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Major Neurological Syndromes with COVID-19: Lessons to Learn

Neeraj Jain [1], Dnyaneshwar Jadhav [1*], Akash Chheda [1], Sangeeta Ravat [1], Rahil Ansari [1], Mayur Thakkar [1], Rishikesh Joshi [1], A. Santosh Sriram [1], Vrug Durge [1]

[1] *Department of Neurology, Seth GS Medical College and KEM Hospital Mumbai, Mumbai, India.*

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Abstract

Objective: Covid-19 is a highly infectious viral disease, and our understanding of the impact of this virus on the nervous system is limited. Therefore, we aimed to do a systematic analysis of the neurological manifestations. *Methods*: We retrospectively studied the clinical, laboratory, and radiological findings of patients with major neurological syndromes (MNS) in Covid-19 over 6 months. *Results*: We had 39 patients with major neurological syndromes (MNS). The most common MNS was cerebrovascular disease (CVD) (61.53%), in which ischemic stroke (83.33%), cortical sinus thrombosis (12.50%), and haemorrhagic stroke (4.16%) were seen. Among ischemic stroke patients, 50% had a large vessel occlusion, and 66.66% of patients with CVD had a significant residual disability. Cranial neuropathy (15.38%), GBS (10.26%), encephalitis (7.26%), and myelitis (5.12%) were the other MNS. Among the three encephalitis cases, two had CSF-Covid-19 PCR positivity and had severe manifestations and a poor outcome. Associated comorbidities included hypertension (30.76%), diabetes mellitus (12.82%), chronic kidney diseases (7.69%), and polycythaemia vera (2.56%). Lung involvement was seen in 64.1% of patients. Mortality was 17.94% in MNS with Covid-19. *Conclusions*: The most common major neurological syndrome associated with Covid-19 is CVD with increased frequency of large vessel occlusion causing significant morbidity and mortality. Simultaneous lung and other systemic involvement in MNS results in a deleterious outcome.

Keywords: Covid-19; Major Neurological Syndromes (MNS); Cerebrovascular Disease (CVD); Encephalitis; GBS; Cranial Neuropathy.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) virus, which is an enveloped, positive-strand RNA virus. [1, 2] Most of these patients present with a mild clinical course beginning with fever, myalgia, and cough, progressing from mild to severe respiratory involvement with an unpredicted response to treatment [3]. Serious complications of infection are common in individuals with underlying comorbidities, which include acute respiratory distress syndrome, acute heart failure, acute kidney injury, sepsis, disseminated intravascular coagulation, and life-threatening metabolic derangements [4]. As knowledge of SARS-CoV-2 and its clinical appearance continues to grow, the literature has shown a significant number of infected patients exhibit neurological symptoms. In this systematic review, we describe the detailed spectrum of various major neurological manifestations encountered in 39 COVID-19-affected patients admitted to our tertiary care center with possible underlying pathophysiology, which may help clinicians and readers understand more about the disease.

* Corresponding author: dnyaneshwarvj@gmail.com

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2. Materials and Methods

We retrospectively reviewed the clinical, laboratory, and radiological findings of all patients admitted to our tertiary care center between April 1 to October 31, 2020, with major neurological syndromes (MNS) developing after a definite COVID-19 infection. Definite COVID-19-related MNS were likely to be associated with COVID-19 on clinical grounds and confirmed by laboratory testing (SARS-CoV-2 RNA PCR positive by nasopharyngeal swab) and were included in the study. The probability of COVID-19-related neurological disease was determined using WHO criteria [Global surveillance for human infection with coronavirus disease (COVID-19)]. Only patients meeting definite criteria (SARS-CoV-2 RNA PCR positive by nasopharyngeal swab or CSF) were included for analysis [5].

Patients with negative SARS-CoV-2 RNA PCR were excluded from the study. MNS included stroke, meningoencephalitis, myelitis, cranial neuropathies, and Guillain Barre Syndrome (GBS) based on various levels of neuraxial involvement. HRCT chest and inflammatory markers (CRP, ESR, IL6, Fibrinogen, and D-dimer levels) were done for all patients with MNS and definite COVID-19. The flowchart of the research methodology that was used to achieve the study's aims is shown in Figure 1.

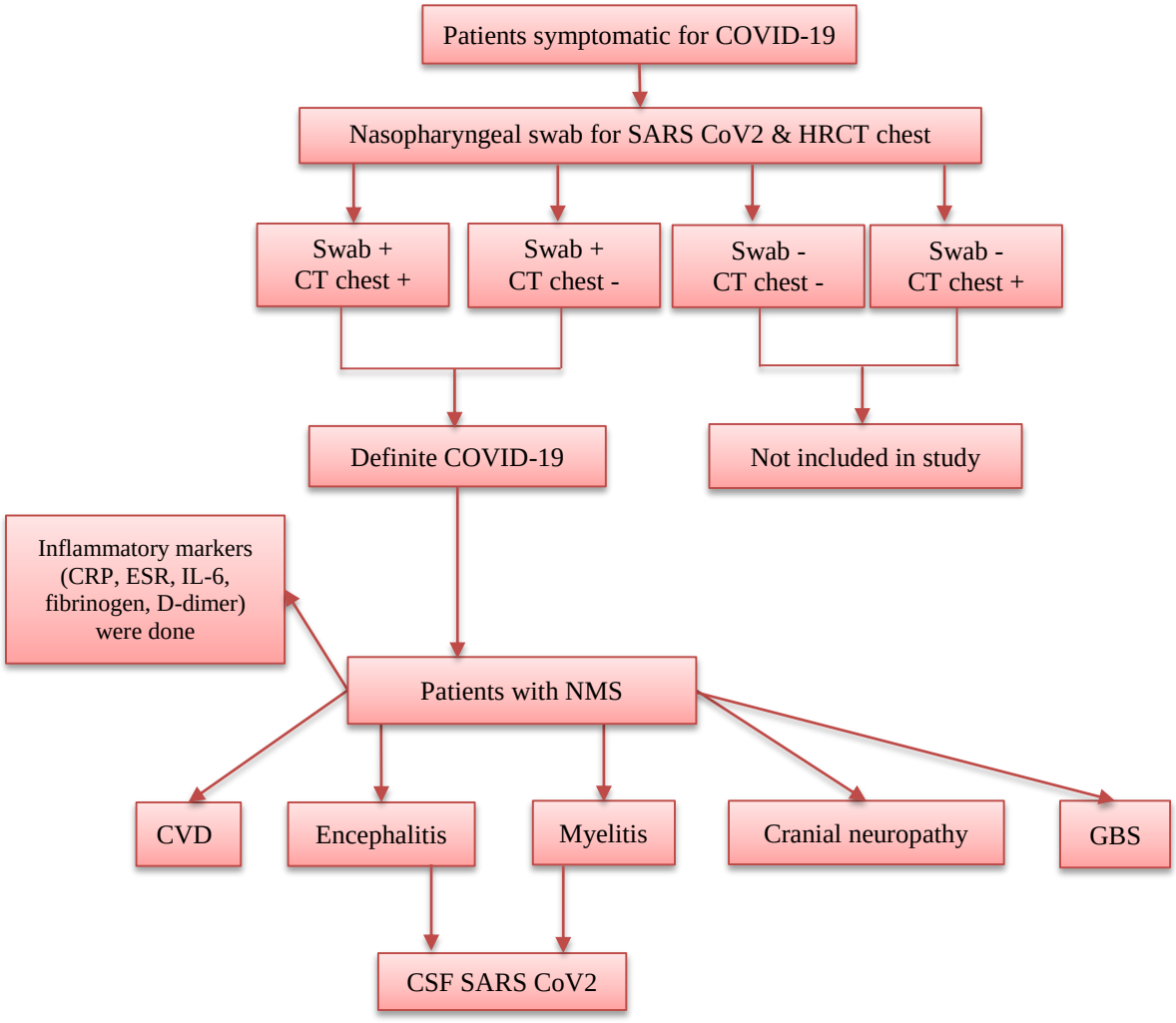


Figure 1. Flowchart of the methodology

3. Result

In our tertiary care center, we analyzed 39 MNS patients with definite COVID-19, of whom 25 (64.1%) were male and 14 (35.89%) were female. Associated comorbidities included hypertension (HTN) in 12 (30.76%), diabetes mellitus (DM) in 5 (12.82%), chronic kidney diseases (CKD) in 3 (7.69%), and polycythemia vera in 1 (2.56%) patient. In MNS, cerebrovascular disease (CVD) was seen in 24 (61.53%), meningoencephalitis in 3 (7.26%), myelitis in 2 (5.12%), GBS in 4 (10.26%) and isolated cranial neuropathy in 6 (15.38%) patients. (Table 1).

Table 1. Summary of clinical features of 39 patients with neurological complications of COVID-19

Cases	Age, median [Range].	Days of COVID-19 infection before neurological presentation, median [range]	Main clinical features	Laboratory investigations	Treatment	Clinical outcome
Cerebrovascular disease						
Ischemic stroke (N:20)	52.43 [12 to 78]	5 [– 5 to 16]	Acute stroke like presentation (21/24) Raises ICT symptoms (3/24)	CXR/CT- pneumonitis (18/24)	Low molecular weight heparin (10/23); Warfarin (2/23)	Complete recovery (4/24); Partial (16/24) Death (4/24)
CVT(N:3)	21.3 [12 to 28]	3 [- 2 to 5]				
Hemorrhagic stroke(N:1)	78	1				
Encephalitis (N:3)	13,45, 75	8, 3, 4	Alerted sensorium, seizure	Abnormal MRI (3/3) Abnormal CSF (3/3)	IV steroid (3/3) IVIG (1/3)	Incomplete recovery (1); death (2/3)
Myelitis (N:2)	13, 75; 50	4 & 7	Paraplegia	Abnormal MRI (2/2) Abnormal CSF (1/2) CXR/CT- pneumonitis (2/2)	IV steroid (2/2) IVIG (1/2)	Complete recovery (1/2); partial (1/2)
Cranial neuropathy (N:6)	35.6 [24-58]	6 [- 5 to 16]	Cranial neuropathy	Abnormal MRI (1/6) Abnormal CSF (1/6) CXR/CT- pneumonitis (3/6)	Steroid (5/6)	Complete recovery (4/6); partial (2/6)
GBS(N:4)	32 [18–54]	4.5 [- 3 to 12]	Quadriparesis	CXR/CT- pneumonitis (2/4)	IVIG (4/4)	Complete recovery (3/4/); death (1/4)

CVT: Cerebral Venous Thrombosis, GBS: Guillain Barre Syndrome, CXR: Chest X Ray.

3.1. Cerebrovascular Disease (CVD)

Among COVID-19 related MNS, CVD was the most common. Among CVD, ischemic stroke was seen in 20 patients; one had haemorrhagic stroke; and cortical venous sinus thrombosis (CVT) was seen in three patients. Out of 24 patients with CVD, 18 had lung involvement due to COVID-19. Four patients died (2 ischemic strokes, 1 haemorrhagic stroke, and 1 CVT). Details of demographic data, clinical presentation, and outcome for all CVD patients are outlined below (Table 2).

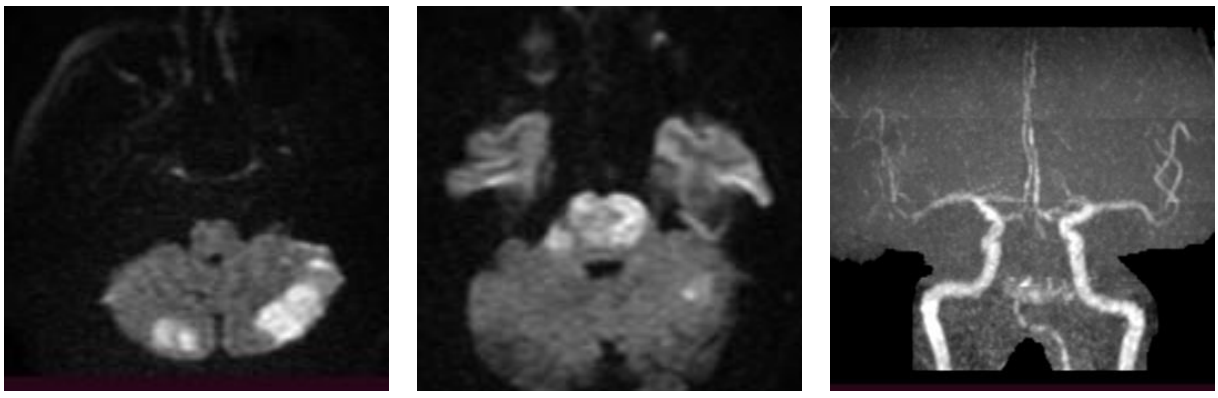
Table 2. Demographic character, clinical profile, and outcomes in patients with acute cerebrovascular diseases [patients 1-24]

Cases	Age / sex, risk factor	CT/MRI	Diagnosis	Investigation	Outcome
1	75/M HTN	Right GC infarct Angio normal	Ischemic stroke	CXR- normal D-dimer, Fibrinogen- Normal	Disability
2	73/F	Right Parieto-occipital infract	Ischemic stroke	CXR- pneumonitis Platelet-80000	Died
3	40/F ANC (9 month)	B/L thalamic, Left midbrain & hemi pons infarct Right ICA 60% occlusion B/L PCA- 30-40 % occlusion	Ischemic stroke	CXR- normal D-dimer, Fibrinogen- Normal	Disability
4	64/M DM, HTN	Right midbrain infarct Angio- normal	Ischemic stroke	CXR- normal D-dimer, Fibrinogen- Normal	Disability
5	76/F DM	Left frontal lobe infarct. Left M2 occlusion	Ischemic stroke	CXR-pneumonitis D-dimer, Fibrinogen- Normal	Improved
6	64/M HTN	Right frontoparietal-temporal infarct, angio- Right ICA + MCA complete occlusion	Ischemic stroke	CXR-ARDS D-dimer, IL-6 -high	Disability
7	57/M DM	**Right Ganglio-capsular, frontal, temporal, parietal infarct. Right cervical ICA thrombosis	Ischemic stroke	CXR- Normal D-dimer, Fibrinogen, IL-6 high	Disability
8	67/F HTN	Left medial occipital infarct. Angio- normal	Ischemic stroke	CXR-ARDS, D-dimer high	Disability
9	56/M	Left GC infarct Angio – normal	Ischemic stroke	CXR-pneumonitis D-dimer, Fibrinogen- Normal	Disability
10	61/F HTN	Left occipito- temporal infarct left PCA occlusion	Ischemic stroke	CXR-Pneumonitis D-dimer, Fibrinogen-High	Disability
11	35/M	Left GC infarct Angio- normal	Ischemic stroke	CXR-ARDS High D-dimer	Disability
12	36/M CKD	Right frontal, parietal & occipital infarct Right – ICA thrombosis	Ischemic stroke	CXR-Pneumonitis D-dimer, Fibrinogen- High	Disability
13	41/F	Right frontal, CR, GC & occipital infarct Right ICA + M1 occlusion	Ischemic stroke	CXR-Pneumonitis D-dimer, Fibrinogen- Normal	Disability

14	65/M HTN	Right GC infarct Angio- normal	Ischemic stroke	CXR-Pneumonitis D-dimer, Fibrinogen- Normal	Died
15	48/M CKD+ HTN	Acute infarct in right half of midbrain Angio- normal	Ischemic stroke	CXR-Pneumonitis D dimer, Fibrinogen - elevated	Disability
16	63/M	Left frontal, parietal infarct. Left supraclinoid ICA thrombus	Ischemic stroke	CXR- normal D-dimer, Fibrinogen- Normal	Disability
17	46/F HTN	Right fronto-temporal & basal ganglia infarct Right MCA occlusion	Ischemic stroke	HRCT-pneumonitis D-dimer, Fibrinogen- Normal	Died
18	45/M HTN, DM, CKD	Right GC infarct Angio normal	Ischemic stroke	CXR-ARDS, D-dimer- high	Improved
19	52/M HTN	B/L cerebellar hemisphere, pons midbrain and GC infarct Angio-distal basilar occlusion (Figure 2)	Ischemic stroke	HRCT- Pneumonitis LDH, CRP -elevated	Disability
20	72/F	Right frontal & Occipital infarct, Angio-normal	Ischemic stroke	CXR-pneumonitis D-dimer, IL- 6 elevated	Disability
21	78/F HTN	Cerebellar bleed with intraventricular extension	Haemorrhagic stroke	CXR-Pneumonitis CRP, IL-6, ESR- elevated	Died
22	12/F	B/l frontal hypodensity Veno- SSS thrombosis	CVT	CXR- pneumonitis D-dimer, Fibrinogen- Normal	Improved
23	24/M Polycythaemia vera	Veno - Left transverse, sigmoid and IJV thrombosis	CVT	CXR- Normal D-dimer, Fibrinogen- Normal	Improved
24	28/M	Right frontoparietal haemorrhagic infarct with midline shift Veno- SSS, right transverse sinus thrombosis	CVT	HRCT chest- ARDS D-dimer, IL-6 elevated	Died

GC- Ganglio-capscular, CR- corona radiata, M: Middle cerebral artery, ICA- internal carotid artery, PCA- posterior cerebral artery, CXR: chest X ray ARDS: Acute respiratory distress syndrome, LDH- lactate dehydrogenase, CRP: C-Reactive protein.

i. Ischemic stroke: was the most common (20 of 39) neurological manifestation in our study patients, seen in 51.28 % cases. Age at presentation varied from 12-78 years, with a mean age of 52.43 years. 15 of these patients (75%) had respiratory system involvement. Among comorbidities, 10 had hypertension, 5 had diabetes mellitus, 3 had chronic kidney disease, and 1 patient was 9 months pregnant. Large vessel occlusion was seen in 10 out of 20 patients (Figure 2). Of the large vessel occlusions, involvement was seen in extracranial ICA (3), intracranial ICA+MCA (3), intracranial ICA+PCA (1), MCA (2), and PCA (1). Inflammatory markers (CRP, D-dimer, and IL-6) were elevated in 10 (50%) patients. Of the 20 ischemic stroke cases, two improved, two died, and sixteen were left with significant residual disability.



(a) (b) (c)

Figure 2. [Patient no. 19]: Posterior circulation stroke (CVD): MRI DWI images shows acute infarct in: a- bilateral cerebellar hemispheres and b- midbrain; c- MR Angiography shows complete basilar occlusion

ii. Haemorrhagic stroke: We had one 78-year-old hypertensive male (patient 21) with haemorrhagic stroke. CXR showed ARDS and inflammatory markers were elevated, CT brain showed left cerebellar bleed with intraventricular extension with significant mass effect. The patient died on day 9 despite optimal management.

iii. Cerebral Venous Sinus Thrombosis: We had three cerebral venous thrombosis patients (aged 12-28, with a mean age of 21.3 years) with the onset of neurological symptoms 2 days before to 3 days after typical COVID-19 symptoms. Two other patients also had lung involvement due to COVID-19, and one had an elevated inflammatory marker. One patient had underlying polycythemia vera. All three were treated with adequate hydration and anticoagulation. Two patients improved, and one died despite extensive efforts.

3.2. Meningoencephalitis

We had three cases with meningoencephalitis, two had COVID-19 encephalitis, and one had hemorrhagic necrotizing encephalitis (Table 3).

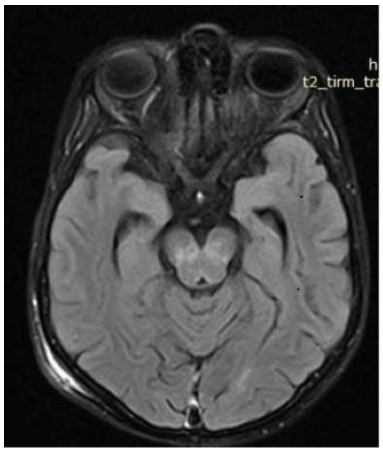
Table 3. Demographic character, clinical profile, and outcomes in patients with encephalitis, myelitis, and optic neuritis: [patients 25-30]

	25	26	27	28	29	30
Age, M/F Comorbidity	**14/M**	**45/M**	**75/F**	**13/F**	**75/M DM/HTN**	**38/M**
Neurological diagnosis	**ADEM**	**AHNE**	**Encephalitis**	**LETM**	**LETM**	**Optic neuritis**
Laboratory investigation	HRCT-normal CSF: P- 84, S-84 Cells- PMN:4 & L:23 NEUTROPHILIC LEUKOCYTOSIS THROMBOCYTOSIS IL-6 RAISED	CSF P: 240, S-114, CELLS :4 LYMPHOCYTES CRP, D-DIMER & IL-6- ELEVATED	HRCT- NORMAL CSF:P-320, S-: 94, CELLS- 160 all LYMPHOCYTES NEUTROPHILIC LEUKOCYTOSIS CRP, D-DIMER, IL-6 ELEVATED	HRCT - pneumonitis CSF: Normal	HRCT-pneumonitis CSF: P- 63.3, S-131, Cells-140(15 % PMN, 85 % lymphocytes)	HRCT-normal CSF- normal except protein-52.2
Brain imaging	MRI - T2/FLAIR hyperintensity in bilateral substantia nigra, cerebral peduncle MRI (Day 10)-ADEM	MRI- T2/FLAIR hyperintensity in b/l thalamus, Cerebral & cerebellar hemisphere with necrosis and haemorrhage	MRI- T2/FLAIR hyperintensity in b/l frontoparietal area	MRI Spine – T2 hyperintensity C6 to D9	MRI- T2 hyperintensity in Dorsal cord	MRI-T2 optic nerve hyperintensity (left)
Treatment and outcome	IVMP 5 days, IVIG, oral prednisolone taper, levetiracetam. incomplete	IVMP, Levetiracetam. Died	IVMP, Levetiracetam. Died	IVMP 5 days, IVIg Residual disability	IVMP 5 days. Oral prednisolone taper Improved	IVMP 5 days. Oral prednisolone taper Improved

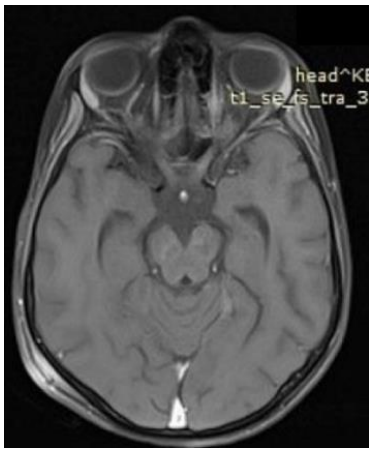
ADEM: Acute Disseminated Meningoencephalitis, AHNE: Acute Haemorrhagic Necrotizing Encephalitis, LETM: Longitudinal Extensive Transverse Myelitis, IVMP: Intravenous methylprednisolone.

3.2.1. Vignette A: COVID-19 Encephalitis

A 14-year-old boy (patient 25) presented with an 8-day history of fever, headache, and myalgia followed by bilateral tonic-clonic seizures. On examination, he had an altered sensorium, his pupils were equal, and he was reacting to light with an extensor plantar response. Laboratory investigation revealed leucocytosis (15000/cumm) and increased IL-6 levels. CSF analysis showed 27 lymphocytes, elevated protein (84 mg/dl), and a normal sugar level (96 mg/dl). The CSF SARS-CoV-2 RT PCR was positive, confirming the diagnosis of COVID-19 encephalitis. MRI showed T2/FLAIR hyperintensity in the bilateral substantia nigra and cerebral peduncle with patchy peripheral rim enhancement (Figures 3-a and 3-b). He was treated with injectable MPS, ceftriaxone, vancomycin, acyclovir, and levetiracetam. His seizures abated; however, his sensorium did not improve. Repeat MRI showed multifocal white matter hyperintensities in bilateral cerebral hemispheres, suggestive of acute disseminated meningoencephalitis (ADEM) (Figures 4a and 4b). In view of worsening sensorium, the patient received IVIG (2 gm/kg). He showed improvement in sensorium after more than 4 weeks of illness and was discharged with mild residual disability.

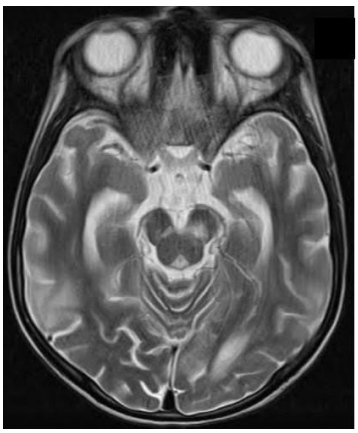


(a) FLAIR images showing hyperintensity in bilateral cerebral peduncle and substantia nigra

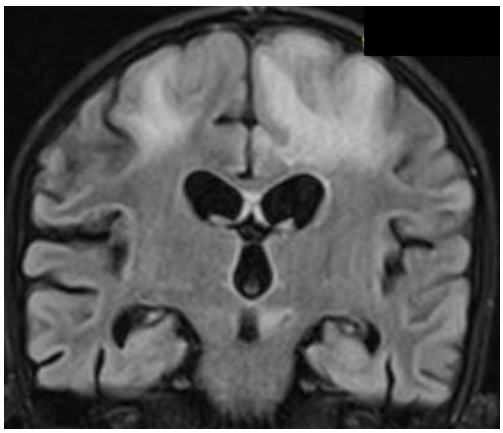


(b) T1 images showing hyperintensity cerebral peduncles

Figure 3. [Patient 25 – Meningoencephalitis]: MRI brain (Day 4)



(a) T2 Axial images showing marked increase in bilateral white matter hyperintensities

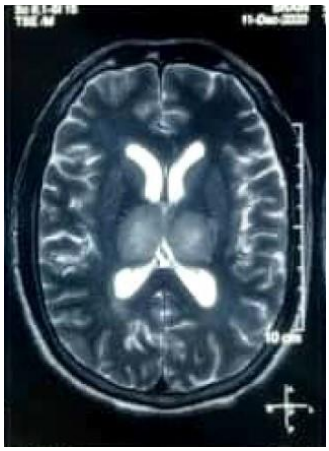


(b) FLAIR (coronal) Images showing hyperintensities in deep hemispheric, periventricular and juxtacortical white matter

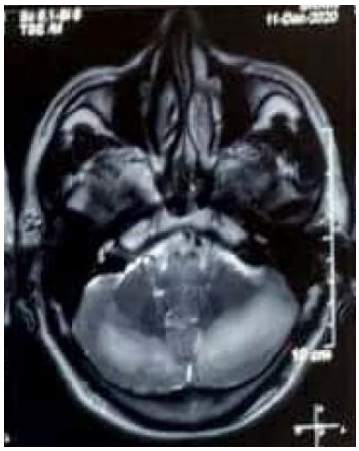
Figure 4. [Patient 25 – Meningoencephalitis]: MRI brain (Day 20)

3.2.2. Vignette B: Acute Haemorrhagic Necrotizing Encephalitis

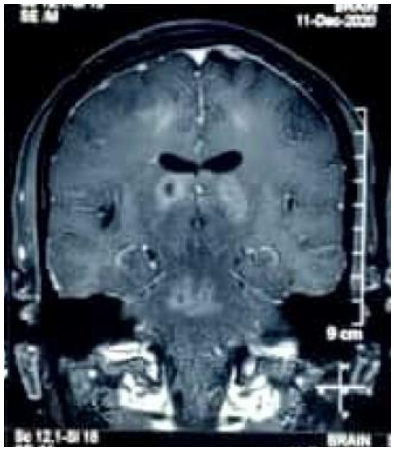
A 45-year-old male (patient 26) presented with 3 days history of fever, sore throat followed by 1 episode of unknown onset bilateral tonic-clonic seizure, and altered sensorium. On examination, GCS was 10/15, patient had neck stiffness along with an extensor plantar response bilaterally. Laboratory investigations revealed raised leukocyte -26000/cumm, IL-6, CRP, deranged renal and liver function. MRI of the brain showed acute haemorrhagic necrotizing encephalopathy (Figure 5). A CSF study revealed 4 lymphocytes, markedly elevated protein (240 mg/dl), and normal sugar (114 mg/dl). His dengue, Leptospirosis, and malaria workups were negative. He was started on injectable methylprednisolone, ceftriaxone, vancomycin, acyclovir, and levetiracetam; however, he continued to deteriorate and died subsequently on day 13.



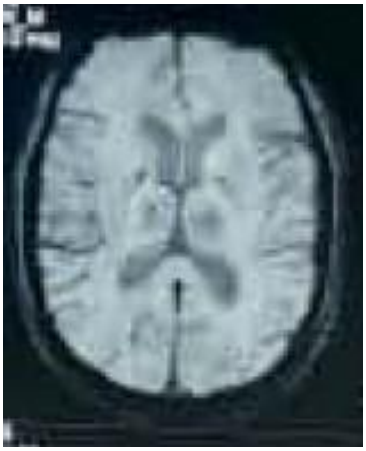
(a) T2 Axial image show hyperintensity in b/l thalamus, cerebellar hemisphere



(b) T2 Axial image show hyperintensity in b/l thalamus, cerebellar hemisphere



(c) T1 contrast coronal images shows contrast enhancing lesion



(d) SWI images shows hypointensity in bilateral thalamus

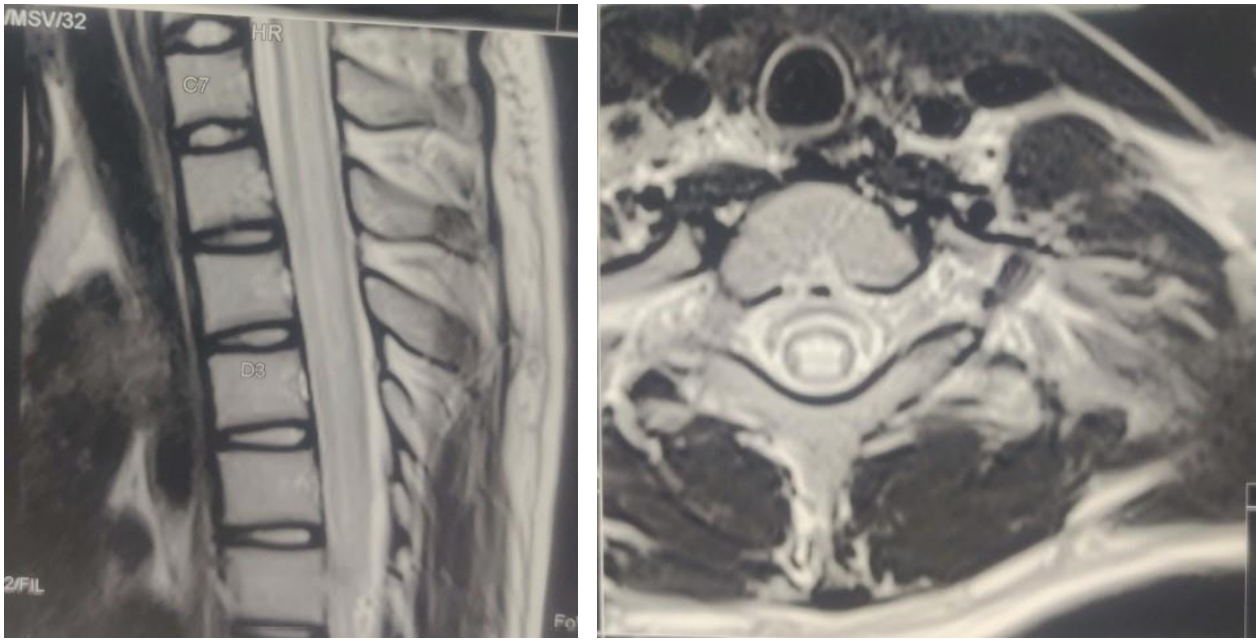
Figure 5. MRI Brain [Patient 26]: Acute necrotising meningoencephalitis)

3.3. Acute Myelitis

We had two cases of myelitis. Both were longitudinally extensive transverse myelitis (LETM) (see Table 3).

3.3.1. Vignette C: Acute Myelitis

A 13-year-old girl (patient 28) presented with acute onset bilateral lower limb weakness and bladder complaints in the form of urinary urgency and urge incontinence. This was preceded by a 7-day history of fever, sore throat, and generalized weakness. On examination, her DTR was brisk and her bilateral plantar responses were extensor. HRCT of the chest showed patchy opacity in bilateral lung fields. MRI spine showed longitudinally extensive transverse myelitis with cord signal extending from C6 to D9. The MRI brain screening was normal (Figure 6). CSF examination and demyelination workup (CSF IgG index, CSF specific oligoclonal bands, CSF anti AQP4 IgG, and anti-MOG IgG antibodies). The serum ANA blot assay and serum ACE level were normal. She was treated with IV methylprednisolone for 5 days, followed by IVIG (2g/kg). However, she had a significant residual disability.



(a) T2 hyperintensity in dorsal cord extending for more than 3 segments

(b) Axial image showing central cord involvement

Figure 6. [Patient 28]: Acute myelitis, MRI spine showing

3.4. Polyradiculoneuropathy (GBS)

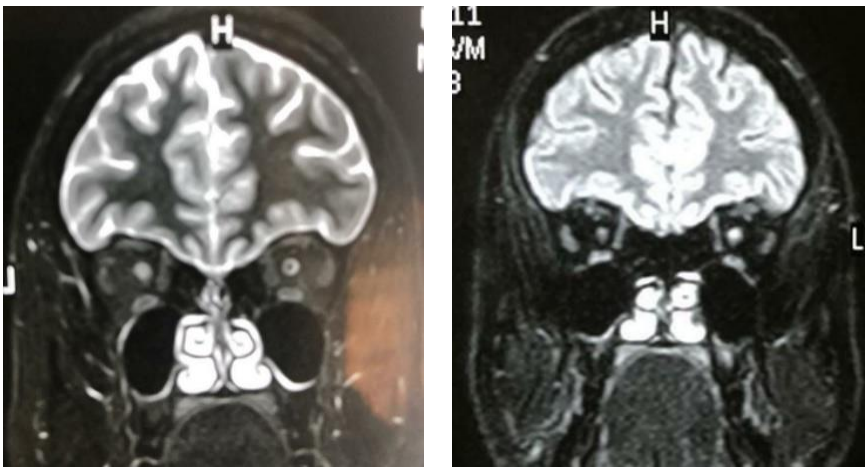
We had 4 GBS patients (aged 18–54, two of each gender), with the onset of neurological symptoms from 3 days before to 12 days after typical COVID-19 symptoms. The CSF examination was normal in all 4 patients. All patients were treated with IVIG 2g /kg given over 5 days. Three patients improved, while one died due to severe autonomic dysfunction.

3.5. Cranial Neuropathy

We had 6 cases with cranial neuropathy (CN VII-4, CN II-1 & CN IV-1 patient). Age of presentation varied from 24-58 with a mean age of 35.6 years and onset of neurological symptoms 5 days before to 16 days after typical covid-19. Inflammatory markers were normal in all. Among four patients with facial nerve palsy, three had pneumonitis on the HRCT chest, and all were treated with a short course of oral steroid treatment, two of which improved, and the remaining two had severe disability. One patient had right IVth nerve palsy with a normal MRI brain. His HRCT chest showed pneumonitis. He was treated with antibiotics and a short course of steroids, after which he showed complete improvement.

4. Vignette D- Optic Neuritis

A 38-year-old male (patient 30; Table 3) presented with a decrease in vision with left eye following COVID-19. MRI brain with optic cuts showed left optic nerve hyperintensity (Figure 7). CSF examination reveals protein -52.2 mg/dl, Sugar-101, and two lymphocytes. Serum NMO, MOG, and ANA blots were negative. He was treated with intravenous steroids and thereafter improved completely.



(a) (b)

Figure 7. [Patient 30- Left Optic neuritis]: MRI T2/FLAIR coronal image shows hyperintensity in left optic nerve

5. Discussion

Coronavirus contains four structural proteins, including the spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). Among them, the S protein plays the most important role in virus attachment, fusion, and entry [6]. Angiotensin converting enzyme 2 (ACE2) receptor is highly expressed in glial cells, neurons, vascular smooth endothelium, the substantia nigra, and the ventricles of the brain. The spike protein (S) of the COVID-19 virus shows strong binding affinity with the ACE2 receptor, producing various neurological manifestations [7, 8]. The virus enters the CNS either through the olfactory nerve via retrograde axon transfer or via a hematogenous route to the cerebral circulation, where it binds to ACE 2 receptors, causing various neurological manifestations [9].

Cerebrovascular disease was the most common manifestation of COVID-19, with an incidence of 0.5–5% in various studies. The incidence of ischaemic stroke, haemorrhagic stroke, and cerebral venous thrombosis reported from various studies ranged from 0.4–4.9%, 0.2–0.9%, and 0.3–0.5% respectively [10, 11]. In our study incidence of ischaemic stroke, haemorrhagic stroke, and cerebral venous thrombosis were 3.07%, 0.15%, and 0.46% respectively.

The exact mechanism of how COVID-19 causes CVD is not known; however, the proposed theory suggests endothelial cell damage with inflammatory and thrombotic pathway activation leading to microangiopathy and coagulopathy [12]. With respect to COVID-19-related intracerebral haemorrhage; few potential explanations exist. In patients with hypertension, ACE2 receptor expression and its ability to lower blood pressure are reduced, which is further reduced by the "S' protein present in SARS-CoV-2. This could potentially lead to uncontrolled hypertension, rupture of the arterial wall, and cerebral hemorrhage in COVID-19-affected patients [13]. Additionally, COVID-19 patients have been reported to have thrombocytopenia and coagulopathy, which additionally contribute to intraparenchymal haemorrhage [14].

Avula et al. [15] from the USA reported four cases of ischemic stroke (aged 43–88 years); all of them had some risk factors, were treated with antiplatelets, and had poor outcomes (only 1 survived). In our study, the median time to cerebrovascular disease from COVID-19 symptom onset was 5 days. Fourteen patients with ischemic stroke were older than 50 years, and fourteen of them had one or more risk factors. 50 % of patients had large vessel occlusion and showed poor recovery, these finding are in concurrence with previous studies by Li Y et al. [10], Tsivgoulis et al. [16] and Mao et al. [17]. We had one patient with an intracerebral bleed and HTN comorbidity, who did not survive. Morassi et al. [18] also reported two patients with intracerebral haemorrhage who had pneumonitis but did not survive.

Many case reports of meningoencephalitis and encephalopathy were reported in COVID-19 patients with incidence varying from 0.1-0.003 %. [19, 20]. It is still not clear how COVID-19 causes encephalitis; however, the proposed theory mentions viral entry into neuronal tissue and binding to ACE2 receptors, which initiates a cycle of viral budding and neuronal damage [21]. This can occur with acute inflammation via cytokine or chemokine pathways or T cell pathways, leading to vascular damage, demyelination, activation of complement, the coagulation cascade causing ADEM, haemorrhagic encephalitis, or without substantial inflammation [22].

Zhang et al. [23] and Zanin et al. [24] reported cases of COVID-19-related acute disseminated encephalitis that were treated with steroids and IVIG and showed mild improvement. We had a similar case of ADEM that improved significantly after being treated with high dose steroids and IVIg.

Acute hemorrhagic leukoencephalitis is a rare and fatal demyelinating disorder. Treatment with high-dose corticosteroid therapy, immunoglobulins, plasma exchange, and monoclonal antibodies such as rituximab has led to survival in only some patients. Filatov et al. [25] have reported a case of acute Haemorrhagic Necrotizing

Encephalopathy (ANE), proposing the cytokine storm to be responsible for disruption in the blood-brain barrier and neuroinflammation, which leads to dysfunction of the brain [26]. Polyiadji et al. [27] reported another case of acute Haemorrhagic Necrotizing Encephalopathy (ANE) in a 54-year-old female who was treated with IVIG but did not improve. We had a similar case of acute Haemorrhagic Necrotizing Encephalopathy (ANE) with cytokine storm, which was treated with steroids and IVIg but did not survive. All three encephalitis patients in our study had significantly elevated inflammatory markers. A clinical trial has shown benefits with tocilizumab and anakinra which block inflammatory cytokine IL-6 and IL-1 receptor respectively [28, 29]. The mortality rate of patients with COVID-19 encephalitis is 13.4%, almost quadruple the rate seen in the general population of COVID-19 patients (3.4%) [30]. Two of our three patients did not survive despite meticulous care and management, and one had a residual disability at the time of discharge.

Zhao et al. [31] described acute myelitis in a 66-year-old patient due to COVID-19, after which many cases were reported. The latency period between COVID-19 infection and the onset of neurological symptoms varies from as short as 2 days and as long as 6 weeks [32]. We had two patients with acute myelitis presentation with latency periods of 4 and 6 days, respectively. Blackburn & Wang [33] proposed that molecular mimicry, polyclonal B cell activation, epitope spreading, and bystander activation are likely mechanisms of post-infectious myelitis.

In both of our patients, the MRI showed longitudinal extensive transverse myelitis (LETM) and they were treated with steroids and IVIG, one of whom showed improvement. However, the other was left with a significant residual disability.

Many cases (>18) of GBS have been reported with COVID-19. Zhao et al. [34] described the first case of GBS in a 61-year-old female with COVID-19. Toscano et al. [35] reported 5 patients from COVID-19 with GBS and symptoms ranging from 1–10 days. All GBS variants, like AIDP, AMAN, AMSAN, and AMSAN variants with severe autonomic neuropathy, MFS, and facial diplegia, have been reported. McGonagle et al. [36] and Quin et al. [37] described immune dysregulation secondary to systemic hyperinflammation and elevated cytokines that produced possible pathogenic mechanisms. We had four patients with COVID-19-related GBS; two of them had pneumonitis, an elevated inflammatory marker, and all were treated with IVIG. Three patients improved, and one died due to severe dysautonomia.

Multiple reported cases of isolated cranial neuropathy due to COVID-19 have been reported. In the Mao et al. [17] study, loss of smell (Olfactory nerve) involvement was seen in 5.1 % and loss of taste was seen in 5.6 % of patients. We had six patients with isolated COVID-19-related IInd, IVth, and VIIth cranial neuropathies; three patients had pneumonitis. All improved except two patients who had severe facial palsy (House-Brackmann Score IV & V).

6. Conclusion

As the outbreak continues to spread, our understanding of the neurological manifestations and their pathophysiology in patients with COVID-19 is also evolving. Most cases have preceding respiratory symptoms; however, at times neurological manifestations precede COVID-19 symptoms. Our systematic review gives comprehensive details of the major neurological syndromes related to COVID-19. COVID-19 can affect structures at various levels of the neuroaxis, with the resultant neurological manifestations. CVD was the most common MNS and was associated with significant morbidity and mortality. This was due to the frequent large vessel occlusion noted in our patients, which is the result of a highly prothrombotic and acute inflammatory environment in patients symptomatic for COVID 19. Acute necrotizing encephalitis can be associated with COVID-19, as with other influenza viruses. The CSF PCR study is useful in the diagnosis as seen in our patient, who had severe manifestations at the onset of illness, leading to a poorer outcome. Cerebral peduncular and substantia nigra involvement on MRI could be the initial finding in COVID-associated encephalitis. As a word of caution, clinicians should be aware that the diagnostic work-up should be as detailed and exhaustive as possible to rule out causes other than SARS-CoV-2 infection before including cases in epidemiological analyses. However, during the ongoing pandemic, one should have a low threshold to perform a SARS-2 CoV2 RT-PCR swab test in MNS patients as the prognosis varies in these patients and early treatment can be helpful. Nevertheless, more detailed information on COVID-19-associated neurological manifestations is needed, and further studies detailing this are the need of the hour.

7. Declarations

7.1. Author Contributions

Conceptualization, D.J. and N.J.; methodology, A.C.; software, D.J.; validation, D.J., N.J. and A.C.; formal analysis, D.J; investigation, D.J.; resources, V.D., R.J., A.S., and A.C.; data curation, R.A., M.T., and A.C.; writing—original draft preparation, A.C.; writing—review and editing, N.J., and S.R.; visualization, N.J., and S.R.; supervision, N.J., and S.R.; project administration, D.J., and A.C.; funding acquisition, NA. All authors have read and agreed to the published version of the manuscript.

7.2. Data Availability Statement

The data presented in this study are available on request from the corresponding author.

7.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

7.4. Ethical Approval

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Seth GS MC and KEM hospital.

7.5. Conflict of Interest

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

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