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 RT-PCR 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,
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%).

**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

![Figure 1: Flow chart depicting the cases of COVID-19-associated neurological disorders and post-vaccinal neurological disorders](image-url)
There were 3 cases of breakthrough seizures and first onset seizures after covid‑19 vaccination. Two of them. Patient 31 had localization‑related epilepsy which was well controlled for all infection. Breakthrough seizures and first onset seizures were 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. 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. 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. 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 COVID‑19. 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. EEG showed bifrontal slowing. Vasculitic workup was negative.

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COVID-19 infection. She had history of left upper premolar tooth extraction 10 days prior. MRI brain was suggestive of rhino-orbital-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.]

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

| Age/Sex | Covid Category | Vaccine | Duration of symptom onset after positive antigen test | Symptom | Last Seizure | Diagnosis | Investigation | Treatment | mRS |
|---------|----------------|---------|-------------------------------------------------------|---------|--------------|-----------|--------------|-----------|-----|
| Patient 27 | 30/F | Moderate | NA | Same day | Breakthrough seizure | 6 years back | Primary Generalised Epilepsy-Recurrence | MRI Brain-Normal | EEG-Generalised epileptiform abnormality (follow up) | Levetiracetam | 1 |
| Patient 28 | 58/M | Moderate | NA | 6 days | Breakthrough seizure | 8 years back-Not on drugs | Localisation related Epilepsy | EEG-Left temporal epileptiform abnormality. | MRI-Not done. | Levetiracetam | 1 |
| Patient 29 | 29/F | Mild | NA | 9 days | First episode | NIL | Late onset Seizures | MRI Brain-Normal | EEG- Generalised epileptiform abnormalities. | Brivaracetam | 0 |
| Patient 30 | 29/F | Moderate | NA | 18 days | Seizure-First episode | NIL | Posterior Reversible Encephalopathy syndrome | MRI-FLAIR/T2 hyperintensity in cortical/subcortical areas of bilateral, frontoparietal lobes with no diffusion restriction. | Levetiracetam | 1 |
| Patient 31 | 71/M | NA | ChAdOx1n Cov-19 Vaccine. | 2 days | Breakthrough seizure | 6 years back | Breakthrough Seizures-Localisation related Epilepsy | EEG-Normal. | Carbamazepine | 1 |
| Patient 32 | 70/M | Moderate | NA | 1 day | Seizure-First episode | NIL | Late onset Seizures | MRI-Normal | EEG-Left temporal epileptiform abnormality. | Brivaracetam | 1 |

mRS: modified Rankin score

The meningococcal encephalitis 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.
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...
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. 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. Other routes of entry proposed are neuronal/nervous system route, lymphatic–cerebrospinal route, infected immune/lymphatic cell route. Aerosol droplets may penetrate through nasal mucosa of COVID-19 infected patients and travel through the cribiform plate 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. 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.

Thrombotic microangiopathy and endothelial dysfunction, related to COVID-19, may be contributory factors in sepsis/critical illness-related cerebral microbleeds. 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. 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. 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. 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. Similarly, a large series of cases of Guillain-Barré syndrome in patients with SARS-CoV-2 has been reported from Maharashtra.
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-\(\alpha\) 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 (Patient 23) 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
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. The mechanism for this is thought to involve the additive adjuvants that initiate an immunomodulatory response within the cells. 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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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