Original Article

Neurological Disorders Seen During Second Wave of SARS-CoV-2 Pandemic from Two Tertiary Care Centers in Central and Southern Kerala

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Abstract

Background and Objective: SARS-CoV-2 infections present with predominant respiratory symptoms. Only a few anecdotal reports of neurological involvement have come out from India so far. Adverse neurological events following immunization (AEFI) were also reported. We present the neurological symptoms seen either in association with vaccination or COVID-19 infection during the second wave. **Methods:** This was a retrospective study that included consecutive COVID-19 patients' admissions during the second wave of COVID-19 pandemic in two tertiary health care centres in Kerala. Neurological symptoms two weeks prior or thirty days after a positive status of antigen or RTPCR was termed as COVID-19-Associated Neurological Disorders (CAND) and those with neurological symptoms within one month of COVID-19 vaccination was termed as Post-Vaccinal Neurological Disorders (PVND). **Results:** During the study period, 1270 COVID-19 admissions were reported. We identified neurological symptoms in 42 patients (3.3%), of which 35 were CAND and 7 were PVND. Stroke was the most common (50%), followed by seizures and peripheral nervous system disorders (14.2% each). Encephalitis/demyelination (11.9%) and COVID-19-associated infections (9.5%) were also seen. **Conclusion:** During the SARS-CoV-2 pandemic, CAND and PVND have been emerging. Association of some of these may be fortuitous; however it is worth mentioning as pathogenic mechanisms of COVID-19 affecting various organ systems still remain unclear. Moreover, this may be helpful in future studies designing management options.

Keywords: COVID associated neurological disorders, COVID-19 infection, COVID-19 vaccination, neurological disorders, post vaccinal neurological disorders

Introduction

Early reports from Wuhan, China detailed a range of neurological symptoms seen in patients with SARS-CoV-2 infection. In up to 25% of COVID-19 cases, manifestations of central nervous system (CNS) involvement have been reported.[1] Recent isolated case reports also described some of these neurological manifestations, which include acute cerebrovascular disorders [CVD],[2,3] encephalopathy or encephalitis, acute demyelinating encephalomyelitis (ADEM), as well as peripheral neurological associations such as Guillain-Barré syndrome (GBS).[4]

Methodology and Data Collection

We conducted a retrospective study in two tertiary health care centres in Kerala representing the central and southern regions. Our tertiary institution in central Kerala holds a capacity of 500 hospitals beds, with 150 beds being allocated for COVID-19 admissions. The tertiary institution in south Kerala has a capacity of 450 beds with 100 beds being allocated to COVID-19 admissions. Consecutive COVID-19 patients admitted in both centres during the time period of second wave of COVID-19 pandemic[5] for a duration of three months from 1 March 2021 to 31 May 2021 were taken. We retrieved all related data from the electronic database registry of the respective centres. A detailed electronic chart review was conducted to identify neurological symptoms among COVID-19 patients admitted to the selected centres during the study period. Incubation period of COVID-19 is thought to extend up to 14 days with a median time of 4 to 5 days from exposure to onset of symptoms.[6] Neurological symptoms which developed 14 days prior or up to 30 days after a positive antigen or a positive COVID-19 RT–PCR status were termed as COVID-19-associated neurological disorders (CAND). Neurological symptoms one month within vaccine intake was termed as post-vaccinal neurological disorders (PVND). We excluded the insignificant symptoms like anosmia, headache,

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myalgia, fatigue, etc., as neurological symptoms. We recorded the clinical profile of the patients in detail with the relevant investigations and treatment. Neurological disorders were classified into stroke, demyelination, infection, seizure, and peripheral nervous system disorder. Ethical clearance from institutional research committee has been obtained for the study (HR/RIMS/234/2021).

Results

During the study period of 3 months, 650 and 620 patients with COVID-19 were identified from the hospital in central and southern Kerala, respectively. Among all patients from both the hospitals, 42 (25 and 17 patients, respectively from hospitals at central and southern Kerala) reported neurological symptoms. Out of 42 patients with neurological symptoms in the study group, 35 reported CAND. Further, seven reported PVND. Mean age of the study population was 59 years (standard deviation, 16.3) with age ranging from 24 to 81 years. There were 29 males (69%) and rest were females. According to the COVID-19 treatment guidelines of Kerala,[7] out of 35 patients with CAND, 15, 12, and 8 were mild, moderate, and severe COVID-19 infections respectively [Figure 1]. The mean duration for onset of symptoms were 6 days with an interquartile range of 2–3 days (Q3–Q1). The onset of neurological symptoms was between 2 days prior to 20 days after the diagnosis or onset of COVID-19 symptoms. Most of the patients (25/35) had symptoms during COVID-19 infections (71.4%), 8 had symptom onset after turning negative for COVID-19 antigen (22.8%), and rest of two patients had symptom onset prior to antigen/RT–PCR positive status. Most common comorbidity noticed was hypertension (45%), followed by diabetes mellitus (28.5%). Seven patients (16%) required critical care admission. Further, 2 patients needed invasive ventilation during hospital stay. Based on the pre-defined neurological phenotype, the study population (42 patients) was grouped into five main categories. Stroke was the most common condition seen (50%). We also noted post infectious or vaccine-related encephalitis or demyelination in 5 patients (11.9%). Additionally, 6 out of 42 patients reported peripheral nervous system disorders (14.2%), and seizure presentations (14.2%). Infections associated with COVID-19 was seen in 4 patients (9.5%).

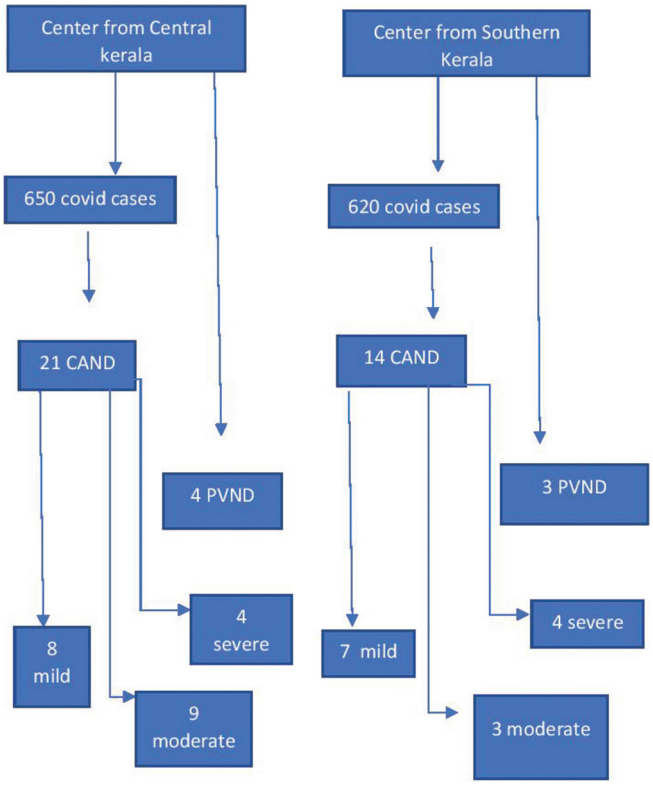

Figure 1: Flow chart depicting the cases of COVID-19-associated neurological disorders and post-vaccinal neurological disorders

Stroke

Twenty one of the 42 patients (50%) with an age range of 24–80 years were diagnosed with stroke [Tables 1 and 2]. 18 had acute ischemic stroke, 2 had cerebral venous sinus thrombosis and one had hemorrhagic stroke [Figure 2]. One presented with stroke post vaccination. One had large vessel occlusion. Only 4 patients presented with a posterior circulation stroke whilst one had multifocal infarcts. There were two cases of cerebral venous thrombosis, one with right transverse and sigmoid sinus [Figure 2] and the other with left transverse sinus thrombosis. Two patients were admitted in the intensive care unit, the former (Patient 18) in view of a large intraparenchymal hematoma [Figure 2] and the latter (Patient 19) with right internal carotid artery occlusion. All patients underwent a computed tomography (CT) and/or a magnetic resonance imaging (MRI) of the head at presentation. None underwent thrombolysis or mechanical thrombectomy. 15 patients recovered fully, 5 survived with disability and one patient died within seven days of the diagnosis due to a large intraparenchymal hematoma and pneumonia. Elevated values of D-dimer were seen in 12 patients.

Inflammatory/demyelinating disorders

We identified 4 cases of post-vaccinal demyelination and one case of post-infectious demyelination [Table 3]. 3 patients (Patients 22, 24, 25) had received first dose of recombinant ChAdOx1 nCov-19 vaccine (COVISHIELD). MRI brain of 28-year-old male (Patient 22) showed T2/FLAIR hyperintensities with no contrast enhancement [Figure 3]. All of them received IV methylprednisolone pulse therapy (one gram daily for 5 days). Two of them (Patient 22 and 25) recovered fully, whereas 48-year-old male (Patient 24), who had retrobulbar neuritis, improved partially (Vision 6/18 right eye and 6/12 left eye).

Patient 23, a 49-year-old female, who was diagnosed with transverse myelitis had received BBV152 COVID-19 vaccine (COVAXIN) 48 hours prior to onset of weakness. She had no previous febrile illness or diarrhea. On examination, she had flaccid paraplegia (bilateral lower limbs MRC grade 1/5 power) with sensory level at T12 with bladder

Table 1: Characteristics of patients with stroke

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, M/F	63, M	65, F	72, M	74, M	50, M
Covid Category	Moderate	Moderate	Moderate	Mild	Mild
Stroke type	Ischemic	Ischemic	Ischemic	Ischemic	Ischemic
Presenting symptom	Right upper limb weakness	Right Ataxic Hemiparesis	Gait Ataxia, Dysarthria	Right upper limb weakness	Slurring of Speech
Duration of onset after covid-19 positive status	13 days	Same day	5 days prior	6 days	14 days
Blood results at admission	CRP-21.19, Ferritin-23.15ng/ml, D-dimer-0.20 µg/ml	CRP- 1.51, Ferritin- 22.17ng/ml, D-dimer-0.74µg/ml.	CRP-0.78, Ferritin- 30.5ng/ml, D-dimer-0.35µg/ml.	CRP- 1.89, Ferritin-81 ng/ml, D-dimer-0.49 µg/ml	CRP- 1.89, Ferritin-102 ng/ml, D-dimer-0.52 µg/ml
Brain Imaging	MRI-Left MCA Infarct.	MRI-Left pontine infarct	MRI-Acute infarct Splenium of corpus Callosum	CT Brain -Left occipital Infarct.	MRI-Acute Infarct left corona radiata
Angiogram	Normal	Normal	Normal	Normal	Normal
Treatment	Antiplatelets	Antiplatelets	Antiplatelets	Antiplatelets	Antiplatelets
mRS Score	0	0	0	1	0
	Patient 6	**Patient 7**	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**
Age, M/F,	45, M	24, F	70, M	80, M	70, M	71, M
CAT	Mild	Severe	Moderate	Severe	Mild	Post vaccine
Stroke type	Ischemic	Cerebral Venous sinus Thrombosis	Ischemic	Ischemic	Ischemic	Ischemic
Presenting symptom	Blurring of vision, Loss of consciousness	Left facial weakness	UMN facial weakness, Gait ataxia	Left Upper limb weakness, Seizures	Aphasia, rt Upper limb weakness	Seizures
Duration of onset after covid-19 positive status	Same day	19 days	3 days	6 days	2 days prior	3 days
Blood results at admission	CRP- 0.98, Ferritin- 59.26, D-dimer- 0.20 µg/mL, Homocysteine 37.62 µmol/L	CRP-45, Ferritin- 98.5 D-dimer-0.78µg/ml.	Ferritin- -718ng/ml, D-dimer- 1800ng/ml	CRP-135, ESR-122, Ferritin- -30.26, D-dimer- 2.7 µg/mL	Ferritin- -20.26, D-dimer- 0.13 µg/mL	Ferritin- -90.26, D-dimer- 0.60 µg/mL
Brain Imaging	CT Brain -Normal	MRI-Right Transverse thrombus	CT Brain-Right Frontal Infarct	MRI-Right hemispheric watershed	CT -Left MCA infarct	MRI-Acute Infarct left Temporoparietal Cortex
Angiogram	Not done	NA	Not done	Normal	Not done	Normal
Treatment	Antiplatelets, B12, B6, B1 supplements	Anticoagulation	Antiplatelets	Antiplatelets, Antiepileptics	Antiplatelets	Antiplatelets, Antiepileptics
mRS	0	0	0	1	2	0

mRS: modified rankin score

involvement. MRI thoracic spine was suggestive of transverse myelitis at T12 level [Figure 3]. COVID-19 IgG and IgM antibody levels were high—50.52 U/ml (Negative <0.80). Her anti-aquaporin4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies in serum were negative. Patient was treated with six cycles of plasmapheresis with pulse methylprednisolone (one gram daily for five days) followed by oral steroids following which she recovered partially (lower limb power of 2/5 as per Medical Research Council (MRC) grade) with mRS of 4.

55-year-old male (Patient 26) who was diagnosed with cauda equina syndrome also improved partially (3/5 MRC grade) with IV methylprednisolone for 5 days followed by oral steroids. On follow-up at 3 months his mRS was 3.

Breakthrough seizures and first onset seizures

Six patients had seizures associated with COVID-19 infection [Table 4]. There were 3 cases of breakthrough seizures (Patients 27, 28, 31). Seizures were well controlled for all of them. Patient 31 had localization-related epilepsy which was well controlled with carbamazepine, had an episode of seizure 48 hours after first dose of recombinant COVISHIELD. Two patients (Patients 29 and 32) had first episode of seizure, after which they recovered with no features of encephalopathy. Patient 30, a 29-year-old pregnant lady, with no h/o pregnancy-induced hypertension, presented with first episode of seizure, 18 days after testing positive for COVID-19 RT–PCR on post-partum day 15. She had no fever, headache, visual symptoms, and her blood pressure was 130/88 mm of Hg. She had no signs of meningeal irritation or any focal deficits; her fundus examination was normal. Her MRI brain was suggestive of atypical posterior reversible encephalopathy syndrome [Figure 4]. EEG showed bifrontal slowing. Vasculitic workup was negative.

COVID-19 related infections

Many mucormycosis cases had to be referred to government hospitals due to non-availability of Amphotericin B. However, we had four cases of mucormycosis during the second wave of pandemic, of which one presented with rhino-orbito-cerebral mucormycosis (ROCM). There was one case of meningitis and two cases of COVID-19-related encephalopathy/encephalitis [Table 5]. Patient 33, a 50-year-old female with new onset type-2 diabetes mellitus, presented with left eye pain and eye movement restriction 4 days after testing positive for

Table 2: Characteristics of patients with Stroke

	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16
Age, M/F,	59/M	74/F	62/M	75/M	52/M
CAT	Mild	Mild	Mild	Mild	Severe
Stroke type	Ischemic	Ischemic	Ischemic	Ischemic	Cerebral Venous Sinus Thrombosis
Presenting symptom	Slurring of speech, Ataxia	Dysarthria, Ataxia	Ataxia	Left hemiparesis	Headache, Aphasia
Duration of symptoms after Covid-19 positive status	Same day	5 days	8 days	Same day	16 days
Blood results at admission	CRP-2.7, ESR-46, D-dimer-0.61µg/ml	ESR-40, D-dimer-0.26µg/ml	Hb-14.7, TC-6770, P-64, L-25, E-6, M-5, PLT-1,62.	Hb-15.2, TC-17220, P86, L10, M3, PLT-2.24	CRP-19.6, D-dimer-0.90µg/ml
Brain Imaging	MRI-Acute Infarct left inferior temporal lobe	MRI-Infarct left Lentiform nucleus	MRI-Hyperacute infarct left lentiform nucleus	MRI-Acute infarct superior parietal and angular gyrus left side	MRI-Haemorrhagic infarct left temporal lobe
Angiogram	Normal	Normal	Normal	Normal	Normal
Treatment	Antiplatelets	Antiplatelets	Antiplatelets	Antiplatelets	Anticoagulation
mRS	0	0	0	1	1
	Patient 17	**Patient 18**	**Patient 19**	**Patient 20**	**Patient 21**
Age, M/F,	60/M	33/M	56/F	66/F	59/F
CAT	Mild	Moderate	Mild	Severe	Mild
Stroke type	Ischemic	Haemorrhagic	Ischemic	Ischemic	Ischemic
Presenting symptom	Ataxia, Left Hemiparesis	Seizures-Recurrent episodes	Ataxia, Left hemiparesis	Ataxia, left hemiparesis	Left Hemiparesis
Duration of Symptoms after positive status	5 days	13 days	16 days	8 days	20 days
Blood results at admission	ESR-100, CRP-23.38, D-dimer-1.2µg/ml	ESR-64, D-dimer-0.71µg/ml	ESR-30, CRP-8, D-dimer-0.12µg/ml	ESR-123, D-dimer-1.02µg/ml	ESR-30, CRP-8, D-dimer-0.22µ/ml
Brain Imaging	Acute Infarct Left Thalamus.	CT-Large intraparenchymal hematoma left basal ganglia	MRI-watershed infarct right hemisphere	MRI-Watershed infarct right hemisphere	MRI-Right hemispheric watershed infarct
Angiogram.	Normal	Antioedema	ICA occlusion.	Normal	Normal
Treatment	Antiplatelets	6	Antiplatelets	Antiplatelets	Antiplatelets
mRS	0		0	0	0

mRS: modified Rankin score

Table 3: Characteristics of patients with Post infectious/Post Vaccinal demyelination

PATIENT	PATIENT 22	PATIENT 23	PATIENT 24	PATIENT 25	PATIENT 26
Age/sex	28y/m	49 y/f	48y/m	81/m	55/m
Covid infection/ vaccination	ChAdO×1nCov-19 Vaccine	Covaxin (BBV152)	ChAdO×1n Cov-19 Vaccine	ChAdO×1n Cov-19 Vaccine	Covid 19 infection-mild
Duration of symptom onset	10 days	2 days	11 days	3 days	15 days (post antigen positive)
COVID-CATEGORY	NA	NA	NA	NA	Mild
Key symptoms	Unsteadiness of gait, facial paraesthesia	Acute onset of paraplegia	Headache, blurring of vision and eye	Seizures, altered sensorium	Bilateral lower limb weakness, urinary retention
Final diagnosis	Post vaccinal demyelination	Transverse myelitis	Optic neuritis-post vaccinal	Post vaccinal encephalitis	Post infectious conus-cauda equina
MRI Study	Periventricular hyperintensities with no contrast enhancement	Demyelinating lesion at T11 level.	Hyperintensity with contrast enhancement optic nerve	Normal	Hyperintensity in T2 in conus region
CSF Study	CSF-2cells (L100%), protein-33mg/dl, sugar-59mg/dl	CSF- Cells - 5 (L 90, P10) protein- 55.50mg/dl sugar- 78 mg/dl	CSF- Cells – 3(L100%) protein- 50.mg/dl sugar- 80 mg/dl	CSF-Cells-8(L 100%), protein-44mg/dl, sugar-69mg/dl	CSF-Cells—5(L90, P10) protein- 60.mg/dl sugar- 70 mg/dl sugar.
Treatment	IV methylprednisolone	Plasmapheresis methyl prednisolone	IV methyl prednisolone	IV methyl prednisolone	IV methyl prednisolone
mRS	0	4	1	0	3

mRS: modified Rankin score

COVID-19 infection. She had history of left upper premolar tooth extraction 10 days prior. MRI brain was suggestive of rhino-orbito-cerebral mucormycosis (ROCM) [Figure 5]. Her nasal swab culture showed Rhizopus growth which was suggestive of mucormycosis. They were advised surgical debridement; however, patient's relatives were not willing for the same and patient expired 10 days after onset of symptoms.[8]

Patient 34 was a 34-year-old male who presented with headache 20 days after onset of COVID-19 symptoms. On examination, he had early papilledema with neck stiffness. His cerebrospinal fluid (CSF) study was suggestive of viral/partially-treated bacterial meningitis. His CSF gram stain, bacterial culture, India ink, cryptococcal antigen and AFB stain was negative. His TB GeneXpert and CSF PCR

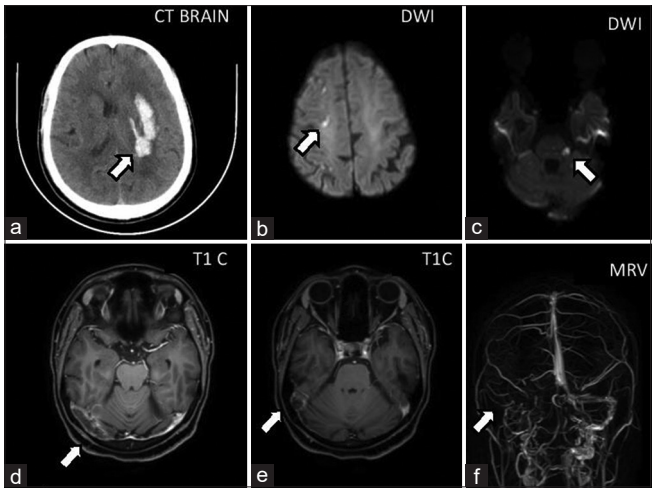

Figure 2: (a) CT of patient 18 " Large intraparenchymal hematoma left basal ganglia. (b) MRI, DW of patient 9 " Right Hemispheric watershed infarct. (c) MRI, DW of patient 2 "Acute infarct involving left middle cerebellar peduncle. (d-f) MRI of patient 7 with CVST. (d and e) T1 contrast axial image "Thrombus in Right transverse and sigmoid sinus. (f) MR Venogram "Thrombus in Right Transverse and Sigmoid sinus

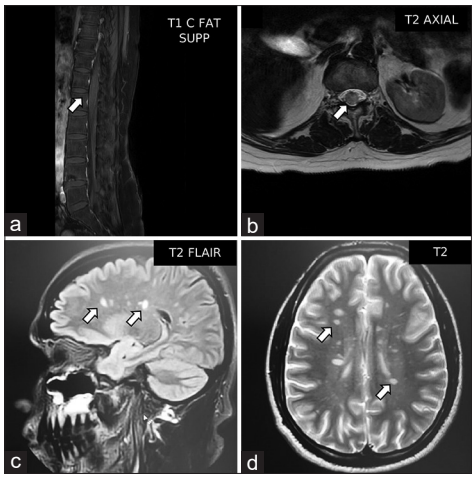

Figure 3: (a) MRI thoracolumbar spine of Patient 23 -T2 sagittal image showing hyperintensity at T12 level. (b) T2 Axial view showing hyperintensity suggestive of demyelination. MRI brain of Patient 22 with post-vaccinal demyelination. (c) T1 contrast Sagittal view showing periventricular hyperintensities. (d) T2 Axial image showing periventricular hyperintensity

Table 4: Characteristics of patients presented with Breakthrough seizures/First onset seizure

	Patient 27	Patient 28	Patient 29
Age/Sex	30/F	58/M	29/F
Covid Category	Moderate	Moderate	Mild
Vaccine	NA	NA	NA
Duration of symptom onset after positive antigen test	Same day	6 days	9 days
Symptom	Breakthrough seizure	Breakthrough seizure	First episode
Last Seizure	6 years back	8 years back-Not on drugs	NIL
Diagnosis	Primary Generalised Epilepsy-Recurrence	Localisation related Epilepsy	Late onset Seizures
Investigation	MRI Brain -Normal	EEG-Left temporal epileptiform abnormality.	MRI Brain-Normal
Treatment	EEG-Generalised epileptiform abnormality (follow up)	MRI-Not done.	EEG- Generalised epileptiform abnormalities.
mRS	Levetiracetam	Levetiracetam	Brivaracetam
	1	1	0
	Patient 30	**Patient 31**	**Patient 32**
Age/Sex	29/F	71/M	70/M
Covid CAT	Moderate	NA	Moderate
VACCINE	NA	ChAdO×1n Cov-19 Vaccine.	NA
Duration of symptom onset after positive antigen test	18 days	2 days	1 day
Symptom	Seizure-First episode	Breakthrough seizure	Seizure-First episode
Last Seizure	NIL	6 years back	NIL
Diagnosis	Posterior Reversible Encephalopathy syndrome	Breakthrough Seizures-Localisation related Epilepsy	Late onset Seizures
Investigation	MRI-FLAIR/T2 hyperintensity in cortical/ subcortical areas of bilateral; frontoparietal lobes with no diffusion restriction.	EEG-Normal.	MRI-Normal
Treatment	Levetiracetam	Carbamazepine	EEG-Left temporal epileptiform abnormality.
mRS	0	1	Brivaracetam
			1

mRS: modified Rankin score

meningoencephalitis panel was not done. He was treated with Meropenem and Dexamethasone following which there was complete improvement of symptoms on follow-up at 14 days. His papilledema improved and he was asymptomatic, with mRS of zero on follow-up.

There were two cases of COVID-19-related encephalitis/ encephalopathy (Patients 35 and 36). Both were severe cases of COVID-19 as per government guidelines and one of them was ventilated [Table 5]. One patient (Patient 35) was re-evaluated when she presented with recurrent seizures

Table 5: Characteristics of patients with covid related infections

PATIENT	PATIENT 33	PATIENT 34	PATIENT 35	PATIENT 36
Age/Sex	50 Y/F	34 Y/M	79Y/F	65/F
COVID INFECTION/ Vaccination	COVID INFECTION	COVID INFECTION	COVID-19 INFECTION	COVID-19 INFECTION
Duration of symptom onset after covid positive status	4 DAYS	20 DAYS	1 DAY	1 DAY
COVID Category	Moderate	Mild	Severe	Severe
Key symptoms and signs	2,3,4,5,6 Cranial Nerve palsy, Decreased sensorium	Headache, vomiting, papilledema	Altered sensorium, seizures on D1, Recurrent seizures D14.	Fever, vomiting, seizures
Final neuro diagnosis	Rhino orbito cerebral mucor mycosis.	Meningitis	Covid encephalitis	Covid encephalitis
Blood investigations	CRP-125.95, ESR-90, INR-1.15	ESR- 3	ESR-26, CRP-30.25, INR-0.99. Serum sodium-128	CRP-3.39. Serum sodium-126
MRI/CT	MRI brain-cavernous sinus thrombosis, Orbital Apex involvement,	MRI Brain - Normal,	MRI- left temporoparietal hyperintensity	MRI Brain-Normal
CSF study	Multiple territory infarct	CSF- 250 cells (L 85%, P 15%) Protein -95.1, Sugar-51.CSF gramstain, culture, Indiaink, cryptococcal antigen, AFB stain -Negative.TB PCR/TB GeneXpert report -Not done.	EEG-Bilateral periodic epileptic discharges.	CSF-4 cells (L100%), P-43, Sugar-78
Treatment	Not done	IV Meropenem, Mannitol	CSF- 8 cells, Protein-45, sugar-106 , HSV PCR-Negative	IV dexamethasone, ceftriaxone.,
mRS	Amphotericin B	0	Hyponatremia correction Dexamethasone, acyclovir, ceftriaxone	2
	6		4	

mRS: modified Rankin score

Table 6: Characteristics of patients with Peripheral Nerve Involvement

Characteristics	Patient 37	Patient 38	Patient 39
Age/Sex	61/M	25/M	51/M
Covid Category	Moderate	Mild	ChAdO×1n Cov-19 Vaccine
Duration of symptom onset afterCovid-19 positive status	One day	20 days	12 days post vaccination
Symptom	Right sided facial deviation, difficulty to close right eye	Right sided facial deviation, difficulty to close right eye	Bifacial weakness
Diagnosis	LMN Facial palsy left	LMN facial palsy left	Bilateral LMN facial palsy
Investigation	NIL	NIL	MRI Brain -Normal
Treatment	Oral Steroids	Oral Steroids	Oral Steroids
mRS	0	0	1
Characteristics	**Patient 40**	**Patient 41**	**Patient 42**
Age/Sex	54/M	60/M	46/M
Covid Category	Severe	Moderate	Severe
Duration of symptom onset after Covid-19 positive status	10 days	6 days	17 days
Symptom	Left foot drop	Left foot drop	Left foot drop
Diagnosis	Left foot drop	Left foot drop	Left foot drop
Investigation	NCS-Axonal Left Peroneal Neuropathy	NCS-Axonal Left Peroneal Neuropathy	NCS-Axonal Left peroneal neuropathy
Treatment	Oral Steroids	Oral Steroids	Oral steroids
mRS	1	2	2

mRS: modified Rankin score

and right hemiparesis after 14 days of antigen positive status and turned out to be left focal encephalitis with residual right hemiparesis. Her MRI and EEG features were supportive [Figures 5 and 6]. Second patient also had seizures at presentation with normal metabolic parameters. Her MRI and CSF were normal and she improved with treatment. Patient 35 had a mRS of 4 on follow-up and patient 36 had mRS of 2.

Peripheral nervous system involvement

There were 3 cases of lower motor neuron (LMN) facial palsy and 3 cases of foot drop [Table 6].

Discussion

In this article, we report a variety of neurological disorders among patients with COVID-19 infection admitted during the "second wave" in two tertiary care centers in Kerala. Our cohort of cases demonstrates a wide range of COVID-19-related neurological disorders, and include ischemic and hemorrhagic cerebrovascular events (50%), seizure symptomatology (14.2%), peripheral nerve disorders (14.2%), post infectious demyelination (11.9%) and infectious disorders (9.5%).

Neurological disorders have been reported in patients who present solely with neurological signs and symptoms as

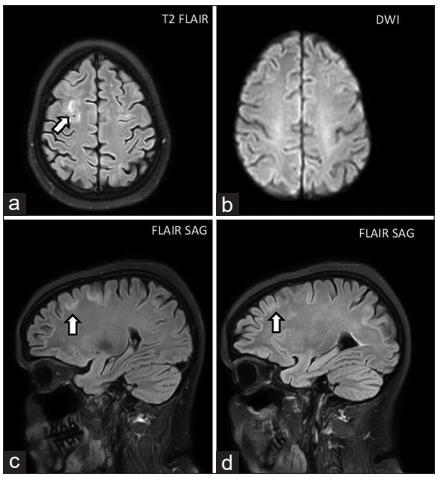

Figure 4: MRI of Patient 30 with posterior reversible encephalopathy syndrome. (a) T2 FLAIR axial image showing bilateral frontoparietal hyperintensity. (b) DW Axial image showing no evidence of diffusion restriction. (c and d) T2 FLAIR Sagittal images showing hyperintensity involving B/L frontoparietal region

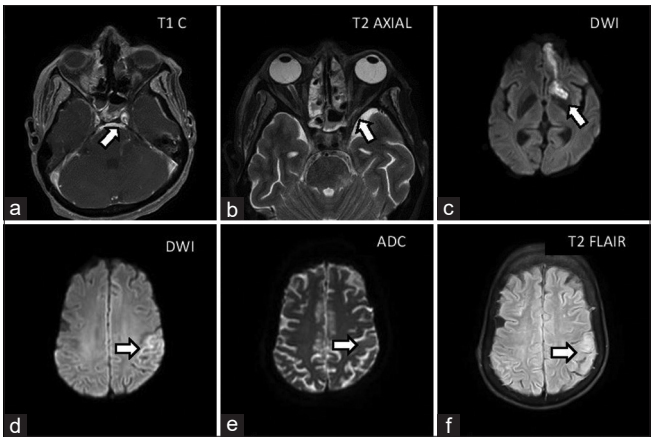

Figure 5: MRI brain images of patient 33 with ROCM. (a) T1 C axial image showing left cavernous sinus thrombus, (b) T2 axial image showing mucor involvement of left orbital apex. (c) DW axial image showing infarct involving left frontal lobe with diffusion restriction. (d and e) DW and ADC images of Patient 36, showing hyperintensity in left temporoparietal region, showing no diffusion restriction. (f) FLAIR images of Patient 36 showing hyperintensity in left temporoparietal region

well as those with established systemic or pulmonary illness related to COVID-19. These neurological features may precede or occur days after the onset of pulmonary symptoms. Some of the proposed mechanisms underlying the increased prevalence of neurological disorders in COVID-19 include widespread systemic inflammatory and cytokine responses, diffuse intravascular coagulation and/or critical illness-related coagulopathy and direct neuronal injury.[9] Several mechanisms have been proposed about the route of entry and associated neurological complications. One is epithelial humoral route in which the virus disrupts the primary epithelial barrier and attain access into the bloodstream. Angiotensin Converting Enzyme 2 is expressed abundantly on alveolar epithelial cells and gastrointestinal tract.[10] On ensuring access to the systemic circulation, SARS-CoV-2 disrupts the endothelial barrier of the blood–brain barrier (BBB) or the blood–cerebrospinal fluid barrier (BCSFB) via its interaction with ACE2 receptors at the endothelial cells and subsequent CNS contact.[11] Other routes of entry proposed are neuronal/nervous system route,[12] lymphatic–cerebrospinal route,[13] infected immune/lymphatic cell route.[14] Aerosol droplets may penetrate through nasal mucosa of COVID-19 infected patients and travel through the cribriform palate into the CNS.

Covid associated neurological disorders

There has been a reported increase in the incidence and severity of cerebrovascular disease associated with COVID-19, particularly in a younger cohort in United Kingdom.[15] Our cohort of patients demonstrated a high percentage of patients with stroke (50%) with 18 of them suffering from ischemic stroke. Coagulopathy, vasculitis and viral endotheliitis have also been reported as potential causes of multi-vessel stroke in patients with COVID-19. The hyper-inflammatory syndrome or "cytokine storm" strongly associated with severe COVID-19 infection could also contribute to the underlying etiology.[16]

Thrombotic microangiopathy and endothelial dysfunction, related to COVID-19, may be contributory factors in sepsis/critical illness-related cerebral microbleeds.[17] Our patient with large intraparenchymal hematoma (Patient 18), who was categorized as severe COVID-19 infection as per government guidelines, was on ventilator with therapeutic anticoagulation and steroids. Few case reports of CVST associated with COVID-19 are available. The increased risk of arterial ischemic stroke or CVST in SARS-CoV-2 infection suggests a pro-coagulant state, which could be caused by either blood flow stasis, particularly in critically ill and immobilized patients, or hypercoagulability.[18] We had two cases of cerebral venous thrombosis, 24-year-old female and 52-year-old male (Patient 7 and 16), both with severe COVID-19 infection with elevated D-dimer values. Among the 21 patients with stroke, D-dimer values were elevated in 12 patients on admission, which points to the fact that monitoring D-dimer values would be helpful to prognosticate the disease course and determine therapy.[19] 20 patients had stroke post COVID-19 infection and one post vaccination.

We report a case of post-infectious demyelination affecting conus/cauda equina in which a 55-year-old male patient presented with lower limb weakness and bladder retention Urinary (Patient 26). Similarly, Mehta *et al*. also reported a case with demyelinating lesions associated with the neurological damage in a case with COVID-19.[20] The brain and spine MRI of the patient exhibited a new onset of multiple, non-enhancing demyelinating lesions. They assumed that following SARS-CoV-2 infection, the pro-inflammatory environment induced by the cytokine storm might be responsible for the activation of glial cells with subsequent demyelination.[16] Similarly, a large series of cases of Guillain-Barré syndrome in patients with SARS-CoV-2 has been reported from Maharashtra.[20]

Patients with underlying seizure disorder may be at an increased risk of breakthrough seizure due to infection with COVID-19.[21] 5 out of 6 patients had seizures following Covid -19 infection. We had two patients (Patients 29 and 32) with first episode of seizure during infection with COVID-19, which later revealed epileptiform abnormalities in EEG [Table 5]. Imaging was normal in both the patients. One patient (Patient 29) was diagnosed as a case of atypical posterior reversible encephalopathy syndrome [Figure 4]. Although there have been case reports of patients with COVID-19 having seizures with no history of epilepsy, it is not clear if this is directly due to SARS-CoV-2 infection or an unmasking of a seizure disorder due to other factors.[22] Yang *et al*. reported that COVID-19 provokes the inflammatory cascade and as a result, releases inflammatory cytokines, including interleukins 2, 6, 7, and 10, tumour necrotizing factors and the granulocyte colony-stimulating factor. It is reported that TNF-α and IL-6 cytokines and C3 of the complement system are the main factors of stimulating the immune system that can drive neuronal hyperexcitability via activation of glutamate receptors and play a role in the development of acute seizures.[23]

COVID-19-associated ROCM is also emerging in India.[24] They suggested that poorly controlled glycemic status in diabetic patients with rampant use of corticosteroids may be the etiological factor for mucormycosis. Rampant use of corticosteroids can impair migration, phagocytosis and phagolysosome formation in the macrophages and lead to immunosuppression. Secondly, they lead to drug induced hyperglycemia and worsening of glycemic control in patients with diabetes.[25] We had 4 patients with mucormycosis during the second wave, and one (Patient 33) turned out to have cerebral involvement. Hence, a high index of suspicion is necessary to detect secondary invasive fungal or bacterial infections in patients with COVID-19 disease.

There are case reports of bacterial meningitis following COVID-19 infection.[26] The clinical and pathophysiological characteristics of most infectious diseases are much more complex than one germ, one disease model because the pathophysiological effects of many infectious agents, and particularly influenza viruses, modify the effects of coinfecting agents. The mechanisms involved in such interactions include breakdown of physical barriers to tissue invasion; decreased mucociliary clearance activity; destruction, depression, and dysregulation of immune system components; increased aerosolization and dispersion of coinfecting agents; production of antibodies that block immune responses to other agents and up-regulation of expressions of genes that code for toxins.[27] In our patient, we could not isolate the organism; however presence of papilledema along with CSF picture and improvement with Meropenem points towards probable etiology of partially treated bacterial/viral infection.

Moriguchi *et al*. from Japan reported the first confirmed case of COVID-19-associated viral meningoencephalitis.[28] Diagnostic criteria for detecting encephalitis have been established and include fever, seizures, focal brain abnormalities, disturbed mental status, and white blood cells in the lymphatic CSF.[29] The conscious level will be impaired in critically ill COVID-19 patients with ARDS. However, several reports suggest that COVID-19 patients exhibited well-established diagnostic markers for encephalitis.[30] The COVID-19 patient showed a marked increase of a variety of inflammatory cytokine and chemokines in CSF and plasma compared to three control subjects including IL-17A, IL-6, IL-8, IP-10, with a unique MCP-1 signature identified in COVID-19 CSF.[31] These patients also had deranged clinical parameters including raised serum inflammatory markers and CSF pleocytosis. Our patients (Patients 35 and 36) presented with seizures as presenting symptom, one had CSF pleocytosis with features of focal encephalitis in MRI [Figure 5].

Bell's palsy related to COVID-19 infection has also been reported in the literature. A study done by Zammit *et al*. showed the duration of onset of symptoms as two-and-a-half days after COVID-19 infection.[32] The binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) may trigger the body's innate immunological systems to cause elevated pro-inflammatory cytokines and, as a result, neuronal damage. ACE2 is also found in the nervous system, therefore implicating a possibly more direct route to nerve injury. There is a similar high neutrophil-to-leukocyte ratio in Bell's palsy when compared to acute demyelinating diseases (such as Guillain–Barré syndrome). However, the pathways causing this remain unclear. One patient presented with facial palsy after one day of infection while other presented after 20 days. In both cases lumbar puncture was not performed and hence we could say that facial palsy is associated with COVID-19 infection and is not a complication There are case reports of foot drop associated with COVID-19 infection in which prone ventilation was explained as the causative factor.[33] We had 3 cases of foot drop, two of them had severe COVID-19 infection, who had attained prone position ventilation during treatment.

Post vaccinal neurological disorders

Adverse events following COVID-19 immunization (AEFI) are relatively rare. We reported neurological disorders post vaccination in few patients.

We reported one case of stroke following vaccination (ChAdOx1n Cov-19) in which patient developed symptoms 2 days post vaccination. Malhotra *et al*. reported a case of transverse myelitis 8 days after vaccination (ChAdOx1-S/nCoV-19 vaccine).[34] However, our patient (Patient23) presented with symptoms within 2 days of vaccination (BBV-152). In view of short duration of onset of symptoms, possibility of post vaccinal demyelination is arbitrary. However, it may be classified as an adverse event following immunization (AEFI). Three patients had (Patients 22, 24, 25), post vaccinal demyelination with complete recovery following treatment (mRS of 0,1, and 0 respectively on follow up). One (Patient 31) had seizures

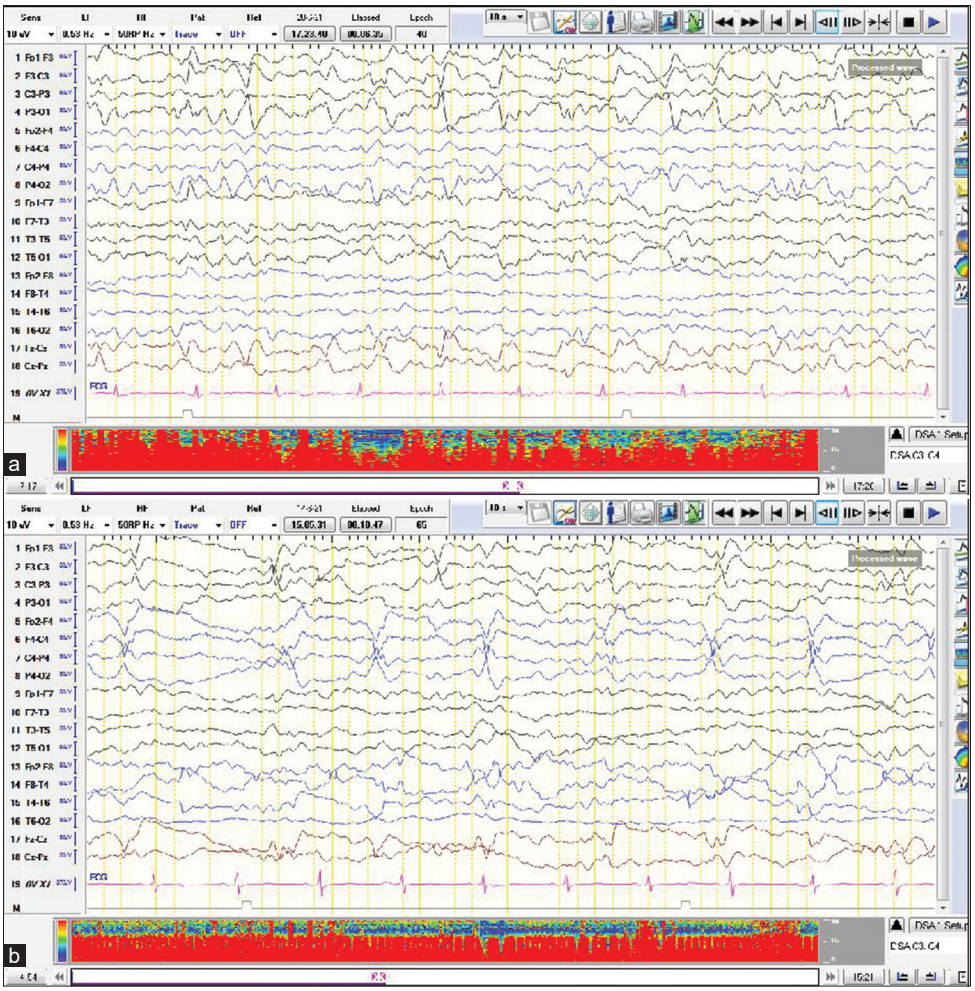

Figure 6: (a) EEG showing periodic epileptiform discharges involving left hemisphere. (b) EEG showing independent periodic epileptiform discharges from both hemispheres

2 days post vaccination (ChAdOx1n Cov-19 Vaccine), who was asymptomatic for 6 years. One patient (Patient 39) had bilateral LMN facial palsy 12 days following ChAdOx1n Cov-19 Vaccine, which completely improved post treatment (mRS 0). Facial palsy following Pfizer-BioNTech a mRNA-based vaccine is reported.[35] The mechanism for this is thought to involve the additive adjuvants that initiate an immunomodulatory response within the cells.[36] Bifacial palsy seen in our patient following ChAdOx1-S/nCoV-19 vaccine was not reported previously.

Limitations of the study

Limitations of our study include a smaller number of patients and lack of statistical analysis. We included only hospitalized patients with COVID-19 in our study. Therefore, the true incidence of the neurological conditions in COVID-19 patients at the community level could not be ascertained from our study. Although the exact mechanism and possible causality of the SARS-CoV-2 infection associated with each of the presented neurological disorders remains unclear, it is likely that shared pathophysiological mechanisms are responsible for the various neurological manifestations of COVID-19. Longitudinal follow-up of these patients is required to determine the long-term effects, treatment response, and outcome of the SARS-CoV-2 infection.

Conclusion

In the current pandemic of SARS-CoV-2 infection, CAND and PVND are emerging. Association of some of these may be fortuitous; however it is worth mentioning as pathogenic mechanisms of COVID-19 affecting various organ systems still remain unclear. Our study can lend further support to the growing body of evidence, aiding better understanding of the neurological features and optimizing management strategies in COVID-19 infected patients.

Author contributions

MG: Concept, design, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, editing and critical review and will act as guarantor of the article. NB: Design, concept, data collection, literature search, manuscript preparation, manuscript editing and critical review. AA: Concept, design, data collection, data analysis and critical review. AR: Data acquisition, study design, manuscript editing

and literature search. SKR: Concept, study design, definition of intellectual content, manuscript editing, critical review.

Ethical clearance

Ethical clearance has been obtained. Ethical clearance number-HR/RIMS/234/2021.

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Conflicts of interest

There are no conflicts of interest.

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