3, Central nervous system demyelination, Table 1) presented with a subacute onset symmetric UMN quadriparesis with LMN bulbar dysfunction 7 days after receiving his first dose of COVISHIELD vaccine, Brain imaging with contrast revealed T2 hyperintense lesion in inferior medulla extending upto C1 vertebra with heterogenous contrast enhancement, while spine and orbital imaging was non-contributory. A 23-year-old female (Case 6, Central nervous system demyelination, Table 1) with a history of first dose of COVISHIELD vaccination 18 days back presented with an acute onset dimness of vision in both eyes with color desaturation (left>right) followed by a tendency to fall towards her left. Neurological examination revealed a visual acuity of 6/36 in her left eye, 6/18 in her right eye and asymmetric cerebellar signs on her left. Although orbital and spinal imaging were non-contributory, brain imaging with contrast revealed a T2 hyperintense lesion in left high parietal lobe and left cerebellar hemisphere abutting the fourth ventricle without any contrast enhancement. A 28-year-old male patient (Case 7, Central nervous system demyelination, Table 1) started to experience persistent hiccups after episodic dizziness and bouts of vomiting 7 days after his second dose of COVISHIELD vaccination. MRI Brain with contrast revealed T2 hyperintensity in dorsal medulla with extension upto left inferior cerebellar peduncle with post - contrast enhancement. Another 22-year-old female (Case 9, Central nervous system demyelination, Table 1) with a history of first dose of COVISHIELD vaccination 25 days earlier, had a subacute encephalopathy, followed by pancerebellopathy and multifocal dystonia on recovery. Brain imaging revealed non-enhancing T2 hyperintensity in dorsal pons, middle cerebellar peduncle. All four patients were managed with intravenous pulse methylprednisolone therapy (1000mg/day) for 5 days followed by oral prednisolone 1mg/kg on a tapering dosage. Follow-up visit at 3 months documented uneventful and complete recovery in the second and third patient while the first and the fourth patient have recovered partially.

Vascular complications

Two patients developed cerebral venous sinus thrombosis (CVST), two patients had experienced intracerebral hemorrhage (ICH) and one patient was detected to have Moyamoya angiopathy after the first dose of vaccination. A 51-year-old male (Case 2, Vascular events, Table 1) without any comorbidities presented with a gradual onset progressive persistent holocranial headache, associated with vomiting 6 days following the first-dose of COVISHIELD vaccination. Subsequently, he developed a binocular horizontal diplopia in right lateral gaze. Neurological examination revealed bilateral lateral rectus paresis with grade-2 papilloedema. Contrast enhanced MRI of brain was normal but contrast MR venography revealed thrombosis in superior sagittal sinus and transverse sinus with presence of extensive venous collaterals. Systemic risk factors like myeloproliferative disorders, sarcoidosis, Behçet's disease, systemic lupus erythematosus, anti-phospholipid antibody syndrome, thyroid disorders and malignancies were excluded with detailed relevant investigations. Genetic causes of thrombophilia were negated. There was no evidence of thrombocytopenia and anti-PF4 antibodies. He was managed conservatively with low molecular weight heparin (LMWH) and warfarin and had an uneventful recovery. A 52-year-old male (Case 1, Vascular events, Table 1) presented with a thunderclap headache followed by one episode of focal to bilateral tonic clonic convulsion 5 days after receiving the first dose of COVISHIELD vaccine. Brain imaging revealed a right parasagittal sulcal bleed with thrombosis of superior sagittal sinus. Extensive investigations negated other causes of CVST. This patient was managed with LMWH and apixaban and had a complete recovery after 3 months. Two patients without any comorbidities presented with an intracerebral bleed after first dose of COVISHIELD vaccination; one patient experienced a right thalamic bleed (ICH score- 0) 8 days after vaccination and another patient had a right parietal lobar bleed (ICH Score-0) 11 days after vaccination. Structural causes, bleeding diatheses and other risk factors were negated with extensive investigations in these two patients and both of them had complete recovery with conservative management. A 49-year-old non-comorbid female (Case 5, Vascular events, Table 1) presented with a right sided complete hemiparesis 4 days after first dose of COVISHIELD vaccination. MRI brain revealed bilateral T2 hyperintensities in deep white matter

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with diffusion restriction in bilateral centrum semiovale (left>right). MR angiogram of intracranial vessels revealed bilateral supraclinoid terminal internal carotid artery occlusion with leptomeningeal collaterals suggestive of Moyamoya angiopathy. Secondary causes of Moyamoya angiopathy were thoroughly negated with suitable investigations. She was managed conservatively and had a partial recovery on followup after 3 months.

Discussion

As per World health organization (WHO), stringent criteria comprising of temporal relationship, consistent evidence, strength of association, specificity and biological plausibility and coherence is essential to claim an event as vaccine induced.[4] Mass vaccination against COVID-19 globally played the most crucial role in order to mitigate the raging pandemic.in a relatively short period; however, the safety profile of these vaccines warrants extensive monitoring, and any adverse event must be duly investigated and reported. A total of 12.14 billion doses have been administered globally, and 5.54 million are now administered each day.[5] The vaccines tend to elicit an immune response by four different cardinal mechanisms. Genetically engineered RNA or DNA are introduced via mRNA vaccines to produce a viral protein subsequently inducing an immune response to itself. Vaccines which rely on vectors deliver the SARS-CoV-2 genome inside cells, which synthesize antigens against which the body mounts an immune response. Protein-based vaccines use the spike protein or its fragments to incite an immune response. Attenuated viral vaccines trigger the immune response with a killed or inactivated virus.[6,7,8,9]

Vaccines contain attenuated infectious agents or immunogenic components leading to immune dysregulation in the recipient and thus represents a unique paradigm of autoimmunity. Neurological complications following vaccination have been reported with many vaccines. These adverse events range from seizures, meningoencephalitis, ADEM, transverse myelitis to GBS and other mild to moderate neurological ailment. Probable pathogenic mechanisms include molecular mimicry, aberrant immune activation, direct neurotoxicity.[10] Neurological adverse events following vaccination has been broadly categorized into a biologically plausible group attributable to a direct effect from a vaccine component e.g., rare risk of acute flaccid paralysis -after oral polio vaccination, where the complication mimics the action of a non-attenuated wild virus at a lower frequency.[11] The unexpected group lacks a plausible biological explanation e.g., mumps-measles-rubella vaccine and autism, narcolepsy and influenza vaccine. The commonly reported vaccinations associated with CNS demyelination include influenza, Hepatitis A or B, rabies, measles, rubella, yellow fever.[12] Moreover, peripheral nervous system involvement has been observed after vaccination against hepatitis B, meningococcus, diphtheria-tetanus-pertussis, varicella, rotavirus, yellow fever.[13]

Neurological complications of COVID-19 vaccination though rare have surfaced up in literature.[14] Moreover, misinformation regarding vaccination against COVID-19 and hesitancy were initial hurdles to combat the global pandemic.[15] Post-vaccination adverse reactions following COVID-19 vaccination may be attributed to constituents of the vaccine namely an antigen, an adjuvant and a delivery system leading to probable molecular mimicry and immune dysregulation. Apart from CNS demyelination and peripheral nervous system involvement, a number of vascular events have been reported after COVID-19 vaccination, which was rarely noticed with pneumococcal, influenza and varicella vaccines in a handful of cases. An overview of neurological complications following COVID-19 is presented in Table 3. [8] However, these neurological adverse events following vaccination may be casual or co-incidental or may have a causal association which warrants structured translational research.

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Table 3. COVID-19 vaccination and neurological complications; ICH- intracerebral hemorrhage, AIS- acute ischemic stroke, CVST- cerebral venous sinus thrombosis, PRES- posterior reversible encephalopathy syndrome, ADEM- acute disseminated encephalomyelitis, NMOSD- neuromyelitis optica spectrum disorder, MOGAD- myelin oligodendrocyte glycoprotein antibody disease, GBS- Guillain-Barre Syndrome.

Brain	
Vascular complications	ICH, AIS, CVST, PRES
Metabolic	Seizures, delirium, Akathisia
Inflammatory	ADEM, Acute encephalitis, first attack of multiple sclerosis, NMOSD, MOGAD
Spinal cord	LETM, ATM, NMOSD, MOGAD
Cranial nerves	Olfactory dysfunction, optic neuritis, lateral rectus palsy, facial palsy, cochlear dysfunction
Peripheral nerves	GBS, Neuralgic amyotrophy, reactivation of herpes zoster, small fibre peripheral neuropathy
Muscle	Myositis, rhabdomyolysis

GBS following COVID-19 infection have been reported in a considerable number of cases and series globally despite paucity of definitive association between SARS-COV-2 and incidence of GBS.[16,17] Similarly, incidence of GBS after vaccination although reported as rare adverse events after vaccination with Pfizer[18], AstraZeneca[19], Janssen[20], Sinovac Biotech, lacks direct causal association. Axonal variants were documented amongst majority of the patients with GBS in this series, compared to existing literature, where demyelinating variants are commoner. An axonal pattern is suggestive of the molecular mimicry between gangliosides and antecedent infectious agents leading to autoimmunity.[21] The spike protein of SARS-CoV-2 has an affinity to bind to sialic acid-containing glycoprotein and gangliosides on cell surfaces, hence an antibody cross-reaction post -vaccination may serve as the linkage.[22] Atypical variants of GBS like Miller-Fisher syndrome, bifacial palsy with paresthesia have also been reported after COVID-19 vaccination.[23]

Literature review by Karussis and colleagues revealed 71 documented cases of post-vaccination CNS demyelination from 1979-2013, whose symptoms appeared within 2 weeks (mean: 14.2 days), although delayed presentation (4 weeks to 5 months after vaccination) has also been noted. [12] CNS demyelination has been reported following all types of approved vaccines against COVID-19 where symptoms have appeared within the first 2 weeks of vaccination. The mRNA-based vaccines have been associated with majority of demyelinating diseases followed by viral vector vaccines, protein-based vaccines and inactivated vaccines. [24]ADEM is considered a post-infectious monophasic entity but considerable cases have been reported after vaccination.[25] The clinical presentation of ADEM may vary, depending on the site of lesions and International Pediatric Multiple Sclerosis Study Group (IPMSSG) mandates encephalopathy not otherwise explained by fever or systemic illness for a definite diagnosis.[26] The current pathogenesis in post-vaccination ADEM apart from molecular mimicry is non-specific activation of antimyelin T-cells and due to compromised function of suppressor or regulatory cells. Newer vaccine preparation techniques which donot use neural tissue, has led to marked reduction in ADEM with vaccines like influenza and human papilloma virus.[27] Post-vaccination ADEM has been usually reported after primary vaccination with very low incidence after revaccination; however, a substantial percentage of post-vaccination ADEM has subsequently developed.[28] Two patients with ADEM in this series were managed with intravenous methylprednisolone followed by oral prednisolone taper and had a satisfactory clinical improvement with favorable outcome in followup. NMOSD have been rarely reported in association with COVID-19 vaccination.[29,30] MOGAD has been reported in a considerable number of cases after SARS-CoV-2 infection[31] The probable pathogenesis involves a post-infectious immune-mediated phenomenon

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rather than direct viral neurotropism. MOGAD triggered by infection encompasses molecular mimicry, spreading of antigenic epitope, bystander activation followed by polyclonal activation of B-cells.[32] The propensity for triggering MOGAD post-vaccination may have similar pathogenesis. Vaccination may trigger monophasic demyelination and may also lead to relapse of a chronic demyelinating disease like MS.[33]. A favorable outcome has been noted in majority of post -vaccination CNS demyelination, where most patients experienced complete recovery within days to weeks in absence of any long-term sequalae.[34] However, even in presence of an apparent temporal relationship between COVID-19 vaccination and these demyelinating diseases, the diagnosis of the latter should be confirmed after satisfying the stringent diagnostic criteria and not merely depending on the serological markers, especially in the presence of red flags.

Cerebrovascular events following vaccination after adenoviral vector vaccines has been a temporary concern as these events either culminate in severe disability or death. Immune-mediated thrombotic thrombocytopenia has been attributed to post -vaccination hypercoagulable adverse events.[8] The bi-directional relation and cross talk between inflammation and thrombotic milieu has been well established with SARS-CoV-2 infection. Genetic material of SARS-COV-2 in vaccines encodes the spike glycoproteins responsible for triggering the inflammatory cascade and subsequent prothrombotic state.[35] CVT following COVISHIELD vaccination have been found to have uncanny resemblance with heparin induced thrombocytopenia in presence of anti-PF4 antibodies leading to immune mediated platelet destruction.[36] Apart from immune-mediated thrombocytopenia, disseminated intravascular coagulation (DIC)-like coagulopathy has been attributed to CVT. The cases of CVST reported in this series are unique with normal platelets counts, negative anti-PF4 autoantibodies, and marked improvement with conventional anticoagulation therapy. Similarly, acute ischemic stroke within 4 weeks of COVID-19 vaccination has been reported with viral vector vaccines.[37] Intracerebral hemorrhage after vaccination albeit rare has been reported sparsely in the literature. The pathogenesis is poorly elucidated, probable insights depict platelet dysfunction and secondary vasculitis.[38,39]. Post -vaccination aberrant inflammatory cascade activation may unmask underlying vasculopathies like Moyamoya angiopathy. The crosstalk between prothrombotic milieu and inflammatory pathway may lead to decompensation of an existing intracranial vasculopathy, although definite causal association warrants extensive research.[40]

However, vaccine adverse events reporting system (VAERS) data in a recent analysis revealed no increased risk of neuroautoimmune complications from COVID-19 vaccination compared to other existing vaccines.[41]

The limitations of this study include a considerably low sample size and exclusion of patients with other neurological events post -vaccination which did not require hospitalization. Majority of the patients have received COVISHIELD in comparison to COVAXIN, leading to an unequal distribution in reporting events after vaccination. Incidence of neurological complications after vaccination could not be calculated as it was not possible to estimate the total number of vaccinated individuals within an area catered by our institution.

Conclusion

This study portrays an observation of patients with neurological adverse events requiring hospitalization after COVID-19 vaccination in a tertiary care centre of Eastern India. Apart from peripheral nervous system involvement and CNS demyelination, a few vascular events were encountered in this series at par with existing literature. Majority of the patients developed neurological complications after the first dose of vaccination and the outcome was favorable in all of these patients. Although the causal relationship between vaccines and these events cannot be claimed till date, reporting of these events may help to identify specific predispositions which may potentiate these complications. However, the benefit of COVID-19 vaccination clearly outweighs the risks and these adverse events are miniscule to hinder large scale vaccination.

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