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Journal of Clinical Neuroscience 108 (2023) 37–75

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.journals.elsevier.com/journal-of-clinical-neuroscience

Co-VAN study: COVID-19 vaccine associated neurological diseases- an experience from an apex neurosciences centre and review of the literature

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ARTICLE INFO

Keywords:
COVID19
COVID19 vaccination
SARS-CoV2 vaccine
AEFI
Vaccine side effect

ABSTRACT

Background: Recent studies have shown various neurological adverse events associated with COVID-19 vaccine.
Objective: We aimed to retrospectively review and report the neurological diseases temporally associated with COVID-19 vaccine.
Methods: We performed a retrospective chart review of admitted patients from 1st February 2021 to 30th June 2022. A total of 4672 medical records were reviewed of which 51 cases were identified to have neurological illness temporally associated with COVID-19 vaccination.
Results: Out of 51 cases, 48 had probable association with COVID-19 vaccination while three had possible association. Neurological spectrum included CNS demyelination (n = 39, 76.5 %), Guillain-Barré-syndrome (n = 3, 5.9 %), stroke (n = 6, 11.8 %), encephalitis (n = 2, 3.9 %) and myositis (n = 1, 2.0 %). Female gender had a greater predisposition (F:M, 1.13:1). Neurological events were more commonly encountered after the first-dose (n = 37, 72.5%). The mean latency to onset of symptoms was 13.2 ± 10.7 days after the last dose of vaccination. COVIShield (ChAdOx1) was the most commonly administered vaccine (n = 43, 84.3 %). Majority of the cases with demyelination were seronegative (n = 23, 59.0 %) which was followed by anti-Myelin oligodendrocyte-glycoprotein associated demyelination (MOGAD) (n = 11, 28.2 %) and Neuromyelitis optica (NMOSD) (n = 5, 12.8 %). Out of 6 Stroke cases, 2 cases (33.3 %) had thrombocytopenia and coagulopathy. At discharge, 25/51 (49.0 %) of the cases had favourable outcome (mRS 0 to 1). Among six patients of stroke, only one of them had favourable outcome.
Conclusion: In this series, we describe the wide variety of neurological syndromes temporally associated with COVID-19 vaccination. Further studies with larger sample size and longer duration of follow-up are needed to prove or disprove causality association of these syndromes with COVID-19 vaccination.

1. Introduction

In the recent years the world has witnessed an unprecedented challenge of the Coronavirus disease 2019 (COVID19) pandemic caused by a beta coronavirus, the novel severe acute respiratory syndrome coronavirus2 (SARS-CoV2). Vaccination against this virus has emerged

Abbreviations: ACE-2, angiotensin-converting enzyme 2; ADEM, Acute disseminated encephalomyelitis; AEFI, Adverse events following immunization; AHEM, Acute haemorrhagic encephalomyelitis; BBB, blood–brain barrier; CLOCC, Cytotoxic Lesion of the Corpus Callosum; COVID-19, Coronavirus disease 2019; CSF, cerebrospinal fluid; EEG, electroencephalography; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; IQR, Interquartile range; MeSH, Medical Subject Headings; MS, Multiple Sclerosis; MOG, anti-Myelin oligodendrocyte-glycoprotein; MOGAD, MOG associated demyelination; NMDAR, *N*-methyl-D-aspartate receptor; NMO, neuromyelitis optica; NMOSD, Neuromyelitis optica spectrum disorders; OCB, oligoclonal bands; PLEX, plasma exchange; RTPCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, Standard deviation; VGKC, voltage-gated potassium channel; VVr, viral vector replicating; VVnr, viral vector non-replicating; WHO GACVS, World Health Organization Global Advisory Committee on Vaccine safety.

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https://doi.org/10.1016/j.jocn.2022.12.015
Received 5 August 2022; Accepted 19 December 2022
Available online 23 December 2022

Table 1
Details of vaccines against SARS-CoV2 and its approval and dosing count in India.

Vaccine generic	Brands	Type of vaccine	Manufacturer	Status in India
AZD1222 (ChAdOx1)	COVID-19 Vaccine AstraZeneca, Covishield, Vaxzevria	Adenovirus vaccine	BARDA, OWS, Serum Institute of India	Approved in India, Total vaccine doses administered as on 26/03/22 is 1,50,80,58,152
BBV152	Covaxin	Inactivated vaccine	Bharat Biotech, ICMR; Ocugen; ViroVax	Approved in India, Total vaccine doses administered as on 26/03/22 is 30,52,68,845
rAd26 and rAd5	Sputnik V	Recombinant adenovirus vaccine	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Approved in India, Total vaccine doses administered as on 26/03/22 is 12,21,106
Corbevax	Corbevax	Adjuvanted protein subunit vaccine	Biological E, Baylor College of Medicine, Dynavax, CEPI	Approved in India, Total vaccine doses administered as on 26/03/22 is 1,20,88,254
BNT162b2	COMIRNATY	mRNA-based vaccine	Pfizer, BioNTech, Fosun Pharma	Approved in India
ZyCoV-D	ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	Approved in India
mRNA-1273	Spikevax	mRNA-based vaccine	Moderna, BARDA, NIAID	Approved in India
rAd26	Sputnik Light	Recombinant adenovirus vaccine	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Approved in India
NVX-CoV2373	Covovax (India), TAK-019 (Japan) Nuvaxovid,	Prefusion protein recombinant nanoparticle vaccine	Novavax; CEPI, Serum Institute of India	Approved in India
Sinopharm COVID-19 Vaccine (BBIBP-CorV)	BBIBP-CorV/NVSI-06–07	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	
EpiVacCorona/ (Aurora-CoV)	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	
JNJ-78436735; Ad26. COV2.S	Janssen	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	
CoviVac	CoviVac	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	
ZIFIVAX	ZF2001	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	
QazCovid-in	QazVac	Inactivated vaccine	Research Institute for Biological Safety Problems	
CoronaVac (formerly PiCoVacc)	CoronaVac	formalin-inactivated and alum-adjuvanted vaccine	Sinovac	
Convidicea (Ad5-nCoV)	Ad5-nCoV /PakVac	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	
WIBP-CorV	WIBP-CorV	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	
COVIran Barekat	COVIran Barekat	Inactivated vaccine	Shifa Pharmed Industrial Group	
CIGB 66	Abdala	Protein subunit vaccine	Center for Genetic Engineering and Biotechnology	
Soberana 02/Soberana Plus	Soberana 02/Soberana Plus	Conjugate vaccine	Finlay Institute of Vaccines; Pasteur Institute	
MVC-COV1901	MVC-COV1901	Protein subunit vaccine	Medigen Vaccine Biologics Corp.; Dynavax	
COVAX-19	Spikogen	Monovalent recombinant protein vaccine	Vaxine Pty ltd.; CinnaGen	
FAKHRAVAC (MIVAC)	FAKHRAVAC (MIVAC)	Inactivated vaccine	The Stem Cell Technology Research Center; Organization of Defensive Innovation and Research	
Turkovac (ERUCOV-VAC)	Turkovac (ERUCOV-VAC)	Inactivated vaccine	Health Institutes of Turkey	
Covifenz (CoVLP)	Covifenz (CoVLP)	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	
VLA2001	Valneva;UK National Institute for Health Research; Dynavax	Inactivated vaccine	France, United States	
Noora	Noora	Recombinant protein vaccine	Baqiyatallah University of Medical Sciences	

As per government of India database (Co-WIN), till 28th February 2022, a total of 1,48,26,49,754 doses of AstraZeneca, Covishield (ChAdOx-1) and 28, 80, 80,355 doses of COVAXIN (BBV152) was administered.

as one of the most efficient armours in curbing the pandemic. Several candidate vaccines have been tried and tested in clinical trials. (Refer to Table 1). As of 25th March 2022, a total of 153 candidate vaccines are undergoing various phases of clinical trials, whereas 196 candidates are in pre-clinical development. [1] Based on variations in core ingredients and delivery systems, several types of vaccines such as mRNA-1273, viral vector replicating (VVr), viral vector non-replicating(VVnr), inactivated virus, live attenuated, protein subunit, DNA, virus-like particle, Bacterial antigen-spore expression vector, Despite their efficacy, the adverse events following vaccination have also been seen. [2–6] Many databases including Vaccine Adverse Event Reporting System (VARES), and VigiBase have been dedicated to report these adverse events. A large

spectrum indeed has been detected so far. In line with rheumatological, hematological, and cardiac adverse events, neurological complications following COVID19 vaccination have also been witnessed. [7–11].

1.1. Background

The wide array of neurological adverse events post-COVID-19 vaccination have included vaccine-induced immune thrombotic thrombocytopenia (VITT) and related cerebral thrombosis, [10,12,21–30,13–20] Guillain Barre Syndrome (GBS), [31–55,55–57], demyelination spectrum including, neuromyelitis optica spectrum disorders (NMOSD), [58]Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), [59]Multiple sclerosis (MS), [60–61] Acute disseminated encephalomyelitis (ADEM), [62–63] acute haemorrhagic encephalomyelitis (AHEM), [64], and optic neuritis. [65].

There has been anecdotal reports describing cases of Bell's palsy, [66–73] olfactory dysfunction, hyposmia, phantosmia, [74–76] oculomotor nerve palsy, [77–78] abducens nerve palsy, [79–80] cochleopathy, [81] tinnitus, [82] vertigo, [83] sudden sensorineural hearing loss, [84–85] encephalitis, [86–89] autoimmune encephalitis, [90–91] meningitis, [92–93] arterial stroke, [94–97] rhabdomyolysis, [98–99] myositis, [100–101] Parsonage-Turner syndrome, [102–106] small fibre neuropathy, [107] acute on chronic inflammatory polyneuropathy, [108] reversible radiculomyelitis, [109] myasthenia gravis, ocular myasthenia, [110–112] transient akathisia, [113] dysautonomia, [114–115] thunderclap headache, [116–118] reactivation of varicella zoster, [119–124]functional neurological disorders, [125–127] reversible cerebral vasoconstriction syndrome (RCVS), [128]Cytotoxic Lesion of the Corpus Callosum (CLOCCs), [129] Gastroparesis, [130] delirium, [131] New-onset refractory status epilepticus (NORSE), [132] non-convulsive status epilepticus, [133] Tolosa-Hunt Syndrome (THS), [134] triggering of moya moya phenomena in existing autoimmune disease, [135] and hypophisitis [136]. While the temporal relation of these adverse events to vaccination were observed, most of the reports couldn't establish causality.

The type of vaccine and dosing have differed significantly in different parts of the world. The World Health Organization (WHO) has approved nine vaccines so far, while the United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMA) have approved two and five vaccines respectively. The safety and side effect profiles of the individual vaccines are expected to show variation since they are biologically different compounds. [5,137] Many observations have shown the neurological complications in different populations with different types of COVID19 vaccines. India's vaccination drive against COVID19 is mostly based on two types of vaccines, i.e. AstraZeneca, Covishield (ChAdOx-1), and COVAXIN (BBV152). As per the government of India database (Co-WIN), till 28th February 2022, a total of 1,482,649,754 doses of AstraZeneca, Covishield (ChAdOx-1), and 28 8,0 80,355 doses of COVAXIN (BBV152) was administered. [138].

Based on this backdrop, we present here a series of 51 cases with various vaccine associated neurological disorders (VAN), temporally associated with vaccination against SARS-CoV2. For delineating the spectrum of the same, we also performed a systematic review of the available medical literature. The proposed hypotheses were reviewed, in accordance of which, the underlying pathophysiological mechanisms were highlighted.

2. Patients and methods

The study was conducted in a tertiary care hospital in India. Retrospective analysis of medical records of all patients who presented to the outpatient, inpatient or emergency services between 1st February 2021 and 30th June 2022 was done for identifying cases with VAN.

Recruitment of patients were conducted in two steps. As a first step, cases with any neurological illness, with a history of a recent vaccination against SARS-CoV2 (i.e. within 6 weeks of onset of the first symptom of neurological disorder), not otherwise explained by any alternate etiology [139] were segregated and then based on the following inclusion and exclusion criteria cases were selected.

Inclusion criteria comprised patients with a new onset neurological syndrome with a) history of first or second or booster dose of COVID-19 vaccination by any route or type, approved in India, b) the last dose of vaccination not beyond 6 weeks (42 days) (as per World Health Organization Global Advisory Committee on Vaccine safety- WHO GACVS) [139], and c) no history of any proven or radiologically suspected COVID-19 infection irrespective of severity, in the past 3 months. Patients with a) history of receipt of any other (non-SARSCoV2) vaccination in the past 6 weeks, b) presence of an alternate diagnosis, c) pre-existing active neurological disease, and d) relapse of a pre-existing neurological syndrome were excluded. Data were extracted with regards to the demographics, clinical examination findings as evaluated by a consultant neurologist, the type, dosing and route of COVID-19 vaccine, investigations, treatment strategies and clinical outcome. The details of investigations including lumbar puncture for cerebrospinal fluid (LP-CSF) analysis, serum with or without CSF anti-Aquaporin 4 antibody i.e. neuromyelitis optica (NMO) antibodies, myelin oligodendrocyte glycoprotein (MOG) antibodies (testing done with IgG1), creatinine phosphokinase (CPK), C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), magnetic resonance imaging (MRI) of the brain and/or spine, muscle MRI, nerve conduction studies, electromyography, evoked potentials including brainstem auditory evoked response (BAER), visual evoked potentials (VEP), somatosensory evoked potential (SSEP), serum and CSF autoimmune antibody profile (NMDA, VGKC, LGI-1, CASPR, GABA-A/B), serum antinuclear antibodies (ANA) profile, antineutrophil cytoplasmic antibodies (ANCA), serum myositis panel, and serum paraneoplastic antibody profile were considered. Other relevant investigations for the exclusion of alternative etiologies were recorded. (Refer to supplementary appendix).

In the second step, the cases were selected for analysis based on the causality label. This was done by two independent authors (SMM, SV) who were blinded to the study design. All selected cases in step 1 were subjected to the proposed criteria for casualty labelling as per the criteria proposed by Butler et al. [140] Accordingly, the cases were categorized to probable, possible and unlikely to be casually related to post-vaccination neurological complication. Only probable and possible cases were included for further analysis, whereas cases with "unlikely" causality association were excluded. Our retrospective recruitment strategy identified some cases of demyelination temporally associated with COVID-19 vaccination which were previously published from the institute (cases 1, 2, 6, 8, 10, 11, 13–15, 16, 17, 20–37). [59] In order to encompass the entire spectrum of COVID-19 vaccine related neurological complications, these cases were included. The cases were reported in accordance with consensus-based clinical case reporting (CARE) guidelines. [141]. Informed consent and ethical committee approval were obtained. A scoping review was done for all published articles pertaining to neurological manifestations following COVID vaccination using PUBMED, SCOPUS, EMBASE, Google Scholar, Ovid and MedRxiv till June 2022.

3. Statistical analysis

In the descriptive statistics, categorical variables were denoted as frequency with percentage while the continuous variables were expressed as median ± IQR and mean ± SD. The categorical variables in multiple groups were analysed with χ^2tests to look for any significant difference overall between the groups. If found significant, Fisher exact test was used to compare the two individual subgroups. The quantitative variables, in the three independent demyelination subgroups were tested for significance using one way ANOVA. If found significant, post-hoc analysis was done between the individual groups. A p value of < 0.05 was considered to be statistically significant. Inter-rater reliability was assessed using Cohen's kappa.IBM-SPSS Version 26 was used for the

Table 2
Enumerates the clinical details of the cases.

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
1	35	F	Body ache, headache, vomiting followed by altered sensorium and, inability to walk, excessive sleepiness and bladder retention. Known case of well controlled T2DM	10	ChAdOx-1/1st dose	9 days	Hypotonia in both lower limbs and lower limb power 2/5 with biceps, supinator and triceps hyperreflexia and knee and ankle hyporeflexia and left extensor plantar.	CRP, RA factor, ANA profile and ANCA- negative. LP-CSF: Cells- 58/hpf cells (50 L),protein- 47 mg/dl. VEP b/l and BAER, SSEPs – Normal. MRI of Brain and spine T2/FLAIR hyperintensities in mid brain, pons, left MCP, bilateral posterior internalcapsule, thalamus, bilateral centrum semiovale and longitudinally extensive transverse myelitis involving cervical cord and conus. **Serum MOG was positive**	MOGAD	IV MP (1gm) * 7daysFollowed Mycophenolate mofetil maintenance	Improved (mRS = 2)	Probable
2	34	M	Headache, right eye visual diminution	14	ChAdOx-1/1st dose	1 days	Rt eye- Visual acuity-perceptionof light present, Lteye 6 /18	CRP, RA factor, ANA profile and ANCA- negative. LP-CSF: Cells- 4/hpf cells (2 L),protein- 26.6 mg/dl. VEP-right eye prolonged P100 and BAER, SSEPs – Normal. MRI of Brain suggestive of right optic neuritis. Serum and CSF aNTI-AQ-4 ANTIBODY and MOG – Negative	Seronegative Optic neuritis	IV MP (1gm) * 5 days followed by oral prednisolone gradual tapering	Improved (mRS = 0)	Probable
3	27	F	Hiccups and vomiting, tingling numbness in all four limbs and decreased sensation over trunk and lower limbs, weakness in left upper and lower limbs, weakness in right upper limb and lower limb, spasms and pain in right upper limb and lower limb and neck	80	BBV152/1st dose	17 days	Right hemiparesis, Tone:- Tone increased in right upper and lower limbsRight upper and lower limb flexor spam present every 30 min. Right Biceps, triceps,knee,ankle jerks brisk, plantar no response b/l. Sensory- Touch, vibration, JPS impaired b/l Ul and LL.	ESR, and CRP – Elevated. LP-CSF: cells-2(lymphocytes-100 %) protein-23.8 mg/dlSSEP showed absence of wave forms. MRI of Brain and spine – s/o cervical myelitis and medullary involvement**Serum aNTI-AQ-4 ANTIBODY – Strongly positive.**	NMOSD	LVPP*5 cylcles f/ bRituximab	Improved (mRS = 1)	Probable
4	38	M	Urinary incontinence, and weakness in all 4 limbs. Known case of well controlled T2DM	4	ChAdOx-1/1st dose	14 days	Quadriparesis with brisk DTRs andsensory loss over V3 division of trigeminal nerve bilaterally, trunk (till C4 level) and all 4 limbs.	LP-CSF- 370 cells (80 percent neutrophils and 20 percent lymphocytes), protein 174 mg/dl. CSF OCB is positive, serum OCB is negative. ACE, RA factor, ANA profile and ANCA- negative. MRI of Brain and spine – longitudinally extensive transverse myelitis from cervico-medullary junction upto D1 and hyper intensity in left middle cerebellar peduncle and pons. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative	Seronegative CNS demyelination	IV MP (1gm) * 5 days followed by PLEX * 7 cycles followed by Rituximab	Mild Improvement (mRS = 2)	Probable
5	54	M	Tingling paresthesia of right Lower limb and associated with transient tonic posturing of right upper limb lasting for seconds.	6	ChAdOx-1/1st dose	14 days	Tone and power normal, brisk DTRs and flexor plantar response. Sensory examination normal.	MRI of Brain and spine – symmetrical T2/FLAIR hyperintensities in b/l corticospinal tract and, cerebral peduncles and middle cerebellar peduncle. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative	Seronegative CNS demyelination	Symptomatic management of paresthesia and antiepileptic	Improved (mRS = 0)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
6	36	F	Tingling parasthesia in both lower limbs, weakness of both lower limb and urinary symptoms	20	ChAdOx-1/2nd dose	32 days	Hypotonia with sluggish DTRs in lower limb and lower limb power 0–1/5, sensory loss till D4.	CRP, RF, ANA, ANCA and Paraneoplastic profile -negative. LP-CSF: 720 cells (lymphocytes-580, polymorphs-20, degenerated cells-120), elevated protein (144 mg/dl), elevated lactate (32 mg/dl) and normal glucose. VEPwas absent in right eye and prolonged in left eye. SSEP- absent wave forms LL and prolonged in UL. MRI of Brain and spine – longitudinally extensive transverse myelitis predominantly involving central and posterior cord sparing anterior part extending from obex till conus with cord swelling with left optic neuritis. **Serum MOG – Positive**	MOGAD	IV MP (1gm) * 5 days followed by PLEX * 7 cycles	Improved (mRS = 1)	Probable
7	30	M	Pain in the right eye and diminution of vision,and pain in left eye and diminution of vision.	13	ChAdOx-1/1st dose	14 days	Right RAPD was present. Right eye perception on light was absent. Left eye 6/60.Fundus showed bilateral papilledema grade 3 (right more than left)	ANA profile and ANCA were negative. Serum NMO MOG panel was negative. Viral markers were negative. CSF analysis showed 1 cell with normal protein. Evoked potentials showed bilateral absence of P100 and BAER and SSEP were normal. MRI brain showed optic nerves hyperintensities bilaterally with volume loss more on left side. MRI spine screening was normal.	Bilateral Optic neuritis	LVPP*5 cylcles f/b1gm IVMP*2 days f/b oral steroid and Rituximab	No improvement (mRS = 5)	Probable
8	50	F	Tingling paresthesia and both upper and right lower limbs weakness. Known case of hypothyroidism on treatment.	10	ChAdOx-1/1st dose	28 days	Right lower limb power 3–4/5, spastic and DTRs in right side, Knee and ankle jerks are brisk with right extensor plantar	ANA profile – PCNA 1 +.LP-CSF: Cells-2/hpf cells (2 L),protein- 28.3 mg/dl. MRI of spine C7 level short segment T2/FLAIR hyperintensities. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative	Short segment transverse myelitis	Oral prednisolone and mycophenolate mofetil	Improved (mRS = 1)	Probable
9	44	M	Imbalance while walking and vomiting, acute urinary retention, band like sensation and double vision	12	ChAdOx-1/1st dose	13 days	Quadriparesis with brisk DTRs andsensory loss over V3 division of trigeminal nerve bilaterally, trunk (till C4 level) and all 4 limbs.	LP-CSF: Lymphocytic pleocytosis with elevated proteinMRI of Brain and spine – T2/FLAIR long segment non expansile hyperintensities in the cervical and dorsal cord and conus medullaris with involvement of 2/3rd cross sectional area of cord. Serum SARS-CoV2 S1,S2 (IgG&IgM)-PositiveSerum MOG – Positive	MOGAD	IV MP (1gm) * 5 days followed by Mycophenolate mofetil	Improved (mRS = 0)	Probable
10	38	M	Vertigo, double vision on looking left, Imbalance while walking and blurring of vision in Right eye with Headache	26	ChAdOx-1/1st dose	6 days	Pupils:3 mm equal and reactiveV/A-6/9 in RE, 6/6 in LEFundus – NormalEOM: fullGaze evoked horizontal and torsional nystagmus.	CRP,RF, ANA profile and ANCA-Negative. LP-CSF- Traumatic tap. MRI of Brain and spine – patchy areas of demyelination in left MCP, right corona radiata with T2/FLAIR hyperintensity in right vestibular apparatus. VEP- Prolonged P100	CNS demyelination with Vestibulopathy	IVMP 1gm *5 days f/b oral steroid	Mild Improvement(mRS = 2)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
								latency and low amplitude BAER waveforms. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative				
11	53	F	Paresthesia of both lower limb, urinary hesitancy, paresthesia and tightness of both upper limbs over trunk,and band like sensation over chest. Known case of medically controlled hypertension since 1 year.	12	ChAdOx-1/2nd dose	1 day	Fine touch reduced bilaterally from toes to epigastrium and in bilateral medial part of forearm and middle and little fingersPain: decreased bilaterally from toes to epigastriumVibration: Absent on both sides till knee. Joint position sense: Absent in great toes, thumbs on both sides. Plantar: Bilateral extensor. Rhomberg s: Positive	ACE levels, ANA Profile, ANCA, CRP, RA Factor- Negative. LP-CSF showed 6 cells, 57 mg/dl protein. Serum anti-recoverin- Positive. MRI of Brain and spine – T2/FLAIR hyper-intensities in the bilateral periventricular white matter, bilateral insula and bilateral cerebellar hemispheres. Few short segment expansive T2 hyperintensities are noted in the cervical cordat C5,6,7 levels and dorsal cord at D6-7 level with involvement of central cord. SARS-CoV2 S1,S2 (IgG&IgM)-PositiveSerum and CSF aNTI-AQ-4 ANTIBODY and MOG – Negative	CNS demyelination	IVMP 1gm *5 days f/b oral steroid	Mild Improvement (mRS = 1)	Probable
12	35	F	Blurring of vision of both eyes, walking difficulty, mild pain thorax and breathing problem in supine position.	20	ChAdOx-1/2nd dose	14 days	Visual acuity-bilateral 6/9. E.O.M.-full. Pupils-bilateral 3 mm,pupils equally reactive to light. Lower limb power 3–4/5, Sensory-90 percent loss of pain,touch,temperature in bilateral lower limbs,bilateral upper limbs. 100 percent pain,touch, temperature sensation present in right side of face. Joint,position sensation, and vibration impaired in bilateral lower limbs.	ESR-raised, CRP,ANA-Negative. LP-CSF: cells-17(all lymphocytes), protein-64 mg/dlV.E.P.-left(P100-115.8), right(P100-125.7),prolonged S.S.E.P inlower limb(P37-43),normal S.S.E.P. in upper limb(N20-19.3)and normal value of ABR. MRI of Brain and spine – few short segment T2 hyperintensities in thecervical (C2-3 level) and dorsal cord (D1 to D3) with patchy heterogeneous enhancement. Posterior intra-orbital segment of bilateral optic nerves, optic chiasm and the bilateral proximal optic tracts also showed T2/ FLAIR hyperintensity with patchy contrast enhancement along with signal change in the hypothalamus, left trigeminal nerve (root entry zone and cisternal segment), right lateral medulla extending to the cervicomedullary junction. Serum aNTI-AQ-4 ANTIBODY and MOG – NegativeCSF OCB- Pattern 4.	Bilateral Optic Neuritis and Brainstem demyelination	LVPP*5 cylcles f/b1gm IVMP*5 days f/b oral steroid and Rituximab	Improved (mRS = 0)	Probable
13	30	F	Shock like sensation on flexing the neck and tingling paraesthesia of B/l hand	3 months	ChAdOx-1/2nd dose	15 days	Tone- Normal. Power-normal in U/L and L/L including intrinsic muscles of handReflexes −2Plantar bilateral-flexorSensory system −40 percent reduction in sensation to touch over both palms.	ESR-68 mm, ACE,RA, ANA profile-negativeMRI of Brain and spine – T2 hyperintensities short segment at C3 level. Evoked potentials are normal. Serum SARS-CoV2 S1,S2 (IgG&IgM)-Positive. CSF OCB- Positive. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative	Seronegative CNS demyelination	LVPP*5 cylcles f/b1gm IVMP*5 days f/b oral steroid	Improved (mRS = 0)	Probable
14	26	F	Weakness of bilateral lower limbs,sensory loss below the chest, urinary	4	BBV152/1st dose	5 days	Quadriparesis Sensory examination – absent sensation to touch and pin prick below T4 Level. JPS and	ANCA, RA factor, and CRP – negative. **ANA profile – anti PCNA strongly positive.** LP-CSF: cells-207	Seronegative CNS demyelination	LVPP*5 cylcles f/b1gm IVMP*5 days f/b oral steroid	Improved (mRS = 2)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
			retention, weakness and paresthesias of both upper limbs				vibrationimpaired in lower limbs. DTRs – upper limb 2, lower limbs absent	(lymphocytes-40 %, PMN-60 %), protein-95.8 mg/dlSSEP showed absence of wave forms. MRI of Brain and spine – long egment transverse myelitis from cervical region to lower lumbar region. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative				
15	27	F	Pain in left upper and lower limb and right lower limb, headache, weakness of left upper and lower limb and right lower limb	30	ChAdOx-1/ 1st dose	5 days	MotorGrade 1 spasticity in left upper limbPower- 5/5Tendon reflexes-3Plantars- Bilaterally flexorSensory-Touch, pain, joint position sense-Normal	ANA profile, ANCA, ACE – negative. LP-CSF: cells-0, protein-27.7 mg/ dlMRI Brain – multifocal mildly expansile discrete T2 heterogeneously hyperintense lesions without FLAIR suppression in periventricular white matter along lateral ventricles, subcortical -deep white matter of bilateral frontal -parietal – temporal lobes, right caudate nucleus body, right PLIC -adjacent thalamus. Larger lesion in bilateral corona radiata show peripheral diffusion restriction and peripheral thin rim of blooming on SWI. Post contrast enhancementin few lesions in bilateral periventricular -deep white matter. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative	Acute disseminated encephalomyelitis (ADEM)	IVMP 1gm*5 days f/b oral steroid	Improved (mRS = 2)	Probable
16	45	F	Bilateral visual loss	4	ChAdOx-1/ 1st dose	5 days	VA- Bilateral lowMotor, sensory, cerebellar- normal	RA factor, and ANA profile – negativeLP-CSF: cells-2(lymphocytes-100 %), protein-52.3 mg/dlVEP- b/l prolonged P100. CSF OCB- Negative. MRI of Brain and spine – No significant signal changes. **Serum MOG – Positive**	MOGAD	LVPP*5 cylcles f/b1gm IVMP*5 days f/b mycophenolate mofetil	Improved (mRS = 1)	Probable
17	20	F	Double vision	5	ChAdOx-1/1st dose	3 days	Brisk DTRs and mild spatic lower limbs.	CRP, RA factor, ANA profile and ANCA- negative. MRI of Brain multple discrete T2/FLAIR hyperintensities in pericallosal, callosal and frontal regions. Serum aNTI-AQ-4 ANTIBODY and MOG – Negative	Seronegative CNS demyelination	IV MP (1gm) * 5 days followed by oral prednisolone gradual tapering	Improved (mRS = 0)	Probable
18	55	F	Right lower limb pain and weakness and then after 2 month paresthesia left lower limbKnown case of medically controlled T2DM	60	ChAdOx-1/ 1st dose	2 days	Pupil, EOM- fullRight hemiparesisRight UL and LL DTRs brisk	ESR (57 mm) and CRP(11 mg/L) – elevated. ANA profile – Negative**Paraneoplastic profile: anti-Tr and anti-GAD65,** LP-CSF: cells-2(lymphocytes-100 %), protein-28.3 mg/dlSSEP showed absence of wave forms. MRI of Brain and spine – multiple T2 hyper intensities in the cervico-dorsal spine. CT abdomen, pelvis, thorax- negative for malignancy. Serum and CSF aNTI-AQ-4 ANTIBODY and MOG – Negative	Seronegative CNS demyelination	1gm IVMP*5 days f/b oral steroid	Improved (mRS = 1)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
19	16	F	Recurrent vomiting, burning sensation of both upper limbs, tremuloousness of b/l upper limbs, imbalance while walking, double vision and swallowing difficulty	90	BBV152/2nd dose	14	EOM: Bilaterally abduction, Upbeat nystagmus in all directions ofgaze. Bilateral LMN facial palsy. Trismus, jaw opening restricted. Power 4/5Cerebellar signs present b/l, DTRs brisk, plantar b/l extensorSevere gait ataxia	Serum ANA, ANCA negative. MRI brain-T2/Flair diffuse white matter hyper-intensities involving lower mid brain to C4 level of spinal cord. LP-CSF: nil cells-2, protein-28.0 mg/dl. Serum and CSF NMO was strongly positive.	NMOSD	LVPP*5 cylcles f/b1gm IVMP*5 days f/b oral steroid and Rituximab	Mild Improved (mRS = 3)	Probable
20	54	M	Imbalance, Dysarthria, weakness of both lower limbs, dysphagia	10	ChAdOx-/2nd dose	14	Dysarthria-scanningVA-Right eye-6/36,Left eye-6/36Tone- Hypotonia b/l LLPower- LL 4/5DTRs- BriskPlantar-Extensor b/lJPS- impairedCerebellar signs- present	ANA profile: AntiRNP,Anti JO 2 + ANCA,Serum.NMOMOG:negative. ESR was 90 mm/hr. MRI Brain:T2 /FLAIR patchy hyper intense lesion in pontine region	Seronegative CNS demyelination	1gm IVMP*5 days f/b oral steroid and Rituximab	Improved (mRS = 1)	Probable
21	29	F	Headache, Rt eyeblurring of vision	15	ChAdOx1nCoV-19 /1st dose	11	Rt: eye RAPD, VA –Rt: hand movementclose to face; Lt − 6/6	CSF: 0 cells, P:18 mg/dl, G: 61 mg/dl Serumand CSF OCB absentANA, ANCA, RAfactor, CRP -negativeSerum MOG- positiveVEP: Rt – absentwaveform, Lt – normalMRI brain: T2 /FLAIRhyperintensity of longintraorbital segment ofRt optic nerve withcontrast enhancement	MOGAD	Inj. MP 1 gm × 5 days 1 cycle ofLVPP T. Prednisolone 40 mg OD followedby taperingdoses	Improved (mRS = 1)	Probable
22	54	F	Progressive quadriparesis followed byaltered sensorium	42	ChAdOx1nCoV-19 /1st dose	14	Drowsy, not openingeyes, bl UL flexionposturing, quadriparesis with2/5 power in UL and0/5 power in LL.	CSF: 8 cellslymphocyticpredominant, P:77 mg/dl, G:98 mg/dlANA, ANCA, CRP-negative Serum NMOMOG-negative MRIbrain: T2/FLAIRhyperintensities in thecorpus callosum, blperiventricular andsubcortical whitematter, infratentorialregion with patchycontrast enhancement	ADEM	Inj. MP 1 gm × 5 days 5 cycles ofLVPP Inj. Iv Ig100 g T. Prednisolone 40 mg OD followedby taperingdoses	Mild Improved (mRS = 2)	Probable
23	44	M	Hiccups, vomiting, urinaryretention, doublevision, Imbalance onwalking	12	ChAdOx1nCoV-19 /1st dose	7	Lt VA: 6/9, Rt – 6/6. spasticquadriparesis, bilateral cerebellarsigns in UL	CSF: Lymphocytic pleocytosis with elevated protein. ANA, ANCA -negativeSerum and CSF MOGStronglypositive, MRI: T2 hyperintensities inthe cervico-dorsalcord and conus	MOGAD	Inj. MP 1 gm × 5 days 5 cycles ofLVPP T. Prednisolone 40 mg OD	Mild Improved (mRS = 2)	Probable
24	39	M	Rt eye painfollowed byblurring of vision	20	ChAdOx1nCoV-19 /1st dose	14	RT eye-RAPD, Rt VA: Finger counting at 2 m Visual field- rightinferonasal quadrantinvolvement	ANA, ANCA, APLA-negative, Serum MOG- positive, VEP- bl prolonged (Right-132 ms, left-115 ms) MRI: T2 /FLAIRhyperintensity of longintraorbital segment ofRt optic nerve withcontrast enhancement	MOGAD	Inj. MP 1 gm × 5daysT. Prednisolone 40 mg OD	Improved (mRS = 0)	Probable
25	54	M	Left eye blurringof vision	21	ChAdOx1nCoV-19 /1st dose	14	VA: Bl 6/12, Lt eyeRAPD present, Rteye-normal pupillaryreaction.	ANA profile anti Jo1 1 + positive, ANCA, VDRL-negative, VEP: Rt- 127 ms, Lt-absentwaveform Serum MOG–Strongly positive MRIbrain and spine: T2/FLAIR hyperintensityin Rt pons	MOGAD	Inj. MP 1 gm × 5 days T. Prednisolone 40 mg OD	Mild Improved (mRS = 1)	Probable
26	31	M	Bladderdisturbances followed byprogressivenumbness	5	ChAdOx1nCoV-19 /1st dose	14	Lower limbspasticity, paraparesis withpower 1/5, decreased sensationsby 70 % below L1, plantars extensor, ULDTRs-3 + and LL 2+	CSF: 370 cells -polymorphicpredominant, P: 174 mg/dl, G: 168 mg/dlANA profile, ANCA, VDRL, RA factor, CRPnegativeSerum	Seronegative CNS demyelination	Inj. MP 1 gm × 5 days T. Prednisolone 40 mg OD 7 cyclesof LVPP Inj. Rituximab 1 gm	Mild Improved (mRS = 2)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
			ofwhole body andLL weakness					andCSF NMO-MOG –negative VEP andBERA- normal, SSEP ofLt. LL prolonged (55.9 ms) MRI: long segmentcervico-dorsal T2/ FLAIR hyperintensitywith subtleenhancement				
27	20	F	Rt ULparaesthesiasfollowed byparaparesis &altered sensorium	2	BBV152 /1st dose	1	VA: Bl 6/6. LLproximal weakness (3/5), distal 4/5, DTRs- 3+, Rt LL50% decreasedsensation, PlantarsEquivocal	CSF: 8 cells -lymphocyticpredominant, P:24.9 mg/dl, G:61 mg/dlANA profile, ANCA, VDRL, RA factor, CRP-negative Serum andCSF NMO-MOGnegative, CSF OCB –Positive VEP, BERA, SSEP-normal MRI: few juxtacortical andshort segment cervicalT2/ FLAIRhyperintensity at C5level with subtleenhancement	Seronegative CNS demyelination	Inj. MP 1 gm × 5 days T. Prednisolone 40 mg OD 5 cyclesof LVPP	Mild Improved (mRS = 2)	Probable
28	33	F	Fever, vomitingfollowed byaltered sensoriumand persistentparaesthesias below midthoracic level	28	ChAdOx1nCoV-19 /1st dose	14	VA: Rt 6/12, Lt 6/9, Bl normal pupillaryreaction, no otherfocal deficits	CSF: 105 cells -lymphocyticpredominant, P: 28.12 mg/dl, G: 70.4 mg/dlSerum MOG –Stronglypositive MRI brain: T2/ FLAIRhyperintensity in Blfronto parietal region, no enhancement	MOGAD	Inj. MP 1 gm × 5 days T. Prednisolone 40 mg OD	Minimal improvement (mRS = 3)	Probable
29	60	M	Acute onsettingling paraesthesias andmotor weaknessin left upper andlower limb, followed bybehavioural andmemory disturbances	34	ChAdOx1nCoV-19 /2nd dose	14	MMSE-27/30 Cranialnerves-VA:R-6/6, L-6/9, nystagmuspresent Motorsystem-Power: normal,DTRs-brisk	CSF: 9 cells – 90 %lymphocytes, P:68.3 mg/dl, G:132 mg/dl, OCBs-negative ANA, ANCA,B12, Homocysteine,VDRLnegative, ACE-normalSerum NMO and MOG-negative, VEP-normalMRI brain: multiplefocal lesions in rightpons, midbrain, medial temporal lobes, splenium of corpuscallosum, high parietallobe with tumefactionand peripheralenhancement	ADEM	Inj MP 1 gm × 5 days T. Prednisolone 40 mg OD T. MMF (1gm)	Mild Improved (mRS = 2)	Probable
30	23	F	Burningparaesthesias inright palmassociated withnumbness andmotor weaknessfollowed byburning sensationin right foot overnext 7 days	41	ChAdOx1nCoV-19 /2nd dose	7	VA-6/6 Bl Cranialnerves-normal Motorsystem-normalSensory systemdecreasedvibrationalong distal rightupper and lower limbjoints	CRP- 23 mg/dl ANAnegativeSerum NMOand MOG-negativeCSF-OCB negative MRIbrain-T2/ flairhyperintensitiesadjacent to rightfrontal horn, ependymal margins ofbilateral lateralventricles MRI spineshortsegmenthyperintensities at C2-C3,C5,D4	SeronegativeCNS demyelination	Inj MP 1 gm × 5 days T. Prednisolone 40 mg OD	Minimal Improved (mRS = 3)	Probable
31	40	M	Blurring of visionfrom left eyefollowed by acuteurinary retentionnd right eyevision loss	77	ChAdOx1nCoV-19 /1st dose	10	VA- 6/18 Bl Cranial, motor and sensoryexamination-normal	CSF: 8 cells – 100 %lymphocytes, P:32 mg/dl, G:68 mg/dl, OCB-positive ANA, ANCA,VDRL-negative, Serum MOG-positive MRI brain: T2 Hyperintensities inpons, bilateralthalami, right frontalcortex MRI spinelongitudinallyextensive myelitisfrom C4-D3	MOGAD	Inj MP 1 gm × 5 days T. Prednisolone 60 mg OD T. MMF (2gm)	Mild Improved (mRS = 2)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
32	45	M	H/o feveraccompanied byurinary retentionand difficulty inwalkingprogressing toaltered sensorium	5	ChAdOx1nCoV-19 /1st dose	10	VA-6/6 BL Cranialnerves-normal Motorsystem-Tone andpower normal inupper limbs LLhypotonia, grade-0 power withhyporeflexia, plantars mute	CSF: 44 cells – 44 %lymphocytes, P:90.9 mg/dl, G:68 mg/dl, rabies CSF PCRNegativeVEP-L-141,R-129,BERA-normal, N20-normal, P37–40 (mildly prolonged), ANA-U1RNP-1+,CANCA-, Serum MOG –strongly positive S. NMO–Negative MRI of brain and spinehyperintensitiesinbrainstem, cervicodorsal cord andsupratentorial regionswith central cordswelling	MOGAD	INJ MP-5 days, LVPP 3 CYCLESTABWYSOLONE 40MG TAB MMF1.5 GM	Mild Improved (mRS = 1)	Probable
33	34	F	H/o recurrentvomiting andhiccupsprogressing toimbalance whilewalking	60	ChAdOx1nCoV-19 /2nd dose	36	Cranial nerves: Rightgaze evokednystagmus, restnormal Motorexamination::Toneand power normal, DTRs brisk BLSensoryexamination: pseudoathetosisLeft > Right,, Romberg's positive, Tandem gaitimpaired	CSF-1 cell,P-15,3 mg/dl, 63 mg/dl, OCBNegative ESR-46 mm/hr Serum NMO-weaklypositive Serum MOGnegativeANA:Ro-521+,ANCA-negativeMRI brain:T2hyperintensity indorsal aspect ofmedulla	NMOSD	I/V MP-5 daysLVPP-3 cyclesTab Wysolone40 mg InjRituximab	Mild Improved (mRS = 2)	Probable
34	31	M	H/o progressiveupper and lowerlimb tingling f/bdifficulty inwalking, urinaryurgency, andconstipation	17	ChAdOx1nCoV-19 /1st dose	42	Cranial nervesnormalUL motorexamination-normal, LL power-4/5,briskDTRs, extensorplantars Sensorylevel at T4	CSF: 32 cells – 100 %lymphocytes, P:49.2 mg/dl, G:74 mg/dlANA,ANCA, VDRL-negative, Serum NMOand MOG -negativeMRI brain: T2Hyperintensities incervicomedullaryjunction, right frontalsubcortical region MRIspine-cervical cord HIC2-C5,also in dorsalcord	SeronegativeCNS demyelination	I/V MP-5 daysLVPP-4 cyclesTab Wysolone40 mg Tab MMF1.5 gm	Mild Improved (mRS = 1)	Probable
35	52	F	H/o progressiveslurring of speechwith right upperlimb and lowerlimb weakness, followed byappearance ofswallowingdifficulty	51	ChAdOx1nCoV-19 /1st dose	35	Spastic anarthria + Gaze restrictedleft > right Rightfacial weaknessMotor examinationhypotonicrightupper and lower limbwith 0/5 power, leftsided power-5/5,BLDTRs brisk andplantars extensor	CSF-2 CELLS,P-40.5 mg/dl,G-56 mg/dlESR-18,CRP-POSITIVEANA,ANCA-Negative, VDRL-Negative S. NMO and MOGNegativeMRI brain: tumefactivedemyelination in leftfrontal hemispherewith insularinvolvement alongwith left more thanright midbraininvolvement	ADEM	I/V MP-5 daysLVPP-4 cyclesTab Wysolone40 mg InjRituximab	Minimal Improved (mRS = 3)	Probable
36	65	F	H/o urinaryretentionfollowed bynumbness andweakness of bothhands andblurring of visionof right eye	30	ChAdOx1nCoV-19 /1st dose	42	V/A-R- handmovements close toface, L-6/18 UL: motor examinationnormal LL: Power-0/5 DTRs absent in LLSensory level:T6	CSF-17 CELLS,P-49 mg/dl,G-59 mg/dlESR-97 ANA,ANCANegative, VDRLNegativeS.NMOStronglypositive S. MOG-Negative VEP-RNotrecordable, LNormalSSEP-LLabsent MRI brain: fewhyperintensities infrontal subcorticalwhite matter MRISpine: D2-D11hyperintensity withpatchy contrastenhancement andbright spotty areas	NMOSD	LVPP – 3 cyclesI/V MP-5 daysTab Wysolone40 mg Tab MMF1.5 gm	Mild Improved (mRS = 2)	Probable
37	20	F	H/o tingling intips of right handfollowed byprogressive imbalance whilewalking	24	ChAdOx1nCoV-19 /2nd dose	39	V/A-6/6 BL Motorexamination: Toneincreased in rightupper limb and lower limb Power − 5/5 inall 4 limbs DTRs: normal Plantar rightextensor and leftflexor Sensorysystem- Pain andtouch	CSF- 4 CELLS,P-23 mg/dl,G-111 mg/dl, CSF- OCB + ANA-,ANCA-,CRP-13 mg/dl,,EBV-IGG + S.NMO and MOG-NegativeMRI brain: hyperintensities in BLjuxtacortical, subcortical, periventricular whitematter,	CNS Demyelination- MS	I/V MP-5 daysTab Wysolone40 mg InjRituximab	Mild Improved (mRS = 1)	Probable

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Table 2 (*continued*)

Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
Demyelination												
							decreased by10 percent in rightupper and lower limbJPS normal Vibrationnormal Rombergpositive Gait ataxic	anteriortemporal lobes as wellas infratentorialregions includingpons, MCP andmedulla MRI Spine: short segment lesionsin cervical and dorsalspine				
38	23	F	Heaviness in the legs followed by weakness of both legs over 7 days	13	ChAdOx1nCoV-19 /2nd dose	1	VA-Right- 6/24, Left- 6/9Power- UL 5/5, LL-0–1/5, DTRs- BriskPlantars-B/l extensorPain touch decreased below T4, JPS- impaired in LL	ANA screening positive (1:80 titres), and anti sm-RNP 2 positive. CSF −9 cells (all lymphocytes) with normal protein and glucose. Serum and CSF NMO- MOG strongly positive for NMO. MRI spine – long segment transverse myelitis in thoracic spinal cord.	NMOSD	LVPP*5 cylcles f/b1gm IVMP*2 days f/b oral steroid and Rituximab	Mild Improved (mRS = 1)	Probable
39	28	M	Right eye visual loss	12	ChAdOx1nCoV-19 /1st dose	11	RAPD right eyeVA- right 6/36, left-6/6	LP-CSF- Normal cell and proteinMRI Brain-Intraneural T2WI-FLAIR hyperintensity noted involving right optic nerve intraconal & intracanalicular segments.	SeronegativeCNS demyelination	IVMP*5 days f/b oral steroid	Mild Improved (mRS = 1)	Probable
Guillain Barre Syndrome												
40	34	F	Numbness in both upper and lower limbs, weakness in all limbs, speech disturbances and swallowing difficulty. Is a known patient of Rheumatoid arthritis since 2014. Currently asymptomatic since 2 years, not on any medication.	10	ChAdOx-1/ 2nd dose	14 days	Bifacial weakness present. tongue movements reduced. Tone: hypotonia in all 4 limbs. Quadriparesis, global areflexia	NCS- Motor axonopathyLP-CSF: Albuminocytological dissociation (cells-Nil, protein-147.0 mg/dl) LFT, RFT, Serum electrolytes, CBC, homocysteine,folate, Vit B12, thyroid function test were within normal limits. Antiganglioside antibody IgM, IgG negative. Serum Rheumatoid factor elevated (33 Iu/ml)	Guillain Barre Syndrome	LVPP * 7 cycles	Improved (mRS = 2)	Probable
41	34	F	Weakness of both lower limbs, weakness of both upper limbs and paresthesias of all 4 limbs	20	ChAdOx-1/ 2nd dose	3 days	Tone: hypotonia in all 4 limbs. Quadriparesis, global areflexia	NCS- Axonal and demyelinating neuropathyLP-CSF: Albuminocytological dissociation (cells-Nil, protein-123.6 mg/dl) ANA profile, ANCA, ACE levels and anti-ganglioside antibodies werenegative. Urine for Bence jones proteins was negative. Serum Rheumatoid factor elevated (33 Iu/ml)	Guillain Barre Syndrome	LVPP * 7 cycles f/b IVMP 1gm * 5 days	Improved (mRS = 2)	Probable
42	44	M	eakness of both upper and lower limbs, and paresthesias of all 4 limbs	10	ChAdOx-1/ 1st dose	16 days	Tone: hypotonia in all 4 limbs. Quadriparesis, global areflexia	NCS- Axonal and demyelinating neuropathyLP-CSF: Albuminocytological dissociation (cells-Nil, protein-75.7 mg/dl) ANA profile, ANCA, ACE levels and anti-ganglioside antibodies werenegative. Urine for Bence jones proteins was negative. Serum Rheumatoid factor elevated (33 Iu/ml)	Guillain Barre Syndrome	IvIg 0.4 g/kg/day * 5 days	Improved (mRS = 1)	Probable

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Table 2 (*continued*)

Demyelination												
Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
Stroe												
43	16	F	Headache followed by right upper and lower limb weakness with slurred speech	3	BBV152/1st dose	5 days	right upper and lower limbs spastic hemiparesis	MRI- acute infarcts in left MCA territory with left M1 MCA occlusionESR-51mmPlatelet-57Lakh/cmmPT,INR,aPTT-NormalANA Profile, ANCA- NegativeFasting lipid profile-Normal panelHbA1C,FBS, PPBS-NormalSickling test-NegativeCardiac evaluation-Normal	Acute ischemic stroke	Statin, antiplatelet and antioedema measures	Status quo (mRS = 3)	Probable
44	35		Headache and left upper limb and face paresthesia and weaknsess	2	ChAdOx-1/ 2nd dose	10 days	left upper and lower limbs spastic hemiparesis	MRI- venous sinus filling defect involving the anterior 2/3rd of the superior sagittal sinus and bilateral frontal and parietal infarctESR-12 mm, CRP- NegativePlatelet-376Lakh/cmmPT,INR,aPTT-NormalPCV-NormalHomocysteine, Vitamin B12-Folate- Normal. Fasting lipid profile-Normal panelHbA1C,FBS,PPBS-NormalCardiac evaluation-Normal	Cerebral Sinus Venous Thrombosis	Anticoagulation	Status quo (mRS = 3)	Probable
45	80	M	Sudden onset right upper and lower limbs weakness.	1	ChAdOx-1/ 1st dose	15 days	Right hemiparesis	MRI-left basal ganglia infarctPlatelet-96Lakh/cmmaPTT-79secCRP-Negative) D-dimer-1381 ng/mlFibronogen- 443 mg/dlFasting lipid profile-Normal panelHbA1C,FBS, PPBS-NormalCardiac evaluation-Normal	Acute ischemic stroke with coagulopathy	Statin, antiplatelet	Status quo (mRS = 4)	Probable
46	56	M	Sudden onset left upper and lower limbs weakness	2	BBV152/1st dose	14 days	left upper and lower limbs spastic hemiparesis	MRI- right MCA-PCA territory watershed infarctPlatelet-254Lakh/cmmPT,INR,aPTT-NormalFasting lipid profile-Normal panelHbA1C,FBS, PPBS-NormalCardiac evaluation-Normal	Acute ischemic stroke	Statin, antiplatelet	Status quo(mRS = 3)	Probable
47	65	M	Tingling paresthesia of left half of the body. Known case of medically well controlled dyslipidemia and T2DM	4	BBV152/1st dose	3 days	Tone, power-normal	MRI- right thalamic infarctPlatelet-293Lakh/cmmPT,INR,aPTT-NormalFasting lipid profile-Normal panelHbA1C,FBS,PPBS-NormalCardiac evaluation-Normal	Acute ischemic stroke	Statin, antiplatelet	Status quo (mRS = 1) (mRS = 1	**Possible**
48	55	M	Headache, and right upper and lower limbs weakness. Known case of medically controlled hypertension	1	ChAdOx-1/ 2nd dose	2 days	Right spastic hemiparesis	MRI-Acute infarct noted involving left corona radiata, posterior putamen and posterior limb of internal capsule. And Eccentric vessel wall enhancement noted involving left MCA distal M1 and M2 segment (inferior division). Platelet-275Lakh/cmmPT,INR,aPTT-NormalCRP-6 mg/dl(Positive) Fasting lipid profile-Normal panelHbA1C,FBS, PPBS-NormalCardiac evaluation-Normal	Acute ischemic stroke	Statin, antiplatelet	Status quo (mRS = 4)	**Possible**

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Table 2 (*continued*)

Serial No	Age (years)	Gender	Presenting Complaints	Total Duration (days) of Illness	Type of Vaccine/dose	Interval from last vaccination to the onset of first neurological symptoms	Examination finding	Investigations	Diagnosis	Treatment	Prognosis	Causality label[$]
Demyelination												
Encephalitis												
49	23	F	Irrelevant talkConfusion and disorientation	2	ChAdOx-1/ 1st dose	2 days	Alopecia, knuckle hyperpigmentationMMSE:9/ 30Speech- suggestive of transcortical sensory aphasiaNo meningeal signsEOM- fullPupils- Equal, reactive to lightOther cranial nerves- normalSensory, motor, cerebellar signs- negativeGait- normalPlantars- flexors	CRP-24 mg/L. Serum homocysteine-132 umol/LVitamin B12- 50 pg/ml (low) LP-CSF: cells-14(PMN-10), protein-27.5 mg/dl. Normal sugar. HSV and other viral agents including chikunguniya, AFB staining, culture sensitivity. ANA profile, ANCA, serum and CSF autoimmune encephalitis panel, RF, creatine kinase, TFT, lipid profile, viral markers including HIV, HbSAg, HCV, VDRL were all normal or negative. Serum dengue and chikunguniya was negative. EEG showed bilateral intermittent slowing (Left more than right). MRI of Brain and spine – left temporal lobe FLAIR hyperintensity suggestive of cerebritis. Serum lactate was persistently elevated (70 mg/dl).	Possible Postvaccinal encephalitis with pre-existing possible mitochondrial cytopathy with primary hyper homocysteinemia	Acyclovir 500 mg iv TID × 7 daysCeftriaxone 1gm iv BD × 7 daysAnd Inj Methyl prednisolone 1gm iv OD × 5 daysFollowed by mitochondrial supplements and oral steroid.	Improved (mRS = 1)	**Possible**
50	52	F	Pain in the both lower limbs and Stiffness of both lower limbs	360	ChAdOx-1/ 2^2nd dose	7	Severe spasticity (grade 4) in both lower limbs(left > right) Plantar- b/l extensor	LP-CSF: nil cell, protein-26.7 mg/dl. ANA profile- anti- SS-A and AntiRo-52 positive. Serum and CSF NMO-MOG were negative. Paraneoplastic antibody- Anti GAD65 ab strongly positive. MRI Brain and Spine: Unremarkable. Whole bodyPET MRI: Normal tracer uptake	Stiff Person Syndrome	Oral steroidDiazepamBaclofen	Mild Improved (mRS = 2)	Probable
Myositis												
51	58	M	Pains of both lower limbs, weakness of both lower limbs, weakness of both upper limbs.	60	BBV152/1st dose	15 days	Wasting of bilateral supraspinatus, ifraspinatus, deltoid, biceps, and triceps was noted. Tone- Hypotonia in all 4 limbs. Quadriparesis, proximal and flexor group predominant weakness in UL and LL. DTRs- Hyporeflexic	ESR was 22 mm/hr and CRP was positive**Serum Creatine kinase (CPK) was elevated (13,786 U/L at presentation).** Urine routine showed 2 plus blood and myoglobin was positive. **ANA profile showed anti-RO52 1plus positive. Myositis profile showed anti-SRP 3 plus positive**. Muscle biopsy: polygonal to rounded, myofibers with moderate variation in fiber size and prominent features of active myopathy in the form of myonecrosis. ACR/ EULAR2017: Definite myositis	Inflammatory Myositis	IVMP 1gm *5days f/b Rituximab	Improved (mRS = 1)	Probable

computation of these statistics.

4. Results

In the given timeframe a total of 4672 medical records were reviewed, out of which 109 cases were identified. Subsequently, 51 cases (probable, n = 48 and possible, n = 3) were included as per causality assessment based on the criteria by Butler et al by two independent authors SMM and SV Cohen's kappa was 0.73 and inter-rater agreement was 86.24 %. Amongst these 51 patients, CNS demyelination (n = 39, 76.5 %) was the most common. This was followed by three cases of GBS (5.9 %), six cases of stroke (11.8 %), two cases (3.9 %) of encephalitis and a single case of myositis (Tables 2 and 3). Female sex was slightly higher than the male counterpart (F:M, 1.13:1). The mean (±SD) age was 40.1 ± 14.5 years. Majority of the patients belonged to the age group between 25 and 45 years (26, 51.0 %). Majority of the patients received ChAdOx-1 nCoV (COVIShield) vaccine (n = 43, 84.3 %) while the rest of the patients received BBV152 (COVAXIN) (n = 8, 15.7 %). The frequency of neurological complications was higher after the first dose (n = 37, 72.5 %) as compared to the second dose (n = 14, 27.5 %). The latency to the onset of neurological symptoms was 14 (IQR 5.5 to 15) days from the first dose and 12 (IQR 3.3 to 14) days from the second dose. Overall, the latency was 13.2 ± 10.7 days from the last dose of vaccination. Majority of the patients presented in the second week after vaccination (n = 20, 39.2 %).

4.1. Demyelination (patient 1–18)

Out of 39 cases with CNS demyelination majority had received ChAdOX-1 vaccine (n = 39, 76.5 %). Majority of the patients were of female sex (F:M, 1.3:1). The mean age of presentation was lower compared to that of overall age in this series (37.8 ± 12.6 years vs 40.1 ± 14.5 years). Majority of the patients belonged to the group of 25 to 45 years. (Tables 2 and 4)The median interval from the last dose to the onset of the neurological symptoms was 13 (10to14) days. Majority of the cases were vaccinated with COVIShield (ChAdOx1) vaccine (n = 35, 89.7 %). The clinical manifestations occurred after first dose in 29/39 (74.4 %) cases. Majority of the cases were seronegative (n = 23, 59.0 %) which was followed by MOGAD (n = 11, 28.2 %) and NMOSD (n = 5, 12.8 %). LETM was the most common mode of presentation (n = 19, 48.7 %). ON was the presentation in 9/39 cases (23.1 %) cases. Interestingly, none of the cases of NMOSD presented with ON. Neuroimaging showed supratentorial lesions in 16/39 (41.0 %) cases while infratentorial lesions were present in 15/39 (38.5 %) cases. (Figs. 1 and 2) As per casuality labelling, all cases were found to be probable temporal association. CSF analysis revealed pleocytosis in 19/37 (77.8 %) and elevated CSF protein in 14/37 (37.8 %), respectively. Favorable mRS scores (0to1) were attained by 21/39 (81.9 %) patients at discharge. There was no significant difference with regards to the latency to presentation, investigational profile or clinical outcomes among the various demyelination subgroups. (Refer to Table 4)

4.2. Guillain-Barré syndrome (patient 40–42)

Patients with a diagnosis of GBS constitutes 10.3 % (3/29) of the total post COVID19 vaccination related neurological diseases. All of them had received ChAdOx-1 vaccine. The mean age of presentation was higher (44.3 ± 10.5 years) than the overall mean age (40.1 ± 14.5 years). Out of three cases, two were female and first clinical symptom started after a mean of 11.0 ± 7.0 days from last vaccination. All three of them had albumin-cytological dissociation with a mean CSF cell of 0 and protein of 115.2 ± 36.2 mg/dl. Nerve conduction studies of sampled nerves were suggestive of motor axonopathy in one case (case 40) and mixed axonal and demyelinating neuropathy (case 41 and 42) in two cases. All patients were treated with large volume plasma exchange for five cycles. One of the patients had favorable mRS at discharge. (Refer to Tables 2 and 3).

4.3. Stroke (patient 43–47)

Out of six cases of stroke, three (50 %) had received ChAdOx-1 and 3 (50 %) were vaccinated with BBV152 vaccine. Based on the [125] criteria for causality labeling four patients were considered as probable vaccine related event. The mean age of presentation (51.1 ± 22.6 years) was higher than the overall mean. Majority of the patients were of male sex (F:M 1:5). They experienced first symptoms after a mean interval of 8.2 ± 5.6 days post vaccination. The spectrum comprised three cases of anterior circulation arterial stroke, and single case each of posterior circulation, watershed infarct and venous stroke. Two cases (Case 47 & 48) were considered to have possible associations since they had vascular risk factors which were well controlled at the time of onset of symptoms. Two cases (33.3 %) had thrombocytopenia and coagulopathy. None of the cases had any definitive evidence of Vaccine induced immune thrombotic thrombocytopenia (VITT) based on American Haematology Society guidelines. Patients were treated as per standard treatment protocols. At discharge, one of the patients (16.7 %) had favorable mRS (0to1). (Refer to Table 3).

4.4. Encephalitis (n = 2)

Patient 49: A 23-year-old lady developed encephalopathy-two days after first dose of ChAdOx 1 vaccination. Brain MRI revealed T2/FLAIR hyperintensities with areas of diffusion restriction predominantly involving cortical grey matter of left parahippocampal gyrus, amygdala, lateral temporal lobe, parieto-temporal junction in a gyriform pattern on left side and deep grey matter of left pulvinar nucleus. (Fig. 3). LP-CSF analysis showed polymorphonuclear cells with predominant pleocytosis with normal protein and sugars. Extensive evaluation for CSF and serum viral markers were unremarkable. Electroencephalogram showed bilateral intermittent slowing (left more than right). Serum and CSF autoimmune mosaic panel were negative. She was empirically treated with antivirals and as there was no response, steroids were started following which she improved completely. Hence a diagnosis of possible post-COVID19 vaccination autoimmune encephalitis was considered.

Patient 50: A 52-year-old lady presented with pain in the bilateral lower limbs and stiffness, 7 days post vaccination with ChAdOx-1 (second dose). Examination revealed severe spasticity in both the lower limbs and extensor plantar response. Secondary work-ups revealed strong positivity for anti-GAD-65 antibody. Neuroimaging including brain and spine MRI, CSF analysis, serum and CSF NMO/MOG antibody titres were negative. PET-MR brain was normal. She was diagnosed as Stiff person syndrome. She was treated with oral steroids and symptomatic measures. At discharge, she made a mild recovery to mRS of 2.

4.5. Myositis (n = 1)

Patient 51: A 58-year aged male, developed myalgia and progressive weakness of limbs, 15 days post-BBV152 vaccination. He presented to us 2 months after symptom onset and was wheel chair bound at the time of admission. He had Creatine Kinase value of 13786U/L with anti-SRP-antibody positivity, hence diagnosed as definite inflammatory myopathy (ACR/EULAR 2017) [142]. Muscle MRI was suggestive of myositis. PET MRI showed increased tracer uptake in the muscles without any sign of malignancy. (Fig. 4) He was treated with intravenous methylprednisolone pulse therapy followed by rituximab 6 monthly regime. At 6 months follow-up, patient was ambulant with mild support. (Refer to Table 3).

5. Discussion

In this series of 51 cases, we present multiple neurological diseases which were found to be temporally associated with COVID19

Table 3
Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN).

	Overall	CNS Demyelination	GBS	Stroke	Encephalitis	Myositis
Number of cases (%)	51	39 (76.5)	3 (5.9)	6 (11.8)	2 (3.9)	1 (2.0)
Demographics						
Mean Age(±SD)	40.1 (14.5)	37.8 (12.6)	44.3(10.5)	51.1(22.6)	37.5(20.5)	
Age group < 25 years	8 (15.7)	6 (15.4)	–	1(16.7)	1 [50]	–
Age group 25–45 years	26 (51.0)	23 (59.0)	2(66.7)	1(16.7)	–	–
Age group 46–60 years	14 (27.5)	9 (23.1)	1(33.3)	2(33.3)	1 [50]	1
Age group > 60 years	3 (5.9)	1 (2.3)	–	(33.3)	–	–
Female/Male	27/24	22/17	2/1	1/5	Both females	Male
Female: Male	1.13:1	1.29:1	2:1	0.2:1		
Vaccine details						
COVIShield (ChAdOx1)(%)	43 (84.3)	35 (89.7)	3 [100]	3 (50.0)	2 [100]	0
COVAXIN (BBV152) (%)	8 (15.7)	4 (10.3)	0	3 (50.0)	0	1 [100]
First dose (%)	37 (72.5)	29(74.4)	2(66.7)	4(66.7)	1(50.0)	1 [100]
Second dose (%)	14 (27.5)	10(25.6)	1(33.3)	2(33.3)	1(50.0)	–
Timelines						
Mean interval from last dose (in days ± SD)	13.2 (10.7)	14.6 (11.6)	13.(5.8)	8.2 (5.6)	5.5(2.1)	–
Median interval (days) from first dose (IQR)	14 (5.5–15)	14	9.5	9.5	–	–
Median interval (days) from second dose (IQR)	12 (3.3–14)	14	14	6.0	–	–
1st week	14 (27.5)	9 (23.1)	1(33.3)	2(33.3)	1	–
2nd week	20 (39.2)	17 (43.6)	1(33.3)	2(33.3)	1	–
3rd week	6 (11.8)	3 (7.7)	1(33.3)	1(16.7)	–	–
4th week	1 (2.0)	1 (2.6)	–	0	–	–
>4 week	10 (19.6)	9 (23.1)	1(33.3)	1(16.7)	–	–
Mean duration of disease (in days ± SD)	29.5(52.9)	26.4(24.8)	13.3(5.8)	2.2(1.2)	–	–
Causality label						
Probable (%)	48(94.1)	39 [100]	3 [100]	4(66.7)	1 [50]	1
Possible (%)	3(5.9)	–	–	2(33.3)	1 [50]	–
Clinical outcomes						
Favourable (mRS 0–1) (%)	25 (49.0)	21 (53.8)	1 (33.3)	1 (16.7)	1 [50]	–

vaccination. Vaccination-associated neurological diseases are well known in the medical literature. Several vaccines, such as influenza, rabies, mumps-measles-rubella (MMR), yellow fever have reported neurological adverse events. [143] However, presence of coexisting confounding factors enhances the risk of false association of any adverse event to a particular vaccine. For instance, several series of post-vaccination GBS were reported following mass vaccination against novel A/NJ/76 (Hsw1N1) influenza, the association which was later refuted in a few observations. [144,145] Similarly, measles vaccines were claimed to be associated with the development of autism, [146] the same was clearly rejected in subsequent studies. [147–148].

In the current scenario, when the mass vaccination campaign is underway with the majority of the world population are in the process of vaccination [149], the coincidental occurrence of a disease, can lead to false labelling of a condition as a vaccine related adverse outcome. Multiple types of vaccines from different manufacturers, different routes of administration, and administration of vaccine candidates in different phases of clinical trials (i.e., phase III or IV) have added to the existing dilemma of causality labelling of AEFIs. (Refer to supplementary appendix). In due course of time, with evolving evidence from larger studies, some of the reports of vaccine-related adverse events get refuted as was seen with sudden sensorineural hearing loss post COVID-19 vaccination. [150–152] A higher incidence, well and above the background incidence of a given clinical entity can serve as an important surrogate marker of a probable vaccine induced association. Post-vaccination GBS had an approximately-four times the higher incidence among Ad26.COV2.S recipients, with an estimated rate of 9.8 cases per million doses. [43,143] Association of ChadOx1 nCoV-19/AZD1222 and Ad26.COV2.S vaccines to a small risk of thrombotic thrombocytopenia, [153–154] and myocarditis with mRNA vaccines, BNT162b2, [155] are pointed out in many observations. In India, the adenoviral vector vaccine was mostly used. We found three cases of vaccination associated with GBS over 1 year, when a total of 1,48,26,49,754 doses of AstraZeneca, COVIShield (ChAdOx-1), and 28, 80, 80,355 doses of COVAXIN (BBV152) are already administered. This implies the incidence of the event lies within the usual incidence of GBS. [156].

In contrast to the higher association of the mRNA-based vaccine with demyelination as shown in the systematic review of 32 cases of post-COVID19 vaccination-associated demyelination, we found a majority (16/18, 69.6 %) to be associated with adenoviral vector vaccine (ChAdOx-1). The similar female predominance, the median age of presentation, median interval from the last dose, and clinical presentation as pointed out in the review are also observed in our series. Similar to previous studies, the most common antibody associated with post-vaccination demyelination in our study was MOG. [59,157–158]. MOG associated demyelination has been reported to occur following vaccinations with Japanese encephalitis, tetanus, measles, rubella etc. Various mechanisms proposed are autoantibody production due to molecular mimicry, induction of autoreactive T cells via bystander activation due to ongoing response against vaccine antigen or adjuvant. Vaccines may also cause unmasking of a preexisting autoimmune disorder [59]. Our series on post-vaccination stroke revealed coagulopathy in two cases, wherein vaccine induced thrombocytopenia, could be a potential consideration. The more frequent occurrence of the neurological events among the ChAdOx-1 recipients could probably be the reflection of the more widespread administration of the ChAdOx-1 vaccine in India. [138].

5.1. Spectrum of COVID vaccine associated neurological symptoms (Co-VAN)

The spectrum of the neurological diseases associated with COVID19

Table 4
Characteristics of cases with CNS demyelination.

	MOGAD	NMOSD	Seronegative Demyelination	p value
Number of cases (%)	11 (28.2)	5 (12.8)	23 (59.0)	–
Demography				
Mean Age (±SD)	41.5 (7.0)	37.25 (19.0)	23.1 (21.7)	0.566
Age < 25 years (%)	0	2 [40]	4(17.4)	0.111
Age 25–45 years (%)	10(90.9)	2 [40]	11(47.8)	0.038*#
Age 46–60 years (%)	1(9.1)	0	8(34.8)	0.106
Age > 60 years (%)	0	1 [20]	0	–
Gender (Female:Male)	4:7	All females	13:10	–
Vaccine details				
COVIShield (ChAdOx1) (%)	11 [100]	3 (60.0)	21 (91.3)	–
COVAXIN (BBV152) (%)	0	2 (40.0)	2 (8.7)	
First dose (%)	10 (90.9)	2 (40.0)	17 (73.9)	0.096
Second dose (%)	1 (9.1)	3 (60.0)	6 (26.1)	
Timelines				
Median latency from last vaccination (IQR) (days)	13 [10–14]	17 [14–36]	14 [4–14]	0.309
Median interval (days) from 1st dose (IQR)	12 [10–14]	29.5(23.3–35.8)	14 [5–14]	0.097
Median interval (days) from 2^n dose (IQR)	32	14(7.5–25)	10.5(2.5–14)	0.528
1st week (%)	1(9.1)	1 [20]	7(30.4)	0.379
2nd week (%)	7(63.6)	1 [20]	9(39.1)	0.211
3rd week (%)	2(18.2)	1 [20]	0	0.096
4th week (%)	0	0	1(4.3)	0.700
>4 week (%)	1(9.1)	2 [40]	6(26.1)	0.344
Mean duration of disease (in days ± SD)	20.5 (20.0)	54.6 (32.6)	23.1 (21.7)	0.019*$
Causality label	All probable	All probable	All probable	
Investigations				
CSF				
Pleocytosis (%)	7/9 (77.8)	2/5 (40.0)	10/22 (45.5)	0.217
Protein elevation (%)	4/9 (44.4)	1/5 (20.0)	9/22 (40.9)	0.636
MRI				
LETM	6/11 (54.5)	4/5 [80]	9/23 (39.1)	0.228
ON	5/11 (45.5)	–	4/23 (17.4)	0.081
Supratentorial lesion	4/11 (36.4)	2/5 (40.0)	10/23 (43.5)	0.924
Infratentorial lesion	3/11 (27.3)	3/5 (60.0)	9/23 (39.1)	0.457
Outcome				
Favourable (mRS 0–1) (%)	7/11 (63.3)	2/5 (40.0)	12/23 (52.2)	0.658

* Denotes p value < 0.05.
$ p value of 0.023 between MOGAD and other demyelination; p value of 0.023 between NMOSD and other demyelination.
# p value of 0.014 between MOGAD and rest of the demyelination group; p value of 0.631 between NMOSD and rest of the demyelination group and 0.111 between other demyelination group and combined NMOSD and MOGAD.

vaccination is yet to be completely explored. Reports of COVID19 vaccine-related adverse events have been tabulated for providing an updated list of neurological diseases attributed to the receipt of COVID-19 vaccine. (Refer to Table 5 Refer to Figs. 5 and 6) (Refer to supplementary appendix for detailed search terms) Although the causality label wasn't justified in many of these reports, awareness of the smallest possibility of any adverse event could enable prompt recognition in subsequent cases. Presence of clustering or detection of signals of AEFI would prompt further investigations. In the current context, an individual developing any neurological illness after the COVID19 vaccination could potentially satisfy-one or more of the following: a) COVID19 vaccine-associated disorder, b) remote COVID19 infection-related, or "long COVID" with vaccination as a bystander, c) vaccine component induced idiosyncratic reaction, d) occurrence of the disease due to the presence of risk factors and/ or vaccination associated triggering, e) expected occurrence of the disease with vaccination as a bystander, or f) immunization stress-related response. (Refer to Fig. 3 for details) (Refer to Supplementary appendix for vaccination related terms).

5.2. Pathogenesis

AEFI may occur due to vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, immunization stress-related reaction, or an unrelated incidental event. Although the underlying pathomechanisms are yet to be completely elucidated, based on the available limited observations and hypotheses the following possible mechanisms are proposed. (Refer to Fig. 7).

5.2.1. Autoimmunity

Similarity of vaccine component with human protein can lead to the production of antibodies which are directed against host's own protein. This mechanism is known as molecular mimicry. [159] Genetic

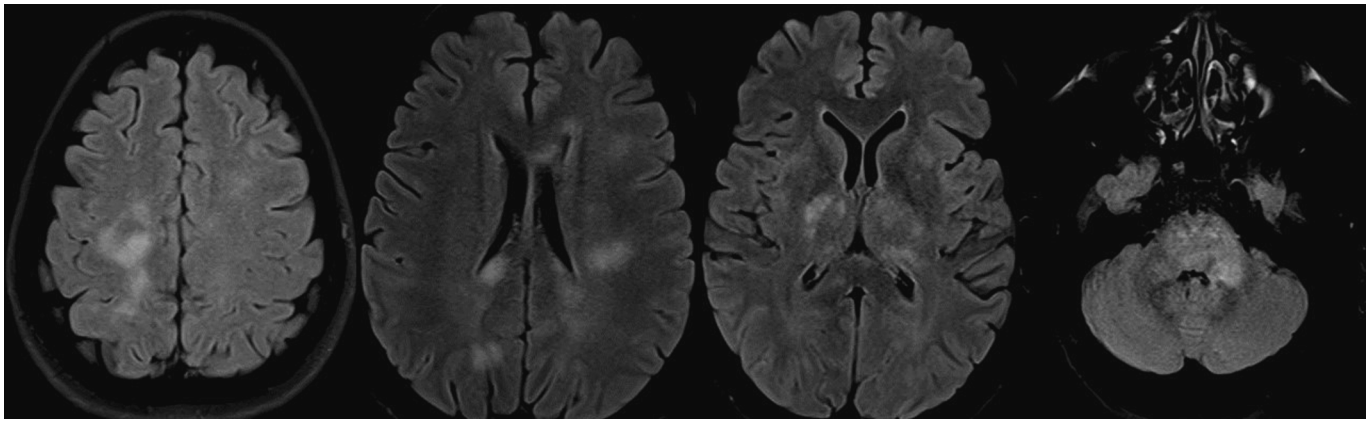

Fig. 1. MRI brain T2/FLAIR shows hyperintensities in mid brain, pons, left MCP, bilateral posterior internal capsule, thalamus, bilateral centrum semiovale in a case of MOGAD. (Case 01).

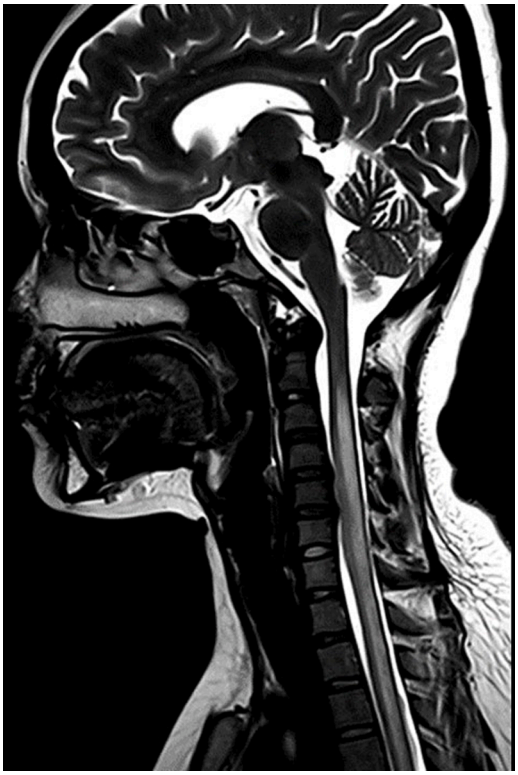

Fig. 2. MRI spine T2 weighted image shows longitudinally extensive cervico-dorsal cord hyperintensities in a case of probable post vaccination myelitis. (Case 14).

predisposition and pre-existing antibodies may recognize the vaccine components and adjuvants which can activate the mast cells leading to degranulation, and hypersensitivity reactions including anaphylaxis. Vaccine adjuvants may also activate the inflammasome pathway leading to interleukin productions and subsequent activation of nuclear factor kB, Th17, and Th1 cells. [160–161] Antibody dependent COVID-19 enhancement has also been attributed to be one of the pathophysiology of the post-vaccinal complications. [162–163].

5.2.2. Theory of anti-idiotype antibodies

SARS-CoV2 virus uses its spike protein (S) to bind to the angiotensin-converting–enzyme 2 (ACE2) receptors on the target cell. Viral infection and its vaccines mount antibodies to the S protein which is called as Ab1. A distinctive sequence in the complementarity-determining region 3 (CDR3), of the idiotype portions of the Ab1 binds and neutralizes the S protein. Subsequently, these antibody-binding regions get down-regulated through generation of antibody responses against themselves which is called anti-idiotype (Ab2) antibodies.

Ab2 antibodies bind to the earlier formed protective neutralizing Ab1 antibody, which results in immune-complex formation and clearance. This impairs the Ab1 efficacy. As the Ab1 is directed against the S protein and the Ab2 is directed against the Ab1, a few binding regions, or paratopes of Ab2 antibodies mirror the S protein. Hence, the Ab2 binds to the same target as the S protein would bind, i.e. the ACE2 receptor. This Ab2-ACE2 interaction blocks the ACE2 function by competitive inhibition of the normal ligand interactions. As Ab2 is an immune response, it may persist even after the original antibody gets cleared off and may lead to the long term adverse events. [164–165].

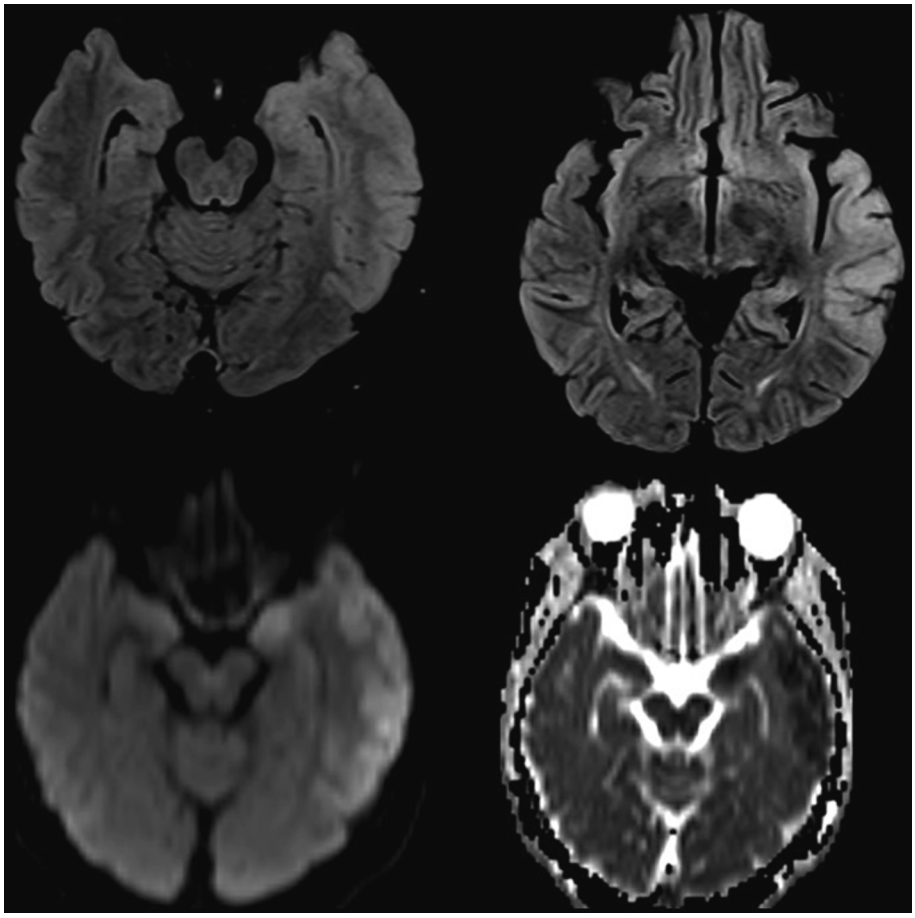

Fig. 3. MRI brain T2/FLAIR hyperintensities with restricted diffusion predominantly involving cortical grey matter of left parahippocampal gyrus, amygdala, lateral temporal lobe, parieto-temporal junction in a gyriform pattern on left side and deep grey matter of left pulvinar nucleus. (Case 28).

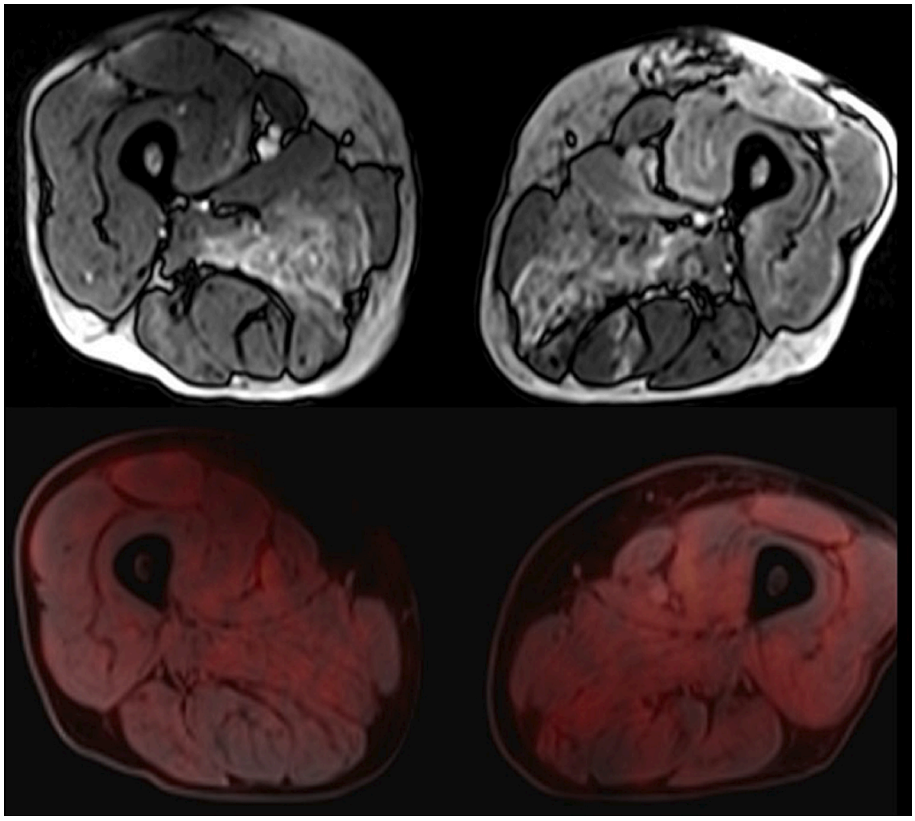

Fig. 4. Muscle MRI shows T2 hyperintensities in the muscles of the anterior, posterior & adductor compartment of thigh bilaterally. 18FDG-PET shows increased tracer uptake in the muscles of the anterior, posterior & adductor compartment of thigh bilaterally.

Table 5
CO-VAN study: scoping review of literature. Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN) – a review of the literature.

Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
Guillain Barre Syndrome						
Fernandez et al. 2021 [31]	Pfizer-BioNTech (BNT162b2) = 22Moderna (mRNA1273) = 9AstraZeneca (ChAdOx1) = 3Janssen = 3 andJohnson & Johnson = 1	GBS	24 cases	1st	7 days (average)	7 patients had CSF albuminocytological dissociation, andAll had a predominant demyelinating pattern
Maramattom et al. 2021 [32]	AstraZeneca (ChAdOx1) = 7	GBS	Seven cases of GBS	1st	2 weeks	All patients developed severe GBS. The frequency of GBS was 1.4- to 10-fold higher than that expected.
Woo et al. 2021 [43]	Jannsen (Ad26.COV2.S) = 130	GBS	Median age = 56 years; (IQR, 45–62 years)		Median time to onset of GBS following vaccination = 13 days (IQR, 10–18 days)	Estimated absolute rate increase of 6.36 per 100 000 person-years
Dang et al. 2021 [52]		Miller-Fisher Syndrome and Guillain-Barre Syndrome overlap syndrome	63/M	1st	9 days laterExperienced new-onset lower back pain and 5 days after developed bilateral oculomotor nerve palsy, ataxia, facial diplegia and lower limb weakness. Later developed diplopia on lateral gaze bilaterally. Examination revealed impaired adduction, restricted upward gaze and intorsion with down gaze bilaterally, consistent with partial cranial nerve III palsies.	LP-CSF: Protein- 2.99 g/L Cells- 5/hpf: Albuminocytological dissociation. NCS- long-standing axonal neuropathy with reduced motor and sensory amplitudes. EMG- and length-dependent chronic neurogenic changes. MRI Brain- enhancement of the facial and oculomotor nerves bilaterally. Serum anti-GQ1b antibody- negative. Showed partial improvement with IvIg 2 g/kg over 5 days.
Kim et al. 2022 [53]	Pfizer-BioNTech (BNT162b2)	Pediatric Case of Sensory PredominantGuillain-Barré Syndrome	16/F	2nd	2 days afterAscending numbness and paresthesia of her bilateral lower and upper extremities	MRI – mild thickening and enhancement of the anterior and posterior spinal nerve roots of the cauda equine. LP-CSF: 1cell/cmm, Protein- 112 mg/dlNCS- prolonged latency and slowed conduction velocity in multiple sensory and motor nerves
David et al. 2021 [54]	Pfizer-BioNTech (BNT162b2)	Recurrence of GBS	Out of 702 patients of previous GBS, 1 had recurrence.	NCS s/o sensorimotor demyelinating polyneuropathy. Was treated with PLEX and improved.		
Demyelination						
Ismail et al. 2022 [60]	Pfizer-BioNTech (BNT162b2) = 11AstraZeneca (ChAdOx1) = 8Moderna (mRNA-1273) = 6Sinovac/ Sinopharm = 5 Sputnik = 1Johnson&Johnson = 1	Transverse myelitisADEMMS-like illnessNMOSD	32 cases of with demyelination. Female predominance (68.8 %) and median age of 44 years.	71.8 % occurred after the first dose of the vaccine, with a median of 9 days.	Types: Transverse myelitis = 12/32MS-like pictures (first diagnosis or a relapse) = 12/32ADEM- like 5/32NMOSD- like = 3/32.	Most MS-like episodes (9/12) were triggered by mRNA-based vaccines, TM occurred following both viral vector and mRNA-based vaccines.
Netravathi et al. 2022 [59]	AstraZeneca (ChAdOx1) = 27COVAXIN (BBV152) = 2	MOGAD& other demyelinations	Myelitis = 11, Optic neuritis = 6, Acute demyelinating encephalomyelitis = 5,	MOG positive = 10Postvaccinial cases were found to have a significantly higher-Mean age,		

(*continued on next page*)

Table 5 (*continued*)

Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
			Brainstem demyelination = 3, andMultiaxial involvement = 4	Presence of encephalopathy (p value:0.0007), CSF pleocytosis (p value: 0.0094) andRaised CSF protein (p value: 0.0062).		
Chen et al. 2021 [58]	Inactivated virus vaccine	NMOSD	A middle aged female	1st	After 3 days of vaccine developed mild fever, vomiting, diarrhoea, cough and unsteadiness and dizziness.	MIR Brain- area postrema and bilateral hypothalamus lesions without Gd enhancement. Investigations: leucopenia of 2.36 × 109/Land positive antibodies for AQP4, ANA, SSA, SSB, Ro-52, and p-ANCA. CSF- Mononuclear pleocytosis with normal protein and negative OCB. Treated with intravenous steroid pulse and patient responded well.
Khayat-Khoei et al. 2021 [61]	Pfizer-BioNTech (BNT162b2) = 4Moderna (mRNA-1273) = 3	Exacerbation of known stable MS = 4, New onset MS = 2, New onset NMO = 1	24 to 64 (mean 39.1) years. Male = 2, Female = 5	First (n = 2), Second(n = 5)	1–21 daysSymptoms: visual loss, dysmetria, gait instability, paresthesias, sphincter disturbance, and limb weakness.	All responded to corticosteroid (n = 7) or plasma exchange (n = 1) therapy.
Arnao et al. 2022 [65]	AstraZeneca (ChAdOx1)	Bilateral optic neuritis	A middle aged female,	After 2 weeks	First dose of vaccine. Developed headache and painful blurred vision worsened by movement in both eyes, decreased bilateral vision acuity.	MRI of the brain in FLAIR axial showed increased signal of the left optic nerve. LP-CSF analysis normal cells and protein. Aquaporin 4 (AQP4)-IgG and MOG-IgG negative. Treated with intravenous steroid pulse and patient responded well.
Ancau1 et al. 2022 [64]	AstraZeneca (ChAdOx1)	Acute HemorrhagicEncephalomyelitis (AHEM)	61Y/M	1st	2daysp/w- fever, headache and apathy followed by seizure and coma.	MRI Brain- bilateral confluent cortical and subcortical FLAIR hyperintense lesions with haemorrhagic involvement of the basal ganglia. CSF- revealed normal cell counts (1 leukocyte per μl) and moderate disturbance of the blood–brain-barrier. Treated with PLEX and IVMP, poorly responded.
			25Y/F	1st	9 days. P/w severe cephalgia, thoracic back pain, mild weakness and ascending numbness in her legs.	MRI- longitudinal edema throughout the thoracic spinal cord exhibiting mild contrast enhancement as well as focal central haemorrhages and brain showed bi-hemispheric white matter lesions with focal contrast enhancement. CSF- granulocytic pleocytosis
VITTS and associated strokes: CSVT						
Sangli et al. 2021 [26]	Moderna (mRNA-1273)	VITTS with CSVT	65/F	2nd	10 days after. With symptoms of headache, lower limb discomfort and breathing difficulties.	She was found to have catastrophic thrombosis including deep venous and cerebral sinus venous thrombosis.
See et al. 2022 [27]	AstraZeneca (ChAdOx1) Janssen (Ad26.COV2.S)	VITTS and venous and/or arterial ischemic strokes/ intracerebral haemorrhage	Younger age (median age 46), female preponderance and 12 days as median time after vaccination are reported.	Vaccine-induced immune thrombotic thrombocytopenia (VITT) is mainly reported in adenovirus vector based vaccines, ChAdOx1 CoV-19 vaccine and Ad26.COV2.S. According to VARES data the incidence of VITT is approximately 1 in 263,000		

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Table 5 (*continued*)

Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
				recipients of Ad26.COV2.S. (PMID 35,038,274)		
Krzywicka et al. 2021 [30]	AstraZeneca (ChAdOx1) Jannsen (Ad26.COV2.S) Pfizer-BioNTech (BNT162b2) Moderna (mRNA-1273)	CVST	**Vaccine types**	**Absolute risk of CVST within 28 days of per million of first-dose vaccination**	**The absolute risk of CVST with thrombocytopenia within 28 days of per million of first-dose vaccination**	Age group between 18 and 24 years had the highest absolute risk of CSVT, with thrombocytopenia (7.3 per million, 95 % CI 2.8–18.8) or without thrombocytopenia (3.7 per million, 95 % CI 1.0–13.3).
			ChAdOx1 nCov-19	7.5 (95 % confidence interval [CI] 6.9–8.3)	4.4 (95 % CI 3.9–4.9)	
			Ad26.COV2.S	0.7 (95 % CI 0.2–2.4)	0.7 (95 % CI 0.2–2.4)	
			BNT162b2	0.6 (95 % CI 0.5–0.7)	0.0 (95 % CI 0.0–0.1)	
			mRNA-1273	0.6 (95 % CI 0.3–1.1)	0.0 (95 % CI 0.0–0.2)	
Stroke-Arterial						
Author	**Vaccine type**	**Neurological diseases**	**Age/Sex**	**Dose of vaccine**	**Interval from last dose**	**Description and observation**
Walter et al. 2021 [94]	AstraZeneca (ChAdOx1)	Thrombosis of Carotid Artery	31/M	1st	8 days. with acute headache, aphasia, and hemiparesis.	MRI brain showed main stem occlusion of middle cerebral artery. Had elevated D-dimer, normal platelet and fibrinogen level. Positive IgG PF4 antibody.
Tiede et al. 2021 [95]	AstraZeneca (ChAdOx1)	Ischemic stroke-arterial	Ischemic stroke in ICA and MCA territory with haemorrhagic transformation in one patient and another had cortical infarctions and aortic arch thrombi. Both had thrombocytopenia, increased D-dimer level, and positive anti-PF4 antibody.			
Al-Mayhani et al. 2021 [96]	AstraZeneca (ChAdOx1)	Strokes	3 patients with MCA infarct, ICA infarct and CVST, and MCA infarct respectively. All had thrombocytopenia, positive anti-PF4 antibody, and increased D-dimer level.			
Cari et al. 2021 [97]	AstraZeneca (ChAdOx1), Jannsen (Ad26.COV2.S)	Post vaccinal thrombosis	Most of the ChAdOx-1 and Ad26.COV2.S vaccine associated venous thrombotic serious adverse events were not associated with thrombocytopenia.			
Bell's Palsy						
Burrows et al. 2021 [66]	Pfizer-BioNTech (BNT162b2)	Sequential contralateral facial nerve palsies	61/M	1st	5 h. Developed unilateral LMN facial palsy.	2 days after the 2nd dose – contralateral LMN facial palsy. Significant improvement with oral steroid course in either occasions.
Wan et al. 2022 [67]		**Number of cases**	**Age-standardised incidence** (cases per 100 000 person-years)	**Age-standardiseddifference for the incidence compared with the background population**	**Equivalent to additional cases per 100 000 people**	**Odds ratio**
	CoronaVac	28	66·9	41·5	4.8 cases	2·385 (95 % CI 1·415 to 4·022)
	Pfizer-BioNTech (BNT162b2)	16	42·8	17·0	2·0 cases	1·755 (0·886 to 3·477)

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
Olfactory dysfunction						
Author	**Vaccine type**	**Neurological diseases**	**Age/Sex**	**Dose of vaccine**	**Interval from last dose**	**Description and observation**
Konstantinidis et al. 2021 [74]	Pfizer-BioNTech (BNT162b2)	Hyposmia	42y/F	2nd dose	3 days after presented with decreased olfactory ability.	Showed partial improvement on olfactory testing after olfactory training with four odors (lemon, rose, eucalyptus, and cloves).
			39y/F	2nd dose	5 days of 2nd dose of vaccine presented with hyposmia.	Improved within a week after the initial assessment.
Keir et al. 2021 [75]	Pfizer-BioNTech (BNT162b2)	Phantosmia	57y/F	2nd dose	Complaining of constantly ‘‘smelling smoke’’ and headaches. Associated with hyposmia to additional odorants and was affecting her quality of life.	CTA postcontrast showed a faint enhancement of left olfactory tract. MRI brain – Asymmetric enlargement and increased T2 hyperintensity in the left olfactory bulb and tract extending posteriorly and thickened, clumped olfactory nerve filia.
Vestibulo-cochlear nerve dysfunction						
Jeong et al. 2021 [84]	AstraZeneca (ChAdOx1)	Sudden sensorineural hearing loss	64/F	1st	1 day afterSudden hearing loss in the right ear.	Initially treated with oral steroid and followed by intratympanic steroid following which had complete recovery
	Pfizer-BioNTech (BNT162b2)		42/M	1st	Same daysudden hearing loss in the left ear	Responded oral steroid and followed by intratympanic steroid injection.
	Pfizer-BioNTech (BNT162b2)		18/M	2nd	2 days aftersudden hearing loss in the right ear	Temporal magnetic resonance imaging showed normal findings. Detriment on steroid therapy.
Parrino et al. 2021 [82]	Pfizer-BioNTech (BNT162b2) = 3	Tinnitus	37y/F	1st dose	7 h after had right ear tinnitus	
			63/M	1st dose	20 h after had left tinnitus associated to hyperacusis and dysacusis,	
			30y/M	2nd dose	1 week after vaccine presented with left tinnitus, hyperacusis and dysacusis.	
P -T Tseng et al. 2021 [81]	AstraZeneca (ChAdOx1)	Cochleopathy	37Y/M	1st dose	5 h. Iintermittent, right ear, high-pitch tinnitus which progressed into continuous high-pitch tinnitus and disturbed the normal hearing along with fever and myalgia.	Audiological evaluation s/o cochleopathy. Responded to short course of steroid.
Zhao et al. 2021 [85]	Sinovac Coronavirus vaccine = 2	SNHL	30Y/M, and 64Y/F	1st dose	4 daysDeveloped hearing loss in the right ear with tinnitus and dizziness.	CT temporal bone and MRI brain were normal. Blood investigations were not remarkable. Poorly responded to vitamin B12 and steroid.
Mauro et al. 2022 [83]	Pfizer-BioNTech (BNT162b2) = 23	Objective vertigo = 16Subjective vertigo = 14Dizziness = 3	Associated *ENT* symptoms: Hearing loss = 4 Tinnitus = 6Ear fullness = 2Hypersensitivity to noise = 1	No presence of nystagmus = 7Presence of horizontal or rotatory nystagmus = 9Presence of positive HST/ “central HINTS” or vertical or oblique nystagmus/ “central HINTS”= 17	Probable clinical diagnosis: No presence of vestibular impairment or central etiology of vertigo/dizziness = 7Benign paroxysmal positional vertigo = 9Probable central etiology = 17	
	AstraZeneca (ChAdOx1) = 5					

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
	Moderna (mRNA-1273) = 4 Jannsen (Ad26.COV2.S) = 1					
Abducens nerve palsy						
Author	**Vaccine type**	**Neurological diseases**	**Age/Sex**	**Dose of vaccine**	**Interval from last dose**	**Description and observation**
Reyes-Capo et al. 2021 [79]	Pfizer-BioNTech (BNT162b2)	Abducens nerve palsy	59Y/F		2 days, after vaccineAcute binocular and painless, horizontal diplopia. And had h/o fever for 1 day.	Mild elevation in ESR and CRP. MRI and other blood investigations were unremarkable. Had persistent deficit on follow up.
Pawar et al. 2021 [80]	AstraZeneca (ChAdOx1)	Recurrent Abducens nerve palsy	23Y/M	1st	1 weekWith sudden-onset diplopia along with severe headache of 1 week's duration. On examination had left esotropia with limited abduction of the left eye (LE 6th cranial nerve palsy)	MRI and blood investigations were unremarkable. Improved in follow up. H/o 2 episodes of similar 6th nerve palsy, one 5 years back following a febrile illness and another 2 years back following chicken pox.
Oculomotor nerve palsy						
Cicalese et al 2021 [77]	Moderna (mRNA-1273)	Third cranial nerve palsy	88/M	1st	3 daysWith objective dizziness, diplopia andgait instability. k/c/o IHD, HTN, Paroxysmal AF. Non diabetic.	Brain CT scan, CT angiographyand MRI ruled out a vascular accident. Treated with oral steroid, made complete recovery. Later vaccinated again with different vaccine at different injection site.
Kerbage et al. 2021 [78]	Pfizer-BioNTech (BNT162b2)	Oculomotor nerve palsy	84/F	1st	1 day, Presented with mydriasis, ptosis, and a "down and out" gaze.	MRI Brain (plain) normal. Serum anti AChR Ab, ANA screening and EMG were unremarkable. Treated with prednisone 40 mg daily for 5 days, followed by valacyclovir 500 mg twice daily for 7 days. On 2 months follow up patient improved completely.
Encephalitis						
Zuhorn et al. 2021 [86]	AstraZeneca (ChAdOx1)	Postvaccinal Encephalitis (Possible Autoimmune Encephalitis)	21/F	1st	1 day afterdeveloped headache and progressive neurological symptoms includingattention and concentration difficulties starting on day 5 after vaccination, resulting in admission to hospital11 days after vaccination. Subsequently had seizure.	MRI Brain- NormalCSF- 46 leukocytes/cmm(lymphocytic). EEG- diffuse abnormally slow thetarhythms without epileptiform activity. Responded to steroid therapy.
			63/F	1st	2 days later diagnosed to have DVT in left left- started on anticoagulation. 6 days post vaccination – gait deteriorated, she developed a vigilance disorder and a twitching all over her body. Later developed severe	MRI Brain- NormalCSF- 115 leukocytes/cmm(lymphocytic). EEG- diffuse abnormally slow theta and delta rhythms without epileptiform activity. No response to initial antibiotic therapy. Later, Responded to steroid therapy.

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
					immobilizing opsoclonusmyoclonus syndrome.	
			63/M		8 days afterisolated aphasia and fever.	MRI Brain- NormalCSF- 7 leukocytes/cmm (lymphocytic). Testing for neurotropic viruses in serum and CSF- Negative. EEG- NormalResponded to steroid therapy.
Baldelli et al. 2021 [87]	AstraZeneca (ChAdOx1)	Hyperacute reversible encephalopathy	77/M	1st	1 day afterConfusion and agitation consistent with delirium with extreme agitation. k/c/osarcoidosis and polymyalgiarheumatica in clinical remission with Methylprednisolone 4 mg/day. Mild COVID-19 five months prior to vaccination.	CRP- elevatedEEG – moderate diffuse slowingCT (contrast)- unremarkableCSF: cell-3, protein-119 mg/dl, glucose-52 mg/dl, IL6-194(high), IL8-162(high) Microbiological testing on CSF-negativeCSFoligoclonal bands, CSF and serum autoimmune encephalitis antibodies, serum onconeural, antinuclear and antineutrophil cytoplasmic antibodies: Negative. Responded to intravenous methylprednisolone pulse therapy.
Moslemi et al. 2022 [88]	AstraZeneca (ChAdOx1)	Herpes simplex encephalitis	27/M	1st	3 days aftersevere headache and altered mental status began to appear, including slowed psychomotor activity and loss of alertness. Subsequently severeheadache, agitation, delirium, and disorientation	LP-CSF: protein levels (3.05 mg/dl), WBC count of 600 per mm3 (predominance of lymphocyte) CSF HSV PCR- +veMRI brain and EEG- Unremarkable. Treated with antiviral, and improved over 21 days.
Al-Mashdali et al. 2021 [89]	Moderna (mRNA-1273)	Acute hyperactive encephalopathy	32/M	1st	2 days afterdeveloped acuteconfusion, memory disturbances, and auditory hallucination	EEG showed features of encephalopathy, CSF: elevated protein levels (0.76 gm/L, reference range = 0.15–0.45) with average cell counts (white blood cells of 3 u/L) and glucose levels., MRI brain-UnremarkableCSF autoimmune encephalitis (including anti-aquaporin-4, anti-myelin basic protein, anti-myelin oligodendrocyte glycoprotein, anti-glial fibrillary acidic protein, anti-NMDAR, anti-GAD, andother autoimmune encephalitis antibodies) was negative. Responded to intravenous steroid pulse therapy.
Autoimmune Encephalitis						
Zlotnik et al. 2022 [91]	Pfizer-BioNTech (BNT162b2)	LGI-1 associated autoimmune encephalitis	48/M	2nd	2.5 weeks later, Started to have memory deficits and anterograde amnesia. O/E- Montreal Cognitive Assessment (MoCA) score of 18/30	Serum sodiumlevel of 132 mEq/ L (normal range 135–145), Tumor markers (CEA, AFP, CA125, CA19–9, CA15–3) andParaneoplastic neuronal antibodiesincluding anti-Hu, Ri, Yo, Ma/Ta, Amphiphysin, CV2, SOX1, Tr (Euroimmun) were negative. EEG-UnremarkableMRI Brain – intense signal on both medial temporal lobes (more on the left) including theparahyppocampal gyrus on T2/FLAIR and DWI. Whole body CT- liver cyst and adrenal adenoma. CSF-Cell, protein and sugar normal. CSF- LGI-

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
						Ab + Treated with methylprednisolone (1gramdailyfor5consecutivedays) with a good response.
Shi et al. 2022 [90]	AstraZeneca (ChAdOx1)	Autoimmune encephalitis	35/F	1st	5 days afterDeveloped dysarthria, abnormalMovements, extreme anxiety, and reduced voluntary movements	MRI brain- mild swelling of the right hippocampus without abnormal enhancementin contrast-enhanced fluid-attenuated inversion recovery (FLAIR) and T1-weightedimages. CSF- WBC-37/cmm (poly 67.6 %, mono 32.4 %)CSF- RBC-14800/cmmCSF-Protein- 50.7 mg/dl, Glucose-68 mg/dlSerum paraneoplastic antibodies, anti-myelin oligodendrocyte (MOG) antibody, serum and CSF synaptic antibodies, serum antiganglioside anti-bodies, and CSF oligoclonal band: Negative. Treated with weekly rituximab.
Meningitis						
Fernandes et al. 2021 [92]	AstraZeneca (ChAdOx1)	Ascetic Meningitis retention syndrome	61/F	1st	18 daysWith headache, fever, paresthesias of the calves and thighs bilaterally and an unsteady gait, diplopia, and urinary retention. O/E: Neck stiffness +	MRI brain- non-enhancing, nonspecific deep white matter lesions. CSF – 200 WBCcells per mm3 with lymphocytic predominance, Mildly elevated protein (65 mg/dl, reference 12–60 mg/dl) and glucose CSF to serum ratio of 0.5. Infection work up and paraneoplastic panel were negative. Treated with IV steroid, responded partially.
Kang et al. 2022 [93]	Pfizer-BioNTech (BNT162b2)	Ascetic Meningitis	32/M	2nd	2 week afterHeadache for 1 week, O/E: Neck stiffness +	LP-CSF: Cells-480/cmm(90 %Lymphocyte) Protein- 118 mg/dlSugar- 56 mg/dl (RBS-91 mg/dl) No response to intravenpus acyclovir. Responded to methylprednisolone.
Myositis						
Author	**Vaccine type**	**Neurological diseases**	**Age/Sex**	**Dose of vaccine**	**Interval from last dose**	**Description and observation**
Faissner et al. 2021 [100]	Moderna (mRNA-1273) = 12	Myositis	28Y/F,	1st dose	5 days after the first dose of vaccine presented with muscle pain of herthigh muscles, radiating to the lower legs, accompanied by an asymmetrical weakness of the lower limbs. Creatine kinase (CPK) was 17,959 U/l (normal range 26–140 U/l).	Myositis profile was negative. MRI muscles- left-dominant edematous signal alterations with contrast enhancement of the quadriceps muscles sparing the M. rectus femoris, and diffuse subcutaneous fluid retention with contrast enhancement, suggestive of fasciitisTreated with steroid, patient improved.
Maramattom et al. 2021 [101]	AstraZeneca (ChAdOx1) = 3	Inflammatory myositis	74/M	1st	48hoursPresented with a 3-week history of intermittent low-grade fever and polyarthralgia. ESR-123 mm/hr (<15 mm/ hr) CRP-269 (<5mg/L) CPK-24 (25 – 170 U/L) ANCA- negativeANA-	18FDG-PET-CT: a tree-root-like uptake pattern in the lower limbs suggestive of small–medium vessel vasculitis. Whole-body short tau inversion recovery (STIR)-MRI showed diffuse ill-defined muscle hyperintensities suggestive of inflammatory myositis. EMG- fibrillations,

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
					negativeMyositis profile-negative	positive sharp waves, and complex repetitive discharges in the distal leg muscles. Skin and muscle biopsy showed features of small–medium vessel vasculitis. Remission achieved with oral steroid therapy.
			75/F	1st.	2 days afterFever, arthralgia, myalgia, tachycardia. ESR-120 (<15 mm/ hr) CRP-271 (<5mg/ L) CPK-30 ((25 – 170 U/L) ANCA-negativeANA- negativeMyositis profile- negative	18 FDG-PET CT- Day 25; Diffuse patchy minimallyincreased FDG avidity in skeletal muscles moreevident in lower limb. Arteries show 'tree root'patterns. MRI – Day 27-Multiple patchy areas of STIRhyperintensity involving the muscles of both thighsincluding all compartments, posterior compartment ofboth legs and pelvic girdle. Treated with Oral Prednisolone 1 mg/ kg + Mycophenolate mofetil. Achieved remission.
			80/F	2nd	2 days. Fever, fatigue, tachycardia. CPK-40 ((25 – 170 U/L) ESR-59 (<15 mm/ hr) CRP-102 (<5mg/L) Myositis profile/ ANCA- negative.	MRI- Hyperintense signal in STIR MRI in mostmuscles of both upper and lower limbs. Treated with oral steroid. Achieved remission.
Rhabdomyolysis						
Gelbenegger et al. 2021 [98]	Janssen (Ad26.COV2.S)	Rhabdomyolysis	18/M	1st	2 days aftermyalgia, muscle weakness, and darkened urine. Creatine kinase (CK) level of 15,638 U/L, serum creatinine of 1.06 mg/dL, a lactate dehydrogenase (LDH) level of 428 U/L and elevated liver enzymes (aspartate transaminase (AST) 340 U/L, alanine transaminase (ALT) 70 U/L), C-reactive protein 1.61 mg/ dL	ANA profile and myositis panel was negative. With symptomatic management (fluid therapy) CPK increased in first week and normalized by 15 days.
Nassar et al. 2021 [99]	Pfizer-BioNTech (BNT162b2)	Rhabdomyolysis	21/M	1st	1 day afterprogressively worsening pain and swelling in the lower back. O/E- tenderness to the paraspinal lumbar area upon palpation.	CPK- 22000U/LAldolase- 97.8U/LAST-675U/LALT-165U/LCRP-6.4 mg/LLDH-1525U/LUrine blood + Myositis profile-NegativeHydrated with high volume IV normalSaline and pain controlled with morphine. Improved.
Parsonage Turner Syndrome						
Mahajan et al. 2021 [102]	Pfizer-BioNTech (BNT162b2)	Parsonage Turner syndrome	50/M	2nd	1weekPain and left hand grip and left wrist extension weakness with no sensory disturbances or other symptoms. Examination – weaknessof left finger extension and left hand grip. Weak(MRC 3/ 5) – left dorsal interossei, extensor digitorum,	MR brachial plexography and NCS- was normal (done early in the disease course). Treated with oral steroid and patient responded significantly.

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
					extensorindicis, and flexor carpi ulnaris. DTR- mildly brisk b/l and symmetrical.	
Shields et al. 2021 [103]	Pfizer-BioNTech = 4, Moderna = 2	Parsonage Turner Syndrome	36/F, 74/M, 50/M53/M, 84/F, 46/F	2 patient after 1st dose4 after 2nd dose	Mean duration of 17 days (5 days–8 weeks). Initial symptom was pain in the shoulder girdle/ upper limb, followed within days by muscle weakness.	Examination and investigation s/o- upper trunk brachial plexopathy in 2 patients, lower trunk plexopathy in 1 patient, posterior cord brachial plexopathy in 1 patient, andanterior/posterior interosseous nerve involvement in 2 patients. All patients either improved or attained complete resolution of the arm pain at follow-up.
Queler et al. 2021 [106]	Pfizer-BioNTech (BNT162b2) = 1, Moderna (mRNA-1273) = 1	Parsonage Turner Syndrome	49/M	1st	13 hoursPain followed by weakness of left upper limb.	MR Neurography- Within the arm, four severe hourglass- like constrictions and T2-weighted signal hyperintensity of the anteromedially positioned fascicular bundle of the median nerve were detected; this bundle represents the PT/FCR bundle based on the known topographic fascicular arrangement of the median nerve. EDx- severe denervation and no motor unit recruitment within thePT or FCR muscles. 3 month follow up- pain decreased but weakness increased.
			44/M	2nd	18 days after developed sudden-onset, Intense, cramping pain in the left lateral deltoid region. Examination- severe weakness in left shoulder abduction (2/5) and external rotation (3/5) Reported hyperesthesias in the left lateral shoulderAnd had diminished sensation to pinprick in the radial nerve distribution.	NCS- mild slowing of the left median and radial sensory responses. EMG- denervation and poor motor unit recruitment in the infraspinatus muscle. MRI- left brachial plexus MR neurography demonstrated enlargement, T2-weighted signal hyperintensity and multiple focal hourglass-like constrictions of the suprascapular nerve with accompanying denervation edemapattern of the supraspinatus and infraspinatus muscles.
Other Neuropathies						
Waheed et al. 2021 [107]	Pfizer-BioNTech (BNT162b2)	Small fiber neuropathy	57/F	2nd	1weekWith subacute onset of intense burning dysesthesias in the feet, gradually spreading to the calves and minimally into the hands, unaccompanied by other neurological or constitutional symptoms. Nerve conduction study was unremarkable.	Skin biopsies showed multifocal involvement. Relevent workups for neuropathy were negative. Treated with gabapentin and improved in 2 weeks.
Souza et al. 2022 [108]	AstraZeneca (ChAdOx1) = 4	Acute onset- Chronic inflammatory demyelinating polyneuropathy (aCIDP)	Between 51 and 72 years. All male	1st	2–3 weeks	In aCIDP a/w COVID vaccination: the acute illness may be severe and associated with cranial nerve dysfunction, particularly bifacial weakness.
Spataro et al. 2022 [109]	AstraZeneca (ChAdOx1)	Reversible radiculomyelitis	Woman in her 20 s	1st	3–4 days after, subacute onset of legs' weakness, cramping pain	CSF- Albuminocytological dissociationOCB (CSF and Serum): Pattern

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
					and fever (38 °C – 39 °C). O/E: Power LL- 2/5 (b/l) Spastic LLPlantar- equivocalVery brisk patellar, abductor and Achilles tendon reflexes with horizontal and vertical extension, and legs paraesthesia. Tactile and pinpricksensation was decreased from T4 dermatomedownward. Passive and active leg movementselicited rigidity and tenderness.	IVMRI Brain & Spine-NormalElectromyography and electroneurography – NegativeNear complete recovery in 2 months of steroid therapy.
Myasthenia gravis						
Chavez et al. 2021 [110]	Pfizer-BioNTech (BNT162b2)	Myasthenia	82/M	2nd	2 days afterWith intermittent bulbar symptoms, present in the evenings. history of laryngeal cancer status post hemi-laryngectomy 40 years previously, Barrett's esophagus, and stage 3a chronic kidney disease	Ach receptor binding Ab 11.4 (normal < 0.02) RNST- Decrement patternSecondary evaluation for thymoma was negative. Treated with pyridostigmine and IVIG. Had improving course.
Galassi et al. 2022 [111]	AstraZeneca (ChAdOx1)	Ocular Myasthenia	73/M	1st	8 days laterPainless left-sided ptosis without diplopia. K/c/o Psoriasis and hypertension, IHD	MRI Brain- NormalPositive rheumatoid factor (240 IU/ml, normal < 20 IU/ml). Low-frequency repetitive nerve stimulation – 14.7 % decrement in amplitude of nasalis muscle of the compound muscle action potential. Serum titer of anti- AChR antibodies (Day 20 after vaccine) = 1.9 nmol/l (normal < 0.25 nmol/L). Positive pyridostigmine test.
Lee et al. 2022 [112]		Triggering of Early-Onset Myasthenia Gravis	33/F	2nd	On the same day: bilateral ptosis and binocular diplopia. On 3rd day: Developed bilateral ptosis. On 4th day: difficulty in raising her arms and moving her neck with a diurnal fluctuation.	RNST- Significant decremental response. CT- Mild thymic hyperplasia. Anti AchR Ab and anti MUSK Ab – NegativeNeostigmine test- Positive. Responded to pyridostigmine.
Movement disorders						
Salinas et al 2021 [113]	Pfizer-BioNTech (BNT162b2)	Transient akathesia	36/F	2nd	12 hoursStarted to experience an urge to move which she described as "restless body syndrome.". k/c/o atopic dermatitis, allergic rhinitis and anxiety (on sertraline 50 mg/day)	She derived temporary relief of symptoms from volitional movement but the internal discomfort and urge to move would soon return. Her movements were alleviated by flexing/extending her trunk and legs as well as getting up and constantly moving. This was followed by fever and myalgia. Her symptoms improved after 24 h.
Dysautonomia						
Galougahi et al. 2021 [114]	AstraZeneca (ChAdOx1)	Autonomic dysfunction	29/M	1st	4 days afterWith intermittent paraesthesia in extremities,	Antinuclear antibody (ANA) was positive at low titre (speckled pattern, 1:40) with

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Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
					which gradually became persistent. Initially was treated with vitamin b12 injection and amitriptyline. 2 months after had increased heart rate, with a significant change when standing (80– 120b.p.m.) vs lying (50–60b.p.m.) and skin colour changes (dark-blue/white/ dark-red) in acral areas (hands/ feet/ penis) which is intermittent.	elevated IgA level [5.06 g/L (0.60–3.96)]. MRI brain and nerve conduction study was unremarkable. Treated with short course of oral steroid. His postural tachycardia improved, but paraesthesia and skin colour changes persisted at 6-months.
Reddy et al. 2021 [115]	Pfizer-BioNTech (BNT162b2)	Postural orthostatic tachycardia syndrome (POTS)	42/M	1st	1 week after vaccination presented with sinus tachycardia, dizziness, headaches, and fatigue that are often triggered after a large meal or standing for a longer duration.	Investigations were not remarkable. Treated with life style modification.
Hadache						
Oonk et al. 2022 [116]	Pfizer-BioNTech (BNT162b2)	Thunderclap headache	62/M		Recurrent episodic thunderclap headache. k/c/o- ocular melanoma.	Laboratory analysis, brain CT and MRI, EEG and CSF analysis including blood pigment and cytologyanalysis were all unremarkable.
	AstraZeneca (ChAdOx1)		21/F	1st	2 h afterDeveloped general malaise with subfebrile temperature6hours later experienceda thunderclap headache, with nausea and vomiting	Neurological examination, blood analysis, and brain CT including CTangiography and venography were all normal. Symptoms improved over 1 day with paracetamol, NSAIDs, intravenous morphine, and oxygen therapy
Mattiuzzi et al. 2021 [117]	**Rate of headache/migraine episodes (per 100,000) voluntarily reported by recipients of COVID-19 vaccines up to May 9, 2021:**			**Risk of developing headache/migraine episodes(Odds)**		
	AstraZeneca	129		AstraZeneca		3.50; 95 % CI, 3.12–3.93; $P < 0.001$
	Pfizer	103		Pfizer		2.78; 95 % CI, 2.47–3.13; $P < 0.001$
	Moderna	21		Moderna		0.58; 95 % CI, 0.49–0.68; $P < 0.001$
	The cumulative rate of headache/migraine episodes after receiving all COVID-19 vaccines was 2.25-fold higher than the daily frequency of headache disorders (odds ratio, 2.25; 95 % CI, 0.83–6.11).					
Suwanwela et al. 2022 [118]	Corona Vac	Prolonged migraine aura resemblingischemic stroke	**Age** between 24 and 48 years and 75 % female.	**Interval from vaccination:** within the first 24 h: 75 %between 1 and 7d:25 %.	All presented with lateralizedsensory deficits, motor deficits, or both, of 2–14 day duration. Migraine headache occurred in half of the patients.	MRI brain during and after the attacks did not demonstrate any abnormalities suggesting ischemic stroke. All patients showed moderately large regions of hypoperfusion and concurrent smaller regions of hyperperfusion on SPECT imaging while symptomatic. None developed permanent deficits or structural brain injury.
Reactivation of Varicella Zoster						
Desai et al. 2021 [119]	mRNA vaccine = 45/54 (86.27 %)Inactivated COVID-19 vaccine = 5/ 54 (5.88 %)Non-	Reactivation of Varicella Zoster cutaneous infection	27 male and 27 female	2nd dose = 36	Mean interval = 7.64 (6.92) days	Based on the criteria of temporal connection with vaccination anda plausible biological link, HZ appears to be a "possible".

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Table 5 (*continued*)

Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
	replicatingviral vector = 4/51 (7.84 %)					
Maldonado et al. 2021 [120]	Pfizer-BioNTech (BNT162b2)		79/M	1st	4 days afterelevated erythematous lesions with vesicles on his right-handsidelumbar area that quickly spread to his lower back, hip, groin, and right-hand-side front and inner thigh, corresponding to L1, L2 and L3 dermatomes. K/c/o Hypercholesterolemia, hyperuricemia and hypertension	Responded to: 800 mg/day of aciclovir for one week; 50 mg of acyclovir applied topically onthe vesicles.
	Pfizer-BioNTech (BNT162b2)		56/F	2nd	16 days afterFever, with haemorrhagic vesicles upon an erythematous base spreading on her arm, hand, and left side ofher chest, with chest pain, and pain in her arm on the same side	Treated with 400 mg/8h of gabapentin and 25 mg/12 h of a vitamin B complex.
Functional Neurological Disorders (FND)						
Butler et al. 2021 [125]	Pfizer-BioNTech (BNT162b2)	Functional Neurological disorder	38/F	1st	After twenty minutes of receiving the vaccine, developed an odd sensation that she described as "weakness" around her left ear. During the rest of the day, this weakness spread to her mouth, left arm, and leg.	The next morning, she had difficulty moving the left side of her face and experienced heaviness in her left leg. Her hoover's sign, hip abduction test results, were positive and symptoms were variabile. Investigations including neuroimaging was unremarkable.
	Moderna (mRNA-1273)	Functional Neurological disorder	36/F	1st	Few minutes after experienced weakness in her right hand and new right-leg limping, which lasted about 2 h. On the second day after vaccination, she experienced severe bilateral leg heaviness and difficulties in fine movements of the right hand. In addition, she had exertional fatigue after walking short distances.	These symptoms persisted for several days. Examination and neuroimaging, routine investigations were unremarkable.
Ercoli et al. 2021 [126]		Functional Neurological disorder	41/M	1st followed by second dose	After a few minutes fromthe injection, reported bilateral facial paralysis withdifficulty to blink and move the facial muscles properly. All the symptoms resolved spontaneously within 40 min. Three weeks later, a few minutes after the second dose, he complained of swollen tongue and respiratory impairment, which was quickly resolved by corticosteroid therapy. Later he developed right-sided weakness,	Few weeks later, he suddenly manifested left-sided facial hypoesthesia. Examination- midline splitting of sensory deficit in the face with tacto-dolorific hypoesthesia. Brain MRI, CT, & carotid artery Doppler ultrasonography: Normal. Sensory disturbance resolved, and the neurological examination become normal in next 2 weeks.

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Table 5 (*continued*)

Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
					at the same side of the injection, lasting for about 40 min.	
Fasano et al. 2022 [127]	Pfizer-BioNTech (BNT162b2)	PNES		2nd dose	20 min aftershort episode of generalised tonic–clonic psychogenic non-epileptic seizures (PNES) which was followed byanother episode of-inability to move the whole body with preserved level of consciousness). No post-ictal period followed these episodes.	VEEG during few events- normal.
	AstraZeneca (ChAdOx1)	Subjective sensory symptoms-FND			2 weeks afterpersistent dizziness and a subjective loss of tactile sensitivity in the right arm and leg.	Brain CT- Normal
Others						
Author	**Vaccine type**	**Neurological diseases**	**Age/Sex**	**Dose of vaccine**	**Interval from last dose**	**Description and observation**
Finsterer et al. 2021 [128]	Moderna (mRNA-1273)	Reversible cerebral vasoconstriction syndrome (RCVS)	38/F	2nd	18daysdeveloped visual impairment due to scotomas and thunderclapheadache.	Multimodal cerebral MRI: Acute cortical ischemic lesion in the territory of the right PCA on T2- weighted images, DWI,ADC maps and absence of the PCA on MRA. Partially responded to Nimodipine(90 mg/d) and Levetiracetam (1 g/d).
Youn et al. 2021 [129]	Pfizer-BioNTech (BNT162b2)	Cytotoxic Lesion of the Corpus Callosum (CLOCCs)	22/M	1st dose	3 daysWith febrile sensation and headache around the eyes and forehead. CSF- Normal cells and protein.	MRI brain- oval shaped restricted diffusion in the corpus callosum with low apparent diffusion coefficient (ADC) values and lack of contrast mediated enhancement
Scott et al. 2021 [130]	Pfizer-BioNTech (BNT162b2)	Gastroparesis	57/M	1st	5daysStarted to have nausea, intractable vomiting and hiccups. Treated with metoclopramide, and erythromycin. Recurred again after receiving the second dose.	Investigation showed significant delay in gastric emptying. No response to H2 receptor blocker, but responded to oral steroid.
Zavala-Jonguitud et al. 2021 [131]	Pfizer-BioNTech (BNT162b2)	Delirium	89/M	1st	2 dayswith a 24-h history of confusion, fluctuating attention, anxiety and inversion of the sleep–wake cycle.	K/c/o type 2 diabetes mellitus, hypertension, stage III-b chronic kidney disease, prostatic hyperplasia, mild hearing impairment and depressive disorder. Managed with antipsychotic, improved in 1 week.
Aladdin et al. 2021 [132]	AstraZeneca (ChAdOx1)	New-onset refractory status epilepticus (NORSE)	42/F	1st	10 days of vaccination presented with f headache and subjective fever that started one day prior and a rising epigastric, jamais vu and followed by new onset generalized tonic-clonic seizure. Brain MRI showed a subtle increase in the signal on FLAIRimages at bilateral hippocampi and insula that was correlating with Postictal changes.	Cerebrospinal fluid analysis showed normal cell count, normal protein at 0.31 g/L, elevated glucose at 4 mmol/L, and negative microbial cultures and serological tests. EEG showed moderate slowing. Treated with 3 AEDs levetiracetam, phenytoin and lacosamide. Responded to pulse intravenous steroid followed by two sessions of plasma exchange on alternate days.

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Table 5 (*continued*)

Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)						
Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose & Symptoms	Description and observation
Liu et al. 2021 [133]	Moderna (mRNA-1273) = 2	Encephalopathy Associated With Nonconvulsive Status Epilepticus	86/F	1st	7dayswith acute confusion with visual hallucinations and left frontal headache. k/c/o: diastolic dysfunction, chronic kidney disease stage 3, glaucoma, cataracts, and Type 2 diabetes mellitus.	CSF studies, including meningitis/ encephalitis panel NAAT, oligoclonal bands, and Lyme antibody, were negative except for West Nile virus IgG but no IgM antibodies with minimal protein elevation. CT head without contrast and MRI brain with and without contrast showed no acute findings. Continuous EEG –non-convulsive focal status epilepticus treated with lorazepam and fosphenytoin.
			73/M	1st	21 dayswith staring episodes, restlessness, and cognitive deficits. K/c/o Crohn's, hereditary hemochromatosis, hypertension, and hyperlipidemia	CSF studies, including meningitis/ encephalitis panel Nucleic Acid Amplification Tests (NAAT), autoimmune encephalitis, and toxoplasma, were negative except for mildly elevated protein and glucose. CT head and MRI brain showed no acute findings. EEG- non-convulsive status epilepticus, which was treated with lorazepam and levetiracetam loading and maintenance.
Chuang et al. 2021 [134]	Moderna (mRNA-1273)	Tolosa-Hunt Syndrome (THS)	45/M		7 days after severe left-sided headache, pain with progressive ptosis in left eye, decreased vision, and binocular diplopia.	Had left RAPD and left eye complete ophthalmoplegia. MRI brain s/o THS.
Lin et al. 2021 [135]	Moderna (mRNA-1273)	Triggered Moyamoya disease with Sjogren disease andautoimmune thyroiditis	40/F	2nd	3 days aftersevere headaches with a decreased level ofconsciousness and a tonic-clonic seizure. k/c/o- Sjogren disease andautoimmune thyroiditisO/E- Febrile with high Blood pressure and PR.	Elevated CRP, anti-PF4 Ab, SSA, fibrinogen, CT Brain – left caudate nucleus, temporal lobe IVH and ICH with hydrocephalusDSA- bilateral distal ICAsteno-occlusion with the constricted flow in middle cerebral arteries and anterior cerebral arteries with cortical collateralization pattern from the external carotid artery system that was consistent with typical moyamoya angiopathy (MMA)-Willis and the Suzuki staging system was stage V.
Murvelashvili et al. 2021 [137]	Moderna (mRNA-1273)	Hypophisitis	51/M	2nd	3 days after vaccination with headache, nausea, vomiting, malaise, and diffuse arthralgias	MRI brain suggestive of diffusely enlarged pituitary gland consistent with acute hypophysitis

Abbreviations: GBS- Guillain-Barré syndrome; NMOSD- Neuromyelitis optica spectrum disorders; MOGAD- Myelin oligodendrocyte glycoprotein antibody-associatd disease; MS- Multiple sclerosis; CSVT- Cerebral Venous Sinus Thrombosis; RCVS- Reversible cerebral vasoconstriction syndrome; PNES- Psychogenic Nonepileptic Seizures; POST- Postural orthostatic tachycardia syndrome; MRI- Magnetic resonance imaging; O/E- On examination; k/c/o- Known case of; LP-CSF- Lumbar puncture cerebrospinal fluid; CSF- cerebrospinal fluid; EEG- Electroencephalogram; CT- computerized tomography; ADC- Apparent diffusion coefficient; FLAIR- fluid attenuation inversion recovery DWI- Diffusion weighted imagine.

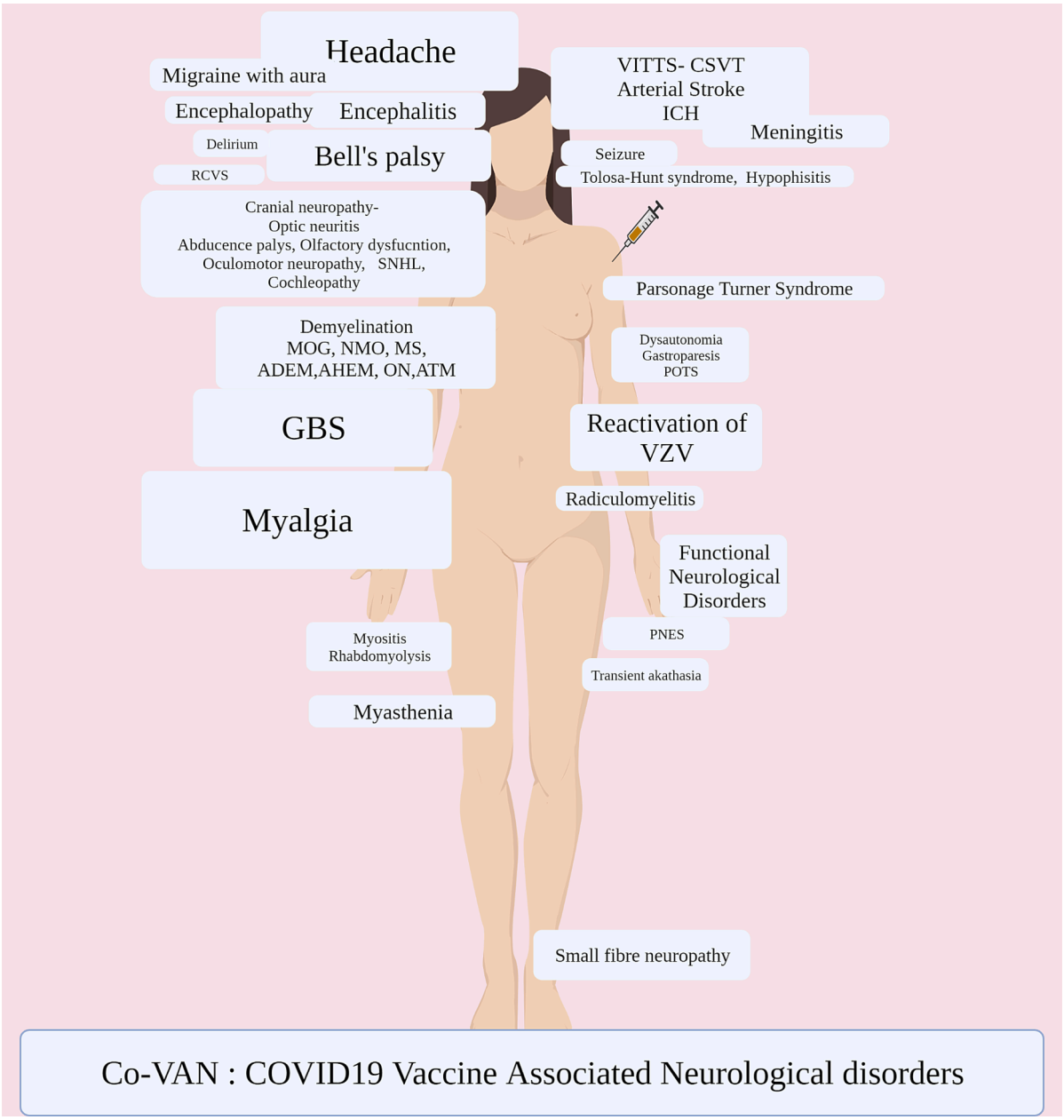

Fig. 5. Depicts the spectrum of possible COVID19 vaccine associated neurological diseases.

5.2.3. Immunization stress related response (ISRR)

In a prospective study consisting eight patients who experienced post vaccination neurological adverse events, 18F-FDGPET/MRI, and 15O-water PET scans were performed at the baseline (immediately following neurological adverse event after the vaccination) and after 7 days of vaccination. All had hypometabolism in the bilateral parietal lobes on both the first and follow-up scans. Metabolic changes in the bilateral cuneus including hypometabolism in six and hypermetabolism in two patients were observed. One showed mildly significant decreases in perfusion in the bilateral thalamus and bilateral cerebellum, whereas another patient was found to have a diffuse increase in the cerebral white matter perfusion. The areas of metabolic abnormalities indicates towards the involvement of the fear network model which has been implicated in anxiety. [166].

5.3. Limitations

Retrospective study design and small size are important limitations in this study. Further studies with larger sample size are needed to establish the causal association with these disorders.

6. Conclusion

The advent of newer vaccines raises the possibility of emergence of novel AEFI. While causality may not always be proven, the replication of similar events over a period of time, serve to generate speculations over a new AEFI. Though subject to further investigations, this study will sensitize the neurologists and vaccine stakeholders regarding the spectrum of neurological diseases of probable or possible temporal

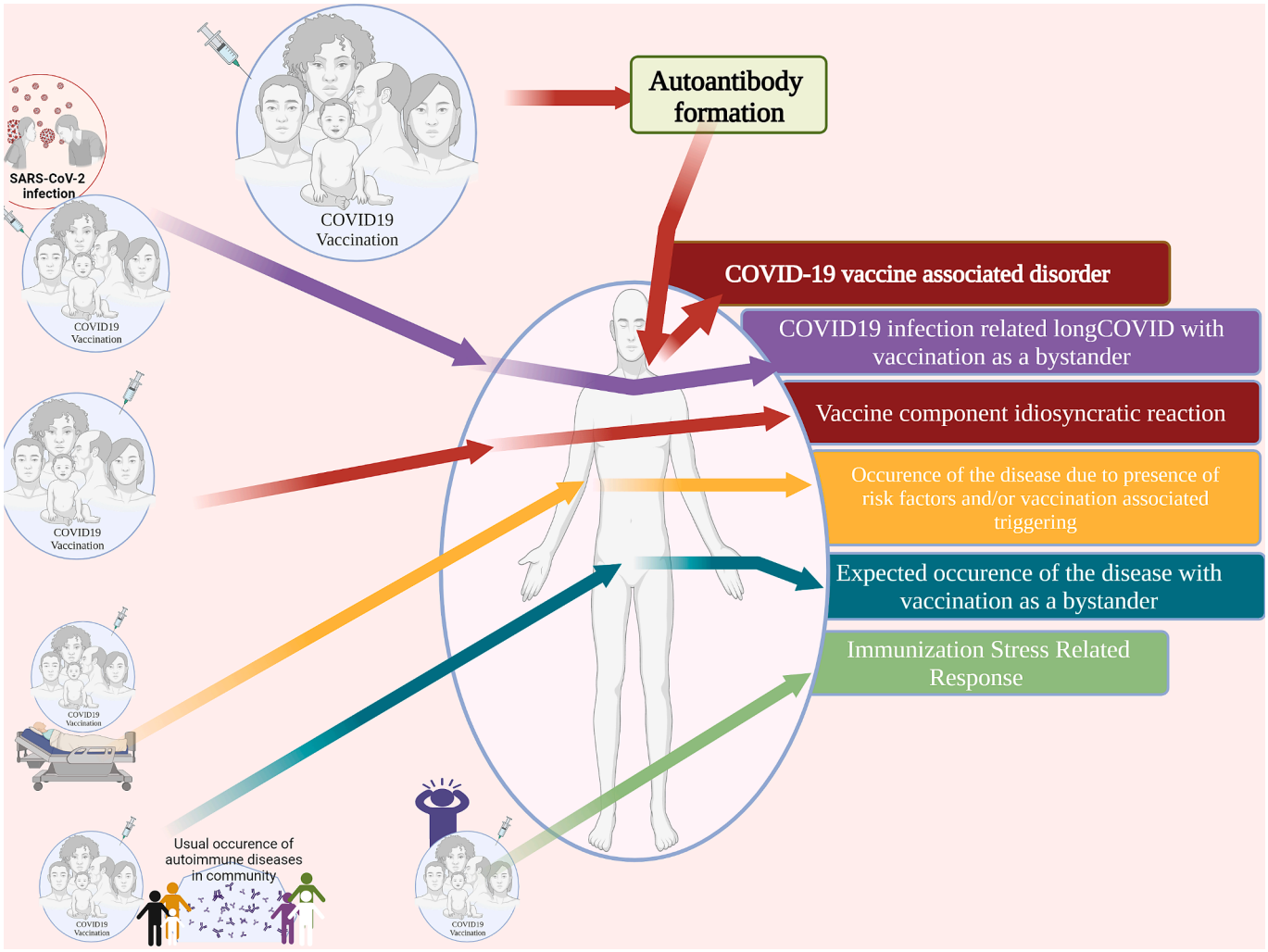

Fig. 6. Illustrates the various possibilities of neurological illness among the recipients of vaccines against SARS-CoV2.

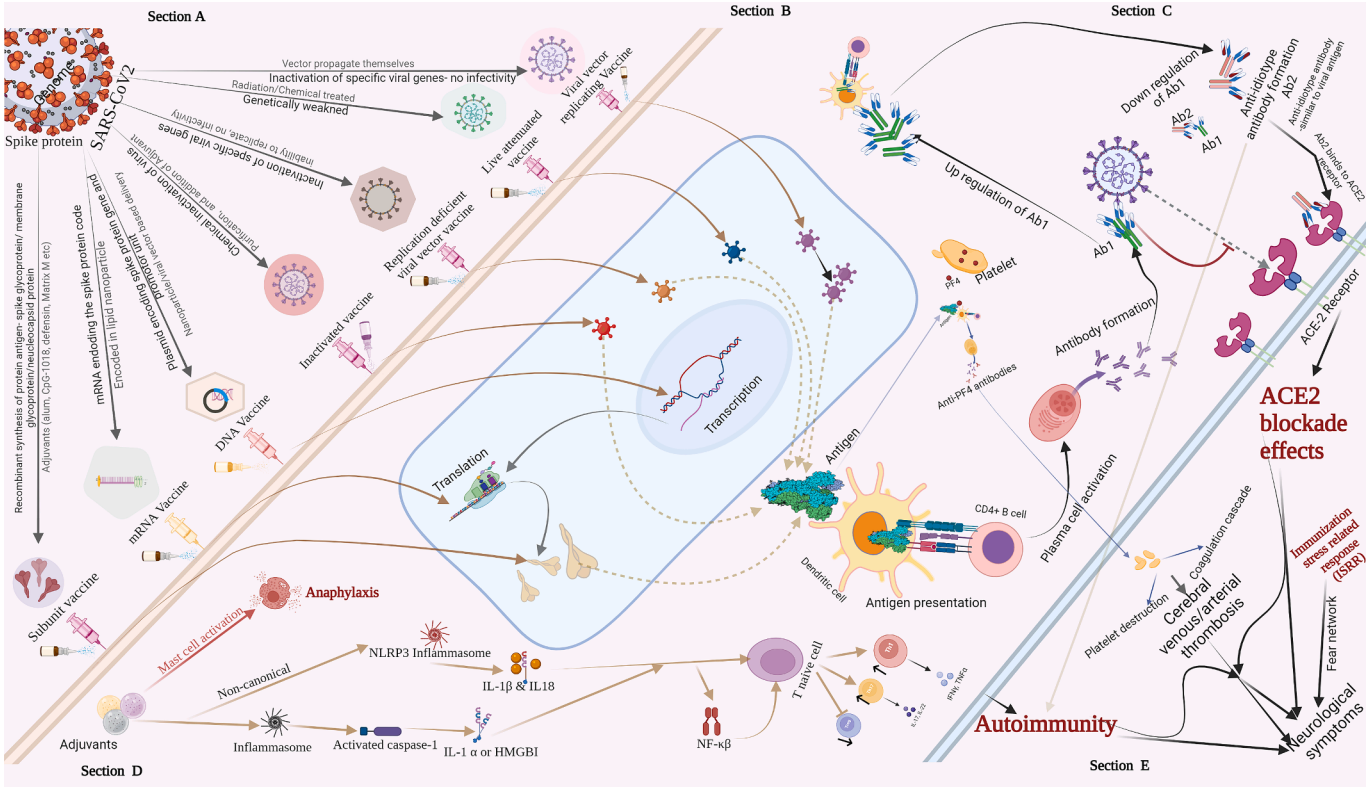

Fig. 7. *Section A*- Enumerates various types of vaccine candidates and their principle components. *Se6tion B*- Illustrates the post vaccination mechanisms of immunogenicity *Section C*- Demonstrates the anti-idiotype antibody hypothesis *Section D*- Explains the role of adjuvants and mast cell activation and mechanism of anaphylaxis. *Section E*- Depicts the autoantibodies formation and ACE2 down regulation leading to various neurological diseases.

association with COVID-19 vaccination. It will also enlighten the practitioner regarding the possible underlying pathophysiology of this evolving entity.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2022.12.015.

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