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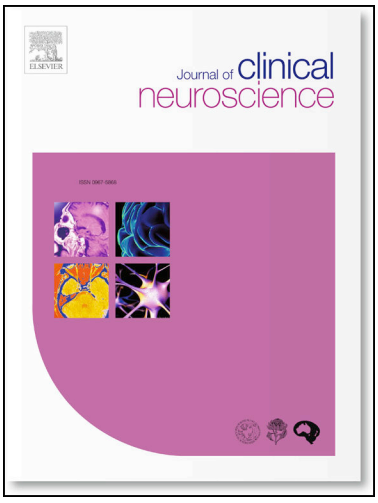

Co-VAN Study: COVID-19 Vaccine Associated Neurological Diseases- An experience from an apex Neurosciences centre and review of the literature

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Title Page

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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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Highlights:

- We retrospectively reviewed neurologic syndromes in temporal association with COVID-19 vaccination.
- The spectrum comprised CNS demyelination, Guillain Barre syndrome, stroke, encephalitis and myositis.
- Female sex had a greater pre-disposition.
- Majority of neurologic events occurred after the first dose (79.3%).
- Majority of the patients had favourable clinical outcome at discharge.
- The incidence of adverse events following COVID-19 vaccination is low and hence the benefits outweigh the risk.

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=37,79.3%). 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.

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

Running title: CoVAN Study

Main Manuscript

Co-VAN Study: COVID-19 Vaccine Associated Neurological Diseases- An experience from an apex referral centre and review of the literature

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 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 01). 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. (2–4)(5,6) 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 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 casuality 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 25-45 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 (10 to 14) 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. (Figure 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 (0 to 1) 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 04)

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 Table 02 and 03)

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 Butler et al.2021 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 (0 to 1). (Refer to Table 03)

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. (Figure 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 (ACE/EULAR 2017)(142) . Muscle MRI was suggestive of myositis. PET MRI showed increased tracer uptake in the muscles without any sign of malignancy. (Figure 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 03)

5. Discussion:

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

5.2. The spectrum of the neurological diseases associated with COVID19 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 02 Refer to Figure 05and Figure 06) (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 Figure 03 for details) (Refer to Supplementary appendix for vaccination related terms)

5.3. 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 figure 07)

5.3.1. 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 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)

5.3.2. 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)

5.3.3. 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)

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

Legends:

Figure 01 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)

Figure 02- MRI spine T2 weighted image shows longitudinally extensive cervico-dorsal cord hyperintensities in a case of probable post vaccination myelitis . (Case 14)

Figure 03- 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)

Figure 04- 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.

Figure 05:

Depicts the spectrum of possible COVID19 vaccine associated neurological diseases.

Figure 06:

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

Figure 07:

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.

Table 01:

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

Table 02: Enumerates the clinical details of the cases.

Table 03: Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN)

Table 04: Characteristics of cases with CNS demyelination

Table 05: CO-VAN study: scoping review of literature

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A, et al. Alterations in 18F-FDG PET/MRI and 15O-Water PET Brain Findings in Patients with Neurological Symptoms after COVID-19 Vaccination: A Pilot Study. Clin Nucl Med. 2022;47(3):E230–9.

Highlights:

- We retrospectively reviewed neurologic syndromes in temporal association with COVID-19 vaccination.
- The spectrum comprised CNS demyelination, Gullain Barre syndrome, stroke, encephalitis and myositis.
- Female sex had a greater pre-disposition.
- Majority of neurologic events occurred after the first dose (79.3%).
- Majority of the patients had favourable clinical outcome at discharge.
- The incidence of adverse events following COVID-19 vaccination is low and hence the benefits outweigh the risk.

Table 01: 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.

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) * 7days Followed 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-perception of light present, Lt eye 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) * 5days 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 limbs Right upper and lower limb flexor spam present every 30 minutes. 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-23.8mg/dl SSEP 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/b Rituximab	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 174mg/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) * 5days 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

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 (144mg/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) * 5days 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/b 1gm 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 protein MRI 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)- Positive Serum MOG – Positive	MOGAD	IV MP (1gm) * 5days 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 reactive V/A- 6/9 in RE, 6/6 in LE Fundus – Normal EOM : full Gaze 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 latency and low amplitude BAER waveforms. Serum ANTI-AQ-4 ANTIBODY and MOG – Negative	CNS demyelination with Vestibulopathy	IVMP 1gm *5 days f/b oral steroid	Mild Improvement(mRS=2)	Probable

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 fingers Pain: decreased bilaterally from toes to epigastrium Vibration: 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, 57mg/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)-Positive Serum 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 3mm,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-64mg/dl V.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	Bilateral Optic Neuritis and Brainstem demyelination	LVPP* 5 cylcles f/b 1gm IVMP* 5 days f/b oral steroid and Rituximab	Improved (mRS=0)	Probable

								lateral medulla extending to the cervicomedullary junction. Serum ANTI-AQ-4 ANTIBODY and MOG – Negative CSF OCB-Pattern 4.				
13	30	F	Shock like sensation on flexing the neck and tingling paraesthesia of B/l hand	3months	ChAdOx-1/2nd dose	15 days	Tone-Normal. Power-normal in U/L and L/L including intrinsic muscles of hand Reflexes -2 Plantar bilateral-flexor Sensory system - 40 percent reduction in sensation to touch over both palms.	ESR-68mm, ACE,RA, ANA profile-negative MRI 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/b 1gm 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 retention, weakness and paresthesias of both upper limbs	4	BBV152/1st dose	5 days	Quadriparesis Sensory examination – absent sensation to touch and pin prick below T4 Level. JPS and vibrationimpaired in lower limbs. DTRs – upper limb 2 , lower limbs absent	ANCA, RA factor, and CRP – negative. **ANA profile – anti PCNA strongly positive.** LP-CSF: cells-207(lymphocytes-40%, PMN-60%), protein-95.8mg/dl SSEP 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	Seronegative CNS demyelination	LVPP* 5 cylcles f/b 1gm IVMP* 5 days f/b oral steroid	Improved (mRS=2)	Probable

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	Motor Grade 1 spasticity in left upper limb Power-5/5 Tendon reflexes-3 Plantars-Bilaterally flexor Sensory-Touch, pain, joint position sense-Normal	ANA profile, ANCA, ACE – negative. LP-CSF: cells-0, protein-27.7mg/dl MRI 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 low Motor, sensory, cerebellar - normal	RA factor, and ANA profile – negative LP-CSF: cells-2(lymphocytes-100%), protein-52.3mg/dl VEP- b/l prolonged P100. CSF OCB-Negative. MRI of Brain and spine – No significant signal changes. **Serum MOG – Positive**	MOGAD	LVPP* 5 cylcles f/b 1gm 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) * 5days 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 a left lower limb Known case of medically controlled T2DM	60	ChAdOx-1/ 1st dose	2 days	Pupil, EOM-full Right hemiparesis Right UL and LL DTRs brisk	ESR (57mm) and CRP(11mg/L) - elevated. ANA profile – Negative **Paraneoplastic profile: Anti-Tr and anti-GAD65,** LP-CSF: cells-2(lymphocytes-100%), protein-28.3mg/dl SSEP 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

19	16	F	Recurrent vomiting, burning sensation of both upper limbs, tremulooussness 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 of gaze. Bilateral LMN facial palsy. Trismus, jaw opening restricted. Power 4/5 Cerebellar signs present b/l, DTRs brisk, plantar b/l extensor Severe 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-28.0mg/dl. Serum and CSF NMO was strongly positive.	NMOSD	LVPP* 5 cylcles f/b 1gm 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-scanning VA-Right eye-6/36,Left eye-6/36 Tone-Hypotonia b/l LL Power-LL 4/5 DTRs-Brisk Plantar-Extensor b/l JPS-impaired Cerebellar signs-present	ANA profile: AntiRNP,Anti JO 2+ ANCA,Serum. NMO MOG :negative. ESR was 90mm/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 eye blurring of vision	15	ChAdOx1 nCoV-19 / 1st dose	11	Rt: eye RAPD, VA – Rt: hand movement close to face; Lt - 6/6	CSF: 0 cells, P:18 mg/ dl, G: 61 mg/dl Serum and CSF OCB absent ANA, ANCA, RA factor, CRP - negative Serum MOG-positive VEP: Rt - absent waveform, Lt – normal MRI brain: T2 /FLAIR hyperintensity of long intraorbital segment of Rt optic nerve with contrast enhancement	MOGAD	Inj. MP 1 gm x 5 days 1 cycle of LVPP T. Prednisolone 40 mg OD followed by tapering doses	Improved (mRS=1)	Probable
22	54	F	Progressive quadriparesis followed by altered sensorium	42	ChAdOx1 nCoV-19 / 1st dose	14	Drowsy, not opening eyes, bl UL flexion posturing, quadriparesis with 2/5 power in UL and 0/5 power in LL.	CSF: 8 cellslymphocytic predominant, P:77 mg/dl, G:98 mg/dl ANA, ANCA, CRP -negative Serum NMOMOG-negative MRI brain: T2/FLAIR hyperintensities in the corpus callosum, bl periventricular and subcortical white matter, infratentorial region with patchy contrast enhancement	ADEM	Inj. MP 1 gm x 5 days 5 cycles of LVPP Inj. Iv Ig 100 g T. Prednisolone 40 mg OD followed by tapering doses	Mild Improved (mRS=2)	Probable

23	44	M	Hiccups, vomiting, urinary retention, double vision, Imbalance on walking	12	ChAdOx1 nCoV- 19 / 1st dose	7	Lt VA: 6/9, Rt – 6/6. spastic quadriparesis, bilateral cerebellar signs in UL	CSF: Lymphocytic pleocytosis with elevated protein. ANA, ANCA - negative Serum and CSF MOGStrongly positive, MRI: T2 hyperintensities in the cervico-dorsal cord and conus	MOGAD	Inj. MP 1 gm x 5 days 5 cycles of LVPP T. Prednisolone 40 mg OD	Mild Improved (mRS=2)	Probable
24	39	M	Rt eye pain followed by blurring of vision	20	ChAdOx1 nCoV- 19 / 1st dose	14	RT eye-RAPD, Rt VA: Finger counting at 2m Visual field-right inferonasal quadrant involvement	ANA, ANCA, APLA -negative, Serum MOG-positive, VEP-bl prolonged (Right-132 ms, left-115 ms) MRI: T2 /FLAIR hyperintensity of long intraorbital segment of Rt optic nerve with contrast enhancement	MOGAD	Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD	Improved (mRS=0)	Probable
25	54	M	Left eye blurring of vision	21	ChAdOx1 nCoV- 19 / 1st dose	14	VA: Bl 6/12, Lt eye RAPD present, Rt eye-normal pupillary reaction.	ANA profile anti Jo1 □ 1+ positive, ANCA, VDRL-negative, VEP: Rt- 127 ms, Lt-absent waveform Serum MOG –Strongly positive MRI brain and spine: T2/ FLAIR hyperintensity in Rt pons	MOGAD	Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD	Mild Improved (mRS=1)	Probable

26	31	M	Bladder disturbances followed by progressive numbness of whole body and LL weakness	5	ChAdOx1 nCoV- 19 / 1st dose	14	Lower limb spasticity, paraparesis with power 1/5, decreased sensations by 70% below L1, plantars extensor, UL DTRs-3+ and LL 2+	CSF: 370 cells - polymorphic predominant, P: 174 mg/dl, G: 168 mg/dl ANA profile, ANCA, VDRL, RA factor, CRPnegative Serum and CSF NMO-MOG – negative VEP and BERA- normal, SSEP of Lt. LL prolonged (55.9 ms) MRI: long segment cervico-dorsal T2/ FLAIR hyperintensity with subtle enhancement	Seronegative CNS demyelination	Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD 7 cycles of LVPP Inj. Rituximab 1 gm	Mild Improved (mRS=2)	Probable

27	20	F	Rt UL paraesthesias followed by paraparesis & altered sensorium	2	BBV152 / 1st dose	1	VA: Bl 6/6. LL proximal weakness (3/5), distal 4/5, DTRs-3+, Rt LL 50% decreased sensation, Plantars Equivocal	CSF: 8 cells - lymphocytic predominant,P:24.9 mg/dl, G:61 mg/dl ANA profile, ANCA, VDRL, RA factor, CRP -negative Serum and CSF NMO-MOG negative, CSF OCB – Positive VEP, BERA, SSEP- normal MRI: few juxtacortical and short segment cervical T2/FLAIR hyperintensity at C5 level with subtle enhancement	Seronegative CNS demyelination	Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD 5 cycles of LVPP	Mild Improved (mRS=2)	Probable
28	33	F	Fever, vomiting followed by altered sensorium and persistent paraesthesias below mid thoracic level	28	ChAdOx1 nCoV- 19 / 1st dose	14	VA: Rt 6/12, Lt 6/9, Bl normal pupillary reaction, no other focal deficits	CSF: 105 cells - lymphocytic predominant, P: 28.12 mg/dl, G: 70.4 mg/dl Serum MOG – Strongly positive MRI brain: T2/FLAIR hyperintensity in Bl fronto parietal region, no enhancement	MOGAD	Inj. MP 1 gm x 5 days T. Prednisolone 40 mg OD	Minimal improvement (mRS=3)	Probable

29	60	M	Acute onset tingling paraesthesias and motor weakness in left upper and lower limb, followed by behavioural and memory disturbances	34	ChAdOx1 nCoV- 19 / 2nd dose	14	MMSE-27/30 Cranial nerves-VA:R-6/6, L-6/9, nystagmus present Motor system-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-normal Serum NMO and MOG -negative, VEP-normal MRI brain: multiple focal lesions in right pons, midbrain, medial temporal lobes, splenium of corpus callosum, high parietal lobe with tumefaction and peripheral enhancement	ADEM	Inj MP 1 gm x 5 days T. Prednisolone 40 mg OD T. MMF (1 gm)	Mild Improved (mRS=2)	Probable
30	23	F	Burning paraesthesias in right palm associated with numbness and motor weakness followed by burning sensation in right foot over next 7 days	41	ChAdOx1 nCoV- 19 / 2nd dose	7	VA-6/6 Bl Cranial nerves-normal Motor system-normal Sensory systemdecreased vibration along distal right upper and lower limb joints	CRP- 23 mg/dl ANAnegative Serum NMO and MOG-negative CSF-OCB negative MRI brain-T2/flair hyperintensities adjacent to right frontal horn, ependymal margins of bilateral lateral ventricles MRI spineshort segment hyperintensities at C2-C3,C5,D4	SeronegativeCNS demyelination	Inj MP 1 gm x 5 days T. Prednisolone 40 mg OD	Minimal Improved (mRS=3)	Probable

31	40	M	Blurring of vision from left eye followed by acute urinary retention and right eye vision loss	77	ChAdOx1 nCoV- 19 / 1st dose	10	VA- 6/18 Bl Cranial, motor and sensory examination- 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 in pons, bilateral thalami, right frontal cortex MRI spinelongitudinally extensive myelitis from C4-D3	MOGAD	Inj MP 1 gm x 5 days T. Prednisolone 60 mg OD T. MMF (2 gm)	Mild Improved (mRS=2)	Probable

32	45	M	H/o fever accompanied by urinary retention and difficulty in walking progressing to altered sensorium	5	ChAdOx1 nCoV- 19 / 1st dose	10	VA-6/6 BL Cranial nerves-normal Motor system-Tone and power normal in upper limbs LLhypotonia, grade-0 power with hyporeflexia, plantars mute	CSF: 44 cells – 44% lymphocytes, P:90.9 mg/dl, G:68 mg/dl, rabies CSF PCRNegative VEP-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 spinehyperintensities in brainstem, cervicodorsal cord and supratentorial regions with central cord swelling	MOGAD	INJ MP-5 days, LVPP 3 CYCLES TAB WYSOLONE 40 MG TAB MMF 1.5 GM	Mild Improved (mRS=1)	Probable

33	34	F	H/o recurrent vomiting and hiccups progressing to imbalance while walking	60	ChAdOx1 nCoV- 19 / 2nd dose	36	Cranial nerves: Right gaze evoked nystagmus, rest normal Motor examination::Tone and power normal, DTRs brisk BL Sensory examination: pseudoathetosis Left>Right,, Romberg's positive, Tandem gait impaired	CSF-1 cell,P-15,3 mg/ dl, 63 mg/dl,OCB Negative ESR-46 mm/ hr Serum NMO-weakly positive Serum MOGnegative ANA:Ro-52 1+,ANCA-negative MRI brain:T2 hyperintensity in dorsal aspect of medulla	NMOSD	I/V MP-5 days LVPP-3 cycles Tab Wysolone 40 mg Inj Rituximab	Mild Improved (mRS=2)	Probable
34	31	M	H/o progressive upper and lower limb tingling f/b difficulty in walking, urinary urgency, and constipation	17	ChAdOx1 nCoV- 19 / 1st dose	42	Cranial nervesnormal UL motor examination-normal, LL power-4/5,brisk DTRs, extensor plantars Sensory level at T4	CSF: 32 cells – 100% lymphocytes, P:49.2 mg/dl, G:74 mg/dl ANA,ANCA,VDRL -negative, Serum NMO and MOG - negative MRI brain: T2 Hyperintensities in cervicomedullary junction, right frontal subcortical region MRI spine-cervical cord HI C2-C5,also in dorsal cord	SeronegativeCNS demyelination	I/V MP-5 days LVPP-4 cycles Tab Wysolone 40 mg Tab MMF 1.5 gm	Mild Improved (mRS=1)	Probable

35	52	F	H/o progressive slurring of speech with right upper limb and lower limb weakness, followed by appearance of swallowing difficulty	51	ChAdOx1 nCoV- 19 / 1st dose	35	Spastic anarthria + Gaze restricted left>right Right facial weakness Motor examinationhypotonic right upper and lower limb with 0/5 power, left sided power- 5/5,BL DTRs brisk and plantars extensor	CSF-2 CELLS,P-40.5 mg/dl,G-56 mg/dl ESR-18,CRP-POSITIVE ANA,ANCA-Negative, VDRL-Negative S. NMO and MOGNegative MRI brain: tumefactive demyelination in left frontal hemisphere with insular involvement along with left more than right midbrain involvement	ADEM	I/V MP-5 days LVPP-4 cycles Tab Wysolone 40 mg Inj Rituximab	Minimal Improved (mRS=3)	Probable

36	65	F	H/o urinary retention followed by numbness and weakness of both hands and blurring of vision of right eye	30	ChAdOx1 nCoV- 19 / 1st dose	42	V/A-R-hand movements close to face,L-6/18 UL: motor examination normal LL: Power-0/5 DTRs absent in LL Sensory level:T6	CSF-17 CELLS,P-49 mg/dl,G-59 mg/dl ESR-97 ANA,ANCANegative, VDRLNegative S.NMOStrongly positive S. MOG-Negative VEP-RNot recordable, LNormal SSEP-LL absent MRI brain: few hyperintensities in frontal subcortical white matter MRI Spine: D2-D11 hyperintensity with patchy contrast enhancement and bright spotty areas	NMOSD	LVPP – 3 cycles I/V MP-5 days Tab Wysolone 40 mg Tab MMF 1.5 gm	Mild Improved (mRS=2)	Probable

37	20	F	H/o tingling in tips of right hand followed by progressive imbalance while walking	24	ChAdOx1 nCoV- 19 / 2nd dose	39	V/A-6/6 BL Motor examination: Tone increased in right upper limb and lower limb Power - 5/5 in all 4 limbs DTRs: normal Plantar right extensor and left flexor Sensory system- Pain and touch decreased by 10 percent in right upper and lower limb JPS normal Vibration normal Romberg positive Gait ataxic	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-Negative MRI brain: hyperintensities in BL juxtacortical, subcortical, periventricular white matter, anterior temporal lobes as well as infratentorial regions including pons, MCP and medulla MRI Spine: short segment lesions in cervical and dorsal spine	CNS Demyelination- MS	I/V MP-5 days Tab Wysolone 40 mg Inj Rituximab	Mild Improved (mRS=1)	Probable

38	23	F	Heaviness in the legs followed by weakness of both legs over 7 days	13	ChAdOx1 nCoV- 19 / 2nd dose	1	VA- Right- 6/24 , Left- 6/9 Power- UL 5/5, LL-0-1/5, DTRs- Brisk Plantars- B/l extensor Pain 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/b 1gm IVMP* 2 days f/b oral steroid and Rituximab	Mild Improved (mRS=1)	Probable
39	28	M	Right eye visual loss	12	ChAdOx1 nCoV- 19 / 1st dose	11	RAPD right eye VA- right 6/36, left- 6/6	LP-CSF- Normal cell and protein MRI 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 axonopathy LP-CSF: Albuminocytological dissociation (cells-Nil, protein-147.0mg/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 neuropathy LP-CSF: Albuminocytological dissociation (cells-Nil, protein-123.6mg/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 * 5days	Improved (mRS=2)	Probable

42	44	M	Weakness 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 neuropathy LP-CSF: Albuminocytological dissociation (cells-Nil, protein-75.7mg/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 0.4g/kg/day * 5days	Improved (mRS=1)	Probable
Stroke											
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 occlusion ESR-51mm Platelet-57Lakh/cmm PT,INR,aPTT-Normal ANA Profile, ANCA-Negative Fasting lipid profile-Normal panel HbA1C,FBS,PPBS-Normal Sickling test-Negative Cardiac evaluation-Normal	Acute ischemic stroke	Statin, antiplatelet and antioedema measures	Status quo (mRS=3)	Probable

44	35	M	Headache and left upper limb and face paresthesia and weaknesses	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 infarct ESR-12mm, CRP- Negative Platelet-376Lakh/cmm PT,INR,aPTT-Normal PCV-Normal Homocysteine, Vitamin B12-Folate- Normal. Fasting lipid profile-Normal panel HbA1C,FBS,PPBS-Normal Cardiac 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 infarct Platelet-96Lakh/cmm aPTT-79sec CRP-Negative) D-dimer-1381 ng/ml Fibronogen-443mg/dl Fasting lipid profile-Normal panel HbA1C,FBS,PPBS-Normal Cardiac 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 infarct Platelet-254Lakh/cmm PT,INR,aPTT-Normal Fasting lipid profile-Normal panel HbA1C,FBS,PPBS-Normal Cardiac 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 infarct Platelet-293Lakh/cmm PT,INR,aPTT-Normal Fasting lipid profile-Normal panel HbA1C,FBS,PPBS-Normal Cardiac 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/cmm PT,INR,aPTT-Normal CRP-6mg/dl(Positive) Fasting lipid profile-Normal panel HbA1C,FBS,PPBS-Normal Cardiac evaluation-Normal	Acute ischemic stroke	Statin, antiplatelet	Status quo (mRS=4)	**Possible**
Encephalitis												

49	23	F	Irrelevant talk Confusion and disorientation	2	ChAdOx-1/ 1st dose	2 days	Alopecia, knuckle hyperpigmentation MMSE:9/30 Speech-suggestive of transcortical sensory aphasia No meningeal signs EOM-full Pupils-Equal, reactive to light Other cranial nerves-normal Sensory, motor, cerebellar signs-negative Gait-normal Plantars-flexors	CRP-24mg/L. Serum homocysteine-132 umol/L Vitamin B12-50pg/ml (low) LP-CSF: cells-14(PMN-10), protein-27.5mg/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 (70mg/dl) .	Possible Postvaccinal encephalitis with pre-existing possible mitochondrial cytopathy with primary hyper homocysteinemia	Acyclovir 500 mg iv TID x 7 days Ceftriaxone 1gm iv BD x 7 days And Inj Methylprednisolone 1gm iv OD x 5 days Followed 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/ 2nd dose	7	Severe spasticity (grade 4) in both lower limbs(left >right) Plantar- b/l extensor	LP-CSF: nil cell, protein- 26.7mg/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 body PET MRI: Normal tracer uptake	Stiff Person Syndrome	Oral steroid Diazepam Baclofen	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

	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)	-

Table 4: Characteristics of patients with CNS demyelination (n=39)

	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 2n 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

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
rome						
(31)	Pfizer-BioNTech (BNT162b2)=22 Moderna (mRNA1273) =9 AstraZeneca (ChAdOx1)=3 Janssen =3 and Johnson & Johnson=1	GBS	24 cases	1st	7 days (average)	7 patients had CSF album dissociation, and All had a predominant de
021 (32)	AstraZeneca (ChAdOx1)=7	GBS	Seven cases of GBS	1st	2weeks	All patients developed se The frequency of GBS wa higher than that expected.
	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 in 000 person-years
		Miller-Fisher Syndrome and Guillain-Barre Syndrome overlap syndrome	63/M	1st	9 days later Experienced 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 Albuminocytological diss NCS- long-standing axon reduced motor and sensor EMG- and length-depend neurogenic changes. MRI Brain- enhancement oculomotor nerves bilater Serum anti-GQ1b antibod Showed partial improvem over 5 days.
	Pfizer-BioNTech (BNT162b2)	Pediatric Case of Sensory Predominant Guillain-Barré Syndrome	16/F	2nd	2days after Ascending numbness and paresthesia of her bilateral lower and upper extremities	MRI - mild thickening an anterior and posterior spir cauda equine. LP-CSF: 1cell/cmm, Prote NCS- prolonged latency a conduction velocity in mu motor nerves

	Pfizer-BioNTech (BNT162b2)	Recurrence of GBS	Out of 702 patients of previous GBS, 1 had recurrence.	NCS s/o sensorimotor demyelinating polyneuropathy. Was treated wit improved.		
	Pfizer-BioNTech (BNT162b2)=11 AstraZeneca (ChAdOx1) =8 Moderna (mRNA-1273)=6 Sinovac/ Sinopharm=5 Sputnik=1 Johnson&Johnson=1	Transverse myelitis ADEM MS-like illness NMOSD	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 =12/32 MS-like pictures (first diagnosis or a relapse) = 12/32 ADEM- like 5/32 NMOSD-like=3/32.	Most MS-like episodes (9/ mRNA-based vaccines, TM occurred following bot mRNA-based vaccines.
2 (59)	AstraZeneca (ChAdOx1) =27 COVAXIN (BBV152)=2	MOGAD & other demyelinations	Myelitis=11, Optic neuritis=6, Acute demyelinating encephalomyelitis=5, Brainstem demyelination=3, and Multiaxial involvement=4		MOG positive= 10 Postvaccinial cases were found to have a signifi Mean age, Presence of encephalopathy (p value:0.0007), CSF pleocytosis (p value: 0.0094) and Raised CSF protein (p value: 0.0062).	
	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 hypothalamus lesions with Investigations: leucopenia and positive antibodies fo SSB, Ro-52, and p-ANCA pleocytosis with normal p OCB. Treated with intravenous patient responded well.
021(61)	Pfizer-BioNTech (BNT162b2)=4 Moderna (mRNA-1273)=3	1. Exacerbation of known stable MS = 4, 2. New onset MS =2, 3. New onset NMO= 1	24 to 64 (mean 39.1) years. Male=2, Female=5	First (n = 2), Second(n = 5)	1-21 days Symptoms: visual loss, dysmetria, gait instability, paresthesias, sphincter disturbance, and limb weakness.	All responded to corticost plasma exchange (n = 1) t
	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 FLAI increased signal of the lef analysis normal cells and Aquaporin 4 (AQP4)-IgG negative. Treated with intravenous patient responded well.
4)	AstraZeneca (ChAdOx1)	Acute Hemorrhagic Encephalomyelitis (AHEM)	61Y/M	1st	2days p/w- fever, headache and apathy followed by seizure and coma.	MRI Brain- bilateral conf subcortical FLAIR hyperi haemorrhagic involvemen CSF- revealed normal cel per µl) and moderate distu brain-barrier. Treated with PLEX and I responded.

			25Y/F	1st	9days. P/w severe cephalgia, thoracic back pain, mild weakness and ascending numbness in her legs.	MRI- longitudinal edema thoracic spinal cord exhib enhancement as well as fo haemorrhages and brain sl white matter lesions with enhancement. CSF- granulocytic pleocy

d strokes: CSVT

	Moderna (mRNA-1273)	VITTS with CSVT	65/F	2nd	10days after. With symptoms of headache, lower limb discomfort and breathing difficulties.	She was found to have cat including deep venous and venous thrombosis.
	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. (http://dx.doi.org/10.1056/NEJMoa2105385)		Vaccine-induced immune thrombotic thrombocy mainly reported in adenovirus vector based vacc 19 vaccine and Ad26.COV2.S. According to VA incidence of VITT is approximately 1 in 263,00 Ad26.COV2.S . (PMID 35038274)	

1(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
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)

Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose	Description and
)	AstraZeneca (ChAdOx1)	Thrombosis of Carotid Artery	31/M	1st	8days. with acute headache, aphasia, and hemiparesis.	MRI brain showed main s middle cerebral artery. Ha normal platelet and fibrino IgG PF4 antibody.
	AstraZeneca (ChAdOx1)	Ischemic stroke-arterial	Ischemic stroke in ICA and MCA territory with haemorrhagic transformation in one patient and another h and aortic arch thrombi. Both had thrombocytopenia, increased D-dimer level, and positive anti-PF4 antib			
21(96)	AstraZeneca (ChAdOx1)	Strokes	3 patients with MCA infarct, ICA infarct and CVST, and MCA infarct respectively. All had thrombocyto PF4 antibody, and increased D-dimer level.			
	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 v with thrombocytopenia.			

6)	Pfizer-BioNTech (BNT162b2)	Sequential contralateral facial nerve palsies	61/M	1st	5hour. Developed unilateral LMN facial palsy.	2 days afte contralater Significan oral steroi occasions.

		Number of cases	**Age-standardised incidence (**cases per 100 000 person-years**)**	**Age-standardised difference for the incidence compared with the background population**	**Equivalen additional cases per 000 peopl**
	CoronaVac	28	66·9	41·5	4.8 case
	Pfizer-BioNTech (BNT162b2)	16	42·8	17·0	2·0 case

n

Author	**Vaccine type**	**Neurological diseases**	**Age/Sex**	**Dose of vaccine**	**Interval from last dose**	**Description and**
2021(74)	Pfizer-BioNTech (BNT162b2)	Hyposmia	42y/F	2nd dose	3 days after presented with decreased olfactory ability.	Showed partial improvem testing after olfactory trai (lemon, rose, eucalyptus,
			39y/F	2nd dose	5 days of 2nd dose of vaccine presented with hyposmia.	Improved within a week a assessment.
	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 of left olfactory tract. MRI brain - Asymmetric increased T2 hyperintensi bulb and tract extending p thickened, clumped olfact

erve dysfunction

	AstraZeneca (ChAdOx1)	Sudden sensorineural hearing loss	64/F	1st	1 day after Sudden hearing loss in the right ear.	Initially steroid intraty follow comple
	Pfizer-BioNTech (BNT162b2)		42/M	1st	Same day sudden hearing loss in the left ear	Respon follow steroid
	Pfizer-BioNTech (BNT162b2)		18/M	2nd	2days after sudden hearing loss in the right ear	Tempo resona normal Detrim

)	Pfizer-BioNTech (BNT162b2)=3	Tinnitus	37y/F	1st dose	7 hours after had right ear tinnitus	
			63/M	1st dose	20 hours after had left tinnitus associated to hyperacusis and	
			30y/M	2nd dose	1 week after vaccine presented with left tinnitus, hyperacusis	
1(81)	AstraZeneca (ChAdOx1)	Cochleopathy	37Y/M	1st dose	5 hours. Iintermittent, right ear, high-pitch tinnitus which progressed into continuous	Audiological evaluation s Responded to short course

					high-pitch tinnitus and disturbed the normal hearing along with fever and myalgia.	
	Sinovac Coronavirus vaccine=2	SNHL	30Y/M, and 64Y/F	1st dose	4 days Developed hearing loss in the right ear with tinnitus and dizziness.	CT temporal bone and MI Blood investigations were Poorly responded to vitam
)	Pfizer-BioNTech (BNT162b2)=23 AstraZeneca (ChAdOx1)=5 Moderna (mRNA-1273)=4 Jannsen (Ad26.COV2.S)=1	Objective vertigo =16 Subjective vertigo =14 Dizziness = 3	Associated ENT symptoms: Hearing loss =4 Tinnitus= 6 Ear fullness= 2 Hypersensitivity to noise= 1	No presence of nystagmus=7 Presence of horizontal or rotatory nystagmus=9 Presence of positive HST/ "central HINTS" or vertical or oblique nystagmus/ "central HINTS"= 17		Probable clinical diagnosi No presence of vestibular etiology of vertigo/dizzine Benign paroxysmal positi Probable central etiology=

y

Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose	Description and
21(79)	Pfizer-BioNTech (BNT162b2)	Abducens nerve palsy	59Y/F		2 days, after vaccine Acute binocular and painless, horizontal diplopia. And had h/o fever for 1 day.	Mild elevation in ESR and MRI and other blood inve unremarkable. Had persistent deficit on f
	AstraZeneca (ChAdOx1)	Recurrent Abducens nerve palsy	23Y/M	1st	1 week With 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 investigati unremarkable. Improved in follow up. H/o 2 episodes of similar years back following a feb another 2 years back follo
lsy						
)	Moderna (mRNA-1273)	Third cranial nerve palsy	88/M	1st	3 days With objective dizziness, diplopia and gait instability. k/c/o IHD, HTN, Paroxysmal AF . Non diabetic.	Brain CT scan, CT angiog and MRI ruled out a vascu Treated with oral steroid, recovery. Later vaccinated again wi different injection site.
8)	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, AN EMG were unremarkable. Treated with prednisone 4 followed by valacyclovir for 7 days. On 2months follow up pa completely.
6)	AstraZeneca (ChAdOx1)	Postvaccinal Encephalitis (Possible Autoimmune Encephalitis)	21/F	1st	1 day after developed headache and progressive neurological symptoms including attention and concentration difficulties starting on day 5 after vaccination, resulting in admission to hospital 11 days after vaccination. Subsequently had seizure.	MRI Brain- Normal CSF- 46 leukocytes/cmm(EEG- diffuse abnormally rhythms without epileptifo Responded to steroid ther
			63/F	1st	2 days later diagnosed to have DVT in left left- started on anticoagulation. 6 days post vaccination - gait	MRI Brain- Normal CSF- 115 leukocytes/cmm EEG- diffuse abnormally rhythms without epileptifo

					deteriorated, she developed a vigilance disorder and a twitching all over her body. Later developed severe immobilizing opsoclonusmyoclonus syndrome.	No response to initial anti Responded to steroid ther
			63/M		8 days after isolated aphasia and fever.	MRI Brain- Normal CSF- 7 leukocytes/cmm(l Testing for neurotropic vi CSF- Negative. EEG- Normal Responded to steroid ther
7)	AstraZeneca (ChAdOx1)	Hyperacute reversible encephalopathy	77/M	1st	1 day after Confusion and agitation consistent with delirium with extreme agitation. k/c/o sarcoidosis and polymyalgia rheumatica in clinical remission with Methylprednisolone 4 mg/day. Mild COVID-19 five months prior to vaccination.	CRP- elevated EEG - moderate diffuse sl CT (contrast)- unremarkal CSF: cell-3, protein-119m 52mg/dl, IL6-194(high), I Microbiological testing or CSF oligoclonal bands, CSF ar encephalitis antibodies, serum onconeural, antinuc antineutrophil cytoplasmi Negative. Responded to intravenous pulse therapy.
8)	AstraZeneca (ChAdOx1)	Herpes simplex encephalitis	27/M	1st	3 days after severe headache and altered mental status began to appear, including slowed psychomotor activity and loss of alertness. Subsequently severe headache, agitation, delirium, and disorientation	LP-CSF: protein levels (3 count of 600 per mm3 (pr lymphocyte) CSF HSV PCR- +ve MRI brain and EEG- Unr Treated with antiviral , an days.
21(89)	Moderna (mRNA-1273)	Acute hyperactive encephalopathy	32/M	1st	2days after developed acute confusion, memory disturbances, and auditory hallucination	EEG showed features of e CSF : elevated protein lev reference range = 0.15–0. counts (white blood cells levels. , MRI brain- Unremarkable CSF autoimmune encepha aquaporin- 4, anti-myelin basic protei oligodendrocyte glycopro anti-glial fibrillary acidic NMDAR, anti-GAD, and other autoimmune enceph negative. Responded to intravenous
alitis						
)	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 range 135-145), Tumor markers (CEA, AF CA15–3) and Paraneoplastic neuronal a including anti-Hu, Ri, Yo, Amphiphysin, CV2, SOX were negative. EEG- Unremarkable MRI Brain – intense signa

						temporal lobes (more on t parahyppocampal gyrus o DWI. Whole body CT- liver cys adenoma. CSF- Cell, protein and su CSF- LGI-Ab + Treated with methylpredn for 5 consecutive days) w
	AstraZeneca (ChAdOx1)	Autoimmune encephalitis	35/F	1st	5 days after Developed dysarthria , abnormal Movements, extreme anxiety, and reduced voluntary movements	MRI brain- mild swelling hippocampus without abn in contrast-enhanced fluid recovery (FLAIR) and T1 images. CSF- WBC-37/cmm (poly 32.4%) CSF- RBC-14800/cmm CSF-Protein- 50.7mg/dl, Serum paraneoplastic anti oligodendrocyte (MOG) a CSF synaptic antibodies, anti-bodies, and CSF olig Negative. Treated with weekly ritux
(92)	AstraZeneca (ChAdOx1)	Ascetic Meningitis retention syndrome	61/F	1st	18 days With headache, fever, paresthesias of the calves and thighs bilaterally and an unsteady gait, diplopia, and urinary retention. O/E: Neck stiffness +	MRI brain- non-enhancin white matter lesions. CSF - 200 WBC cells per mm3 with lymph Mildly elevated protein (6 60mg/dl) and glucose CSF to serum Infection work up and par were negative. Treated with IV steroid, r
	Pfizer-BioNTech (BNT162b2)	Ascetic Meningitis	32/M	2nd	2week after Headache for 1 week , O/E: Neck stiffness +	LP-CSF: Cells-480/cmm(90%Lym Protein- 118mg/dl Sugar- 56mg/dl (RBS-91 No response to intravenpu Responded to methylpred

Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose	Description and
00)	Moderna (mRNA-1273)=12	Myositis	28Y/F,	1st dose	5 days after the first dose of vaccine presented with muscle pain of her thigh 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 nega MRI muscles- left-domina alterations with contrast e quadriceps muscles sparin femoris, and diffuse subcu retention with contrast enh of fasciitis Treated with steroid, patie

021(101)	AstraZeneca (ChAdOx1)=3	Inflammatory myositis	74/M	1st	48hours Presented with a 3-week history of intermittent low-grade fever and polyarthralgia. ESR-123 mm/hr (< 15mm/ hr) CRP-269 (< 5mg/L) CPK-24 (25 – 170 U/L) ANCA- negative ANA- negative Myositis profile- negative	18FDG-PET-CT: a tree-ro in the lower limbs suggest vessel vasculitis. Whole-body short tau inv (STIR)-MRI showed diffu hyperintensities suggestiv myositis. EMG- fibrillations, positiv complex repetitive discha muscles. Skin and muscle biopsy sh small–medium vessel vas Remission achieved with
			75/F	1st .	2 days after Fever, arthralgia, myalgia, tachycardia. ESR-120 (< 15mm/ hr) CRP-271 (< 5mg/L) CPK-30 ((25 – 170 U/L) ANCA- negative ANA- negative Myositis profile- negative	18 FDG-PET CT- Day 25 minimally increased FDG avidity in evident in lower limb. Art patterns. MRI – Day 27-Multiple p hyperintensity involving t thighs including all compartmen compartment of both legs and pelvic girdl Treated with Oral Prednis Mycophenolate mofetil. A
			80/F	2nd	2days. Fever, fatigue, tachycardia. CPK-40 ((25 – 170 U/L) ESR-59 (< 15mm/ hr) CRP-102 (< 5mg/L) Myositis profile/ ANCA-negative.	MRI- Hyperintense signal muscles of both upper and Treated with oral steroid. Achieved remission.
21(98)	Janssen (Ad26.COV2.S)	Rhabdomyolysis	18/M	1st	2 days after myalgia, 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 With symptomatic manag CPK increased in first we 15 days.
)	Pfizer-BioNTech (BNT162b2)	Rhabdomyolysis	21/M	1st	1 day after progressively worsening pain and swelling in the lower back. O/E- tenderness to the paraspinal lumbar area upon palpation.	CPK- 22000U/L Aldolase- 97.8U/L AST-675U/L ALT-165U/L CRP-6.4mg/L LDH-1525U/L Urine blood+ Myositis profile- Negative Hydrated with high volum Saline and pain controlled Improved.
ndrome						
102)	Pfizer-BioNTech (BNT162b2)	Parsonage Turner syndrome	50/M	2nd	1week Pain and left hand grip and left wrist extension weakness with	MR brachial plexography normal (done early in the

					no sensory disturbances or other symptoms. Examination - weakness of left finger extension and left hand grip. Weak(MRC 3/5) - left dorsal interossei, extensor digitorum, extensor indicis, and flexor carpi ulnaris. DTR- mildly brisk b/l and symmetrical.	Treated with oral steroid a significantly.
3)	Pfizer-BioNTech = 4, Moderna= 2	Parsonage Turner Syndrome	36/F, 74/M, 50/M 53/M, 84/F, 46/F	2 patient after 1st dose 4 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 investiga brachial plexopathy in 2 p lower trunk plexopathy in posterior cord brachial ple and anterior/posterior inteross involvement in 2 patients. All patients either improv complete resolution of the up.
6)	Pfizer-BioNTech (BNT162b2)=1, Moderna (mRNA-1273)=1	Parsonage Turner Syndrome	49/M	1st	13 hours Pain followed by weakness of left upper limb.	MR Neurography- Within hourglass- like constrictio signal hyperintensity of th positioned fascicular bunc nerve were detected; this l PT/FCR bundle based on topographic fascicular arr median nerve. EDx- severe denervation a recruitment within the PT or FCR muscles. 3 month follow up- pain d weakness increased.
			44/M	2nd	18days 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 shoulder And had diminished sensation to pinprick in the radial nerve distribution.	NCS- mild slowing of the radial sensory responses. EMG- denervation and po recruitment in the infraspi MRI- left brachial plexus demonstrated enlargemen hyperintensity and multip constrictions of the supras accompanying denervatio pattern of the supraspinatu muscles.
07)	Pfizer-BioNTech (BNT162b2)	Small fiber neuropathy	57/F	2nd	1week With 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 mul Relevent workups for neu negative. Treated with gabapentin a weeks.
)	AstraZeneca (ChAdOx1)=4	Acute onset-Chronic inflammatory demyelinating polyneuropathy	Between 51 and 72 years. All male	1st	2–3 weeks	In aCIDP a/w COVID va illness may be severe and cranial nerve dysfunction, weakness.

		(aCIDP)				
09)	AstraZeneca (ChAdOx1)	Reversible radiculomyelitis	Woman in her 20s	1st	3-4 days after, subacute onset of legs' weakness, cramping pain and fever (38°C−39°C). O/E: Power LL- 2/5 (b/l) Spastic LL Plantar- equivocal Very brisk patellar, abductor and Achilles tendon reflexes with horizontal and vertical extension, and legs paraesthesia. Tactile and pinprick sensation was decreased from T4 dermatome downward. Passive and active leg movements elicited rigidity and tenderness.	CSF- Albuminocytologica OCB (CSF and Serum): P MRI Brain & Spine- Norr Electromyography and ele Negative Near complete recovery ir therapy.
0)	Pfizer-BioNTech (BNT162b2)	Myasthenia	82/M	2nd	2days after With 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 RNST- Decrement pattern Secondary evaluation for negative. Treated with pyridostigmi improving course.
1)	AstraZeneca (ChAdOx1)	Ocular Myasthenia	73/M	1st	8 days later Painless left-sided ptosis without diplopia. K/c/o Psoriasis and hypertension, IHD	MRI Brain- Normal Positive rheumatoid facto < 20 IU/ml). Low-frequency repetitive 14.7% decrement in ampl muscle of the compound r potential. Serum titer of anti- AChR after vaccine)= 1.9 nmol/ nmol/L). Positive pyridostigmine te
		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 decren CT- Mild thymic hyperpl Anti AchR Ab and anti M Neostigmine test- Positive Responded to pyridostigm
3)	Pfizer-BioNTech (BNT162b2)	Transient akathesia	36/F	2nd	12 hours Started to experience an urge to move which she described as "restless body syndrome.". k/c/o atopic dermatitis, allergic rhinitis and anxiety (on sertraline 50mg/day)	She derived temporary rel volitional movement but t and urge to move would s Her movements were alle flexing/extending her trun getting up and constantly This was followed by feve Her symptoms improved a

(114)	AstraZeneca (ChAdOx1)	Autonomic dysfunction	29/M	1st	4days after With intermittent paraesthesia in extremities, 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– 120 b.p.m.) vs. lying (50–60 b.p.m.) and skin colour changes (dark-blue/white/ dark-red) in acral areas (hands/ feet/penis) which is intermittent.	Antinuclear antibody (AN low titre (speckled pattern IgA level [5.06 g/L (0.60– MRI brain and nerve cond unremarkable. Treated wi steroid. His postural tachy paraesthesia and skin colo at 6-months.
5)	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 re with life style modificatio
)	Pfizer-BioNTech (BNT162b2)	Thunderclap headache	62/M		Recurrent episodic thunderclap headache. k/c/o- ocular melanoma.	Laboratory analysis, brain EEG and CSF analysis inc and cytology analysis were all unremarl
	AstraZeneca (ChAdOx1)		21/F	1st	2hours after Developed general malaise with subfebrile temperature 6hours later experienced a thunderclap headache, with nausea and vomiting	Neurological examination brain CT including CTang venography were all norm Symptoms improved over paracetamol, NSAIDs, int and oxygen therapy
(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;
	Pfizer	103		Pfizer		2.78; 95% CI, 2.47–3.13;
	Moderna	21		Moderna		0.58; 95% CI, 0.49–0.68;
	The cumulative rate of headache/migraine episodes after receiving all COVID-19 vaccines was 2.25-fold higher than the daily frequency of headach ratio, 2.25; 95% CI, 0.83-6.11).					
2(118)	Corona Vac	Prolonged migraine aura resembling ischemic stroke	**Age** between 24–48 years and 75% female.	**Interval from vaccination:** within the first 24 h : 75% between 1-7d :25%.	All presented with lateralized sensory deficits, motor deficits, or both, of 2–14 day duration. Migraine headache occurred in half of the patients.	MRI brain during and afte demonstrate any abnorma ischemic stroke. All patients showed mode hypoperfusion and concur of hyperperfusion on SPE symptomatic. None developed permanen brain injury.

cella Zoster

	mRNA vaccine= 45/54 (86.27%) Inactivated COVID-19 vaccine= 5/54 (5.88%) Non-replicating viral vector= 4/51 (7.84%)	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 te with vaccination and a plausible biological link "possible".
1(120)	Pfizer-BioNTech (BNT162b2)		79/M	1st	4 days after elevated erythematous lesions with vesicles on his right-handside lumbar 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/da week; 50 mg of acyclovir the vesicles.
	Pfizer-BioNTech (BNT162b2)		56/F	2nd	16 days after Fever, with haemorrhagic vesicles upon an erythematous base spreading on her arm, hand, and left side of her chest, with chest pain, and pain in her arm on the same side	Treated with 400 mg/8 h o mg/12 h of a vitamin B co .
ical Disorders (FND)						
)	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 hac the left side of her face an heaviness in her left leg. H abduction test results, wer symptoms were variabile. Investigations including n 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 hours. 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 Examination and neuroim investigations were unrem
		Functional Neurological disorder	41/M	1st followed by second dose	After a few minutes from the injection, reported bilateral facial paralysis with difficulty 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	Few weeks later, he sudde sided facial hypoesthesia. Examination- midline spli deficit in the face with tac hypoesthesia. Brain MRI, CT, & carotid ultrasonography: Normal. Sensory disturbance resol neurological examination

					tongue and respiratory impairment, which was quickly resolved by corticosteroid therapy. Later he developed right-sided weakness, at the same side of the injection, lasting for about 40 min.	next 2 weeks.
7)	Pfizer-BioNTech (BNT162b2)	PNES		2nd dose	20min after short episode of generalised tonic–clonic psychogenic non-epileptic seizures (PNES) which was followed by another episode of- inability to move the whole body with preserved level of consciousness). No post-ictal period followed these episodes.	VEEG during few events-
	AstraZeneca (ChAdOx1)	Subjective sensory symptoms- FND			2 weeks after persistent dizziness and a subjective loss of tactile sensitivity in the right arm and leg.	Brain CT- Normal

Author	Vaccine type	Neurological diseases	Age/Sex	Dose of vaccine	Interval from last dose	Description and ob
128)	Moderna (mRNA-1273)	Reversible cerebral vasoconstriction syndrome (RCVS)	38/F	2nd	18days developed visual impairment due to scotomas and thunderclap headache.	Multimodal cerebral MRI: Acut lesion in the territory of the righ weighted images, DWI,ADC m the PCA on MRA. Partially responded to Nimodip Levetiracetam (1g/d) .
)	Pfizer-BioNTech (BNT162b2)	Cytotoxic Lesion of the Corpus Callosum (CLOCCs)	22/M	1st dose	3 days With febrile sensation and headache around the eyes and forehead. CSF- Normal cells and protein.	MRI brain- oval shaped restricte corpus callosum with low appar coefficient (ADC) values and la mediated enhancement
	Pfizer-BioNTech (BNT162b2)	Gastroparesis	57/M	1st	5days Started to have nausea, intractable vomiting and hiccups. Treated with metoclopramide, and erythromycin. Recurred again after receiving the second dose.	Investigation showed significan emptying. No response to H2 re responded to oral steroid.
al. 2021(131)	Pfizer-BioNTech (BNT162b2)	Delirium	89/M	1st	2 days with a 24-h history of confusion, fluctuating attention, anxiety and inversion of the sleep–wake cycle.	K/c/o type 2 diabetes mellitus, I III-b chronic kidney disease, pr mild hearing impairment and de Managed with antipsychotic, im
32)	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 FLAIR	Cerebrospinal fluid analysis sho count, normal protein at 0.31 g/ 4 mmol/L, and negative microb serological tests. EEG showed r Treated with 3 AEDs levetirace lacosamide. Responded to pulse followed by two sessions of pla alternate days.

					images at bilateral hippocampi and insula that was correlating with Postictal changes.	
	Moderna (mRNA-1273)=2	Encephalopathy Associated With Nonconvulsive Status Epilepticus	86/F	1st	7days with 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 meningi NAAT, oligoclonal bands, and negative except for West Nile v antibodies with minimal protein without contrast and MRI brain contrast showed no acute findin Continuous EEG -non-convulsi epilepticus treated with lorazepa
			73/M	1st	21 days with staring episodes, restlessness, and cognitive deficits. K/c/o Crohn's, hereditary hemochromatosis, hypertension, and hyperlipidemia	CSF studies, including meningi Nucleic Acid Amplification Tes autoimmune encephalitis, and t negative except for mildly eleva glucose. CT head and MRI brain showed EEG- non-convulsive status epi treated with lorazepam and leve maintenance.
34)	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 con ophthalmoplegia. MRI brain s/c
	Moderna (mRNA-1273)	Triggered Moyamoya disease with Sjogren disease and autoimmune thyroiditis	40/F	2nd	3days after severe headaches with a decreased level of consciousness and a tonic-clonic seizure. k/c/o- Sjogren disease and autoimmune thyroiditis O/E- Febrile with high Blood pressure and PR.	Elevated CRP, anti-PF4 Ab, SS CT Brain - left caudate nucleus temporal lobe IVH and ICH wit DSA- bilateral distal ICA steno-occlusion with the constri cerebral arteries and anterior ce cortical collateralization pattern carotid artery system that was c moyamoya angiopathy (MMA) staging system was stage V.
021(137)	Moderna (mRNA-1273)	Hypophisitis	51/M	2nd	3 days after vaccination with headache, nausea, vomiting, malaise, and diffuse arthralgias	MRI brain suggestive of diffuse gland consistent with acute hyp

Table 05: Spectrum of COVID19 vaccine associated neurological disorders (Co-VAN) – a review of the literature

Abbreviations:

GBS- Guillain-Barré syndrome

NMOSD- Neuromyelitis optica spectrum disorders

MOGAD- Myelin oligodendrocyte glycoprotein antibody-associated 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