Original Article

The Spectrum of Neuro-COVID: A Study of a Comprehensively Investigated Large Cohort from India

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Abstract

Background: Though reports of neurological manifestations of COVID-19 have emerged from various parts of the world, the cohorts reported are from the West and mostly derived from electronic databases. Much remains unknown regarding neuro-COVID in developing countries. India is the second-worst affected country, and this study reports the neurological manifestations of COVID-19 in a comprehensively evaluated cohort. **Objective:** The aim of this study was to describe the range of neurological manifestations of COVID-19 in India with an emphasis on the risk factors, laboratory and imaging findings and short-term outcome. **Methods:** Retrospective review of hospital records of all confirmed COVID-19 patients with neurological manifestations, receiving inpatient care in two neurology referral hospitals were done. All demographic, clinical details, investigations, and treatment were analysed. **Results:** A total of 120 confirmed COVID-19 cases presenting with neurological symptoms were included. The mean age of illness and duration of illness was 48.03 ± 17.3 years and 10.9 ± 17.3 days respectively. New onset of neurological symptoms occurred in 100 cases while 20 patients had worsening of pre-existing neurological illness. Stroke was the commonest neurological disorder (43%), followed by encephalopathy (23%) and Guillain-Barre syndrome (10%). Other unusual neurological manifestations included new-onset headache (7%), seizures including denovo status epilepticus (5%) and meningo-encephalitis (5%). Nearly half of the patients had preceding COVID-19 symptoms. Poor outcome at discharge was seen in 40% and mortality occurred in 15%. **Conclusion:** Stroke and encephalopathy constitute the most common neurological manifestations. The absence of preceding COVID-19 symptoms in nearly half the cases is striking. Poor outcome was seen in nearly 50% despite early recognition and management.

Keywords: COVID-19, encephalopathy, neurological manifestations, stroke

Introduction

Coronavirus disease-19 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of the worst pandemics faced by mankind, affecting more than 134 million people and causing nearly 29 lakh deaths, as of April 2021.[1] While the primary manifestation of the COVID-19 is an influenza-like illness and pneumonia, it has become increasingly evident that multiple organs including central and peripheral nervous system can be affected.[2,3]

Neurological manifestations have been reported in various studies from different parts of the world,[4-10] most of them relying on electronic databases, with a bias toward reporting more severe disease. India stands the second-worst affected country by the pandemic.[1] There are few reports of neurological manifestations of COVID-19 from low- and middle-income countries.[11-13] Incidence of neurological manifestations like stroke varies with ethnicity and hence it was necessary to have a comprehensive report of the neurological manifestations of COVID-19 from a developing country like India. We undertook this study to report the diverse spectrum of neurological diseases associated with COVID-19 from two different states in southern India.

Methods

This multicentre, chart review was carried out in two neurology referral hospitals in Southern India.: (i) National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka and (ii) Yashoda Hospital, Hyderabad, Telangana. Hospital records of all confirmed SARS-CoV2 patients admitted from March to September 2020 (both adult and pediatric age group) with neurological symptoms were analysed[4] (Case definitions used, as per WHO guidelines, are given below). Cases admitted under psychiatry department were not analysed. Institutional ethics committee approvals were taken.

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Definitions used are as follows:

Confirmed case of SARS-CoV2 infection was defined as nasopharyngeal and/or oropharyngeal swab real-time reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test positive cases.[6]

i. COVID-19-associated neurological disease was defined as confirmed, probable or possible based on WHO definitions as outlined below:

SARS-CoV-2 meningitis, encephalitis, myelitis or CNS vasculitis

a. Confirmed
   i. SARS-CoV-2 detected in CSF or brain tissue or evidence of SARS-CoV-2-specific intrathecal antibody; and
   ii. No other explanatory pathogen or cause found
b. Probable
   i. SARS-CoV-2 detected in respiratory or other non-CNS sample, or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection and
   ii. No other explanatory pathogen or cause found
c. Possible
   Patient meets suspected case definition of COVID-19 according to national or WHO guidance based on clinical symptoms and epidemiological risk factors; in the context of known community SARS-CoV-2 transmission, supportive features include the following: the new onset of at least one of cough, fever, muscle aches, loss of smell, or loss of taste; lymphopenia or raised D-dimer level; and radiological evidence of abnormalities consistent with infection or inflammation (e.g. ground glass changes)
   ii. COVID-19 severity was classified as per the WHO guidelines:
      a. Mild (no features of pneumonia)
      b. Moderate (pneumonia without significant hypoxia or respiratory distress)
      c. Severe (pneumonia with hypoxia or signs of respiratory distress)
      d. Critical (acute respiratory distress syndrome or sepsis ± shock)

Data collection

Data were collected regarding socio-demographic profile, symptoms of COVID-19 infection, neurological illness, and co-morbidities. Details of pre-existing neurological illness, if any, were collected. Neurological manifestations were classified into central (encephalopathy, meningoencephalitis, neuro-cognitive, neuro-affective disorders, acute cerebrovascular events, new-onset seizures, headache, acute disseminated encephalomyelitis) and peripheral (Guillain-Barre syndrome and its variants, muscle injury, rhabdomyolysis).[4,5] Other possible aetiologies were ruled out by appropriate investigations. Blood investigations including inflammatory markers and CSF reports were collected. Findings of blood investigations/CSF reports and radiological investigations were analysed. Findings of radiological investigations – magnetic resonance imaging (MRI) brain/spine, angiography/venography, high-resolution computed tomography of chest – were analysed. The National Institutes of Health Stroke Scale (NIHSS) score for stroke cases, the subtype classification of acute ischemic stroke using Trial of Org 10172 in acute stroke treatment (TOAST) and outcome assessment at the time of discharge according to modified Rankin scale (mRs) were done.

Statistical analysis

The categorical variables were expressed as frequency and percentage and continuous variables as mean, median with standard deviation and inter-quartile range. Statistical analysis was done using SPSS Statistical Software Package (release 22.0, SPSS, Chicago, Illinois).

Results

Among 3200 patients treated with neurological illness during the study period, 120 (3.75%)(M: F – 80:40) patients had confirmed COVID-19 infection with neurological disorder. The mean age is 48 ± 17.4 years with a median of 49 years (range is 3–84 years). The mean duration of illness was 10.9 ± 17.3 days. History of preceding fever was present in 59 (49%) patients. Seventeen (14.2%) patients had anosmia, 56 (47%) patients had altered level of consciousness and 25 (21%) patients had seizures. The frequency of the various clinical symptoms is depicted in Table 1. Pre-existing neurological illness was present in 20 patients and they presented with worsening of their neurological condition. COVID infection was mild in 53 patients, moderate in 32 patients and severe in 35 patients. Other comorbidities such as hypertension, diabetes or ischemic heart disease were present in 46 patients. The different clinical presentations of new-onset neurological illness (n = 100) due to COVID-19 are shown in Table 2. The neurological features, categorised as central nervous system (CNS) and peripheral nervous system (PNS) involvement, were as follows:

CNS manifestations were as follows:

1. *Stroke (n = 43):*
   Acute ischemic stroke (AIS) occurred in 22 patients. Two patients presented with transient ischemic attacks (TIA) in the territory of carotid artery, 13 patients had cerebral venous sinus thrombosis (CVST) and six patients had intracerebral bleed.
   - *AIS (n = 24):*

   The mean age of patients was 50.1 ± 11.8 (31–71 years; M: F – 17:7). The mean duration of symptoms was 1.9 ± 2.6 (1–10) days. The median duration between fever, cough, and onset of stroke was 5 days; 9 (37.5%) patients had preceding fever and 2 (8.3%) had cough. Thirteen patients had altered level of consciousness and 2 had seizures. The mean Glasgow coma scale (GCS) score was 11.7 ± 3.3 (range: 4–15). Comorbid illnesses were hypertension (6), diabetes mellitus (10), and ischemic heart disease (3). Fourteen patients (58.3%) had no traditional stroke risk factors. The probable

AIS due to COVID-19 were 14 (58.3%) and 10 (41.6%) patients were possible AIS due to COVID-19. Large artery territory AIS was noted in 20, TIA in 2 and 2 had multi-infarct state. Twelve patients had middle cerebral artery (MCA) AIS [Figure 1], 3 had internal carotid artery AIS, 4 had vertebral artery AIS, and 1 had lacunar capsular infarct. The mean NIHSS score was 18.3 ± 9.2 (range: 4–36). Stroke severity was moderate (NIHSS 5–15) in 6 (27.2%), moderate to severe (NIHSS 16–20) in 6 (27.2%) and severe (NIHSS 21–42) in 10 (45.4%) patients. The inflammatory markers showed elevated values in the form of: elevated CRP was observed in all patients (n = 10, mean 128 ± 98 mg/L), D-dimer in 8 of the 9 patients (3261 ± 2940 mcg/L), ferritin (n = 10, mean 616 ± 665 mcg/mL) and IL-6 (n = 7,105 ± 61.5 pg/mL) were elevated in all the patients tested (n = 10 and 7, respectively). One patient with MCA territory stroke underwent decompressive craniectomy. None of the patients were eligible for thrombolysis. The median mRs score at discharge was 4 (range: 0–6) in all the patients as well those with comorbidities. Six patients (excluding 2 with TIA) had mRs score ≤ 2 whereas 16 (69.5%) had poor outcome with mortality (21.7%) in 5 patients.

- *CVST (n = 13):*

The mean age at illness was 33.7 ± 13.0 (range: 22–58) years; male: female 7:6. The mean duration of symptoms was 4.4 ± 7.9 days (1–10 days). Two patients had CVST in past. One patient had history of cough and two patients had anosmia. Eight patients each had altered level of consciousness and seizures. The mean GCS score was 11.7 ± 3.6 (range: 3–15). Nine patients had haemorrhagic infarct while 4 did not have parenchymal lesion. Thrombosis was seen in superior sagittal sinus (SSS) (3), transverse sinus (TS) (6), cortical veins (1) both SSS and TS thrombosis (3). The various risk factors noted were as follows: alcoholism (6), hyperhomocysteinemia (3), anaemia (haemoglobin < 9 g % in 3), post-partum status (2). One patient each was on hormonal supplementation and chemotherapy for acute lymphoid leukemia. One patient was diabetic. Inflammatory markers were elevated in all the tested 4 patients. All patients were treated with heparin; however, five patients required decompressive craniectomy. The median mRs score at discharge was 3 (range: 1–6) with 7 patients having mRs >2 suggesting poor outcome.

- *Intracerebral bleed (n = 6):*

The mean age of the patients was 49.6 ± 12.9 years (35–70); 5 patients were male. The mean duration of symptoms was 3.8 ± 4.1 days. Two patients had preceding fever, cough. Three patients were hypertensive and one had diabetes mellitus. The mean GCS score was 8.2 ± 1.7 (range: 7–11). Three patients had basal ganglia bleed while

Table 1: Frequency of clinical symptoms in confirmed COVID-19 cases with neurological disease (n=120)

Presenting symptoms	Number (%) of patients
Systemic	
Fever	59 (49.1)
Shortness of breath	40 (33.3)
Cough	39 (32.5)
Fatigue	13 (10.8)
Gastrointestinal complaints	09 (7.5)
Neurological	
Altered sensorium	56 (47)
Limb weakness	53 (44.5)
Headache	45 (37.8)
Seizure	25 (21)
Vomiting	25 (21)
Blurred vision	20 (16.8)
Speech problem	20 (16.7)
Anosmia	17 (14.3)
Loss of taste	09 (7.6)
Diplopia	09 (7,5)
Dizziness	08 (6.7)
Myalgia	06 (5)
Dysphagia	05 (4.2)

Table 2: Frequency of new-onset neurological manifestations associated with COVID-19

	Number of patients (n=100)%	Frequency of COVID-19 symptoms (n/%)	Good outcome at discharge (n/%)	Poor outcome at discharge (n/%)
Stroke n=43				
AIS	24	9 (37.5%)	6 (25%)	16 (75%)
CVST	13	2 (15.4%)	6 (46.1%)	7 (53.8%)
Intracerebral bleed	6	2 (33.3%)	0	6 (100%)
Encephalopathy	23 (23)	19 (82.6%)	10 (43.4%)	13 (56.5%)
Meningoencephalitis	5 (5)	5 (100%)	1 (20%)	4 (80%)
New onset seizures	5 (5)	4 (80)	5 (100)	0
New onset headache	7 (7)	4 (57.1)	7 (100)	0
ADEM	1 (1)	1 (100)	1 (100)	0
Anxiety	1 (1)	1 (100)	1 (100)	0
GBS	10 (10)	5 (50)	3 (30)	7 (70)
Isolated cranial neuropathy	2 (2)	1 (50)	2 (100)	0
Critical illness neuropathy	3 (3)	3 (100)	1 (33.3)	

AIS: Acute Ischemic stroke; CVST: Cerebral venous sinus thrombosis; ADEM: Acute demyelinating encephalomyelitis; GBS: Guillain barre syndrome

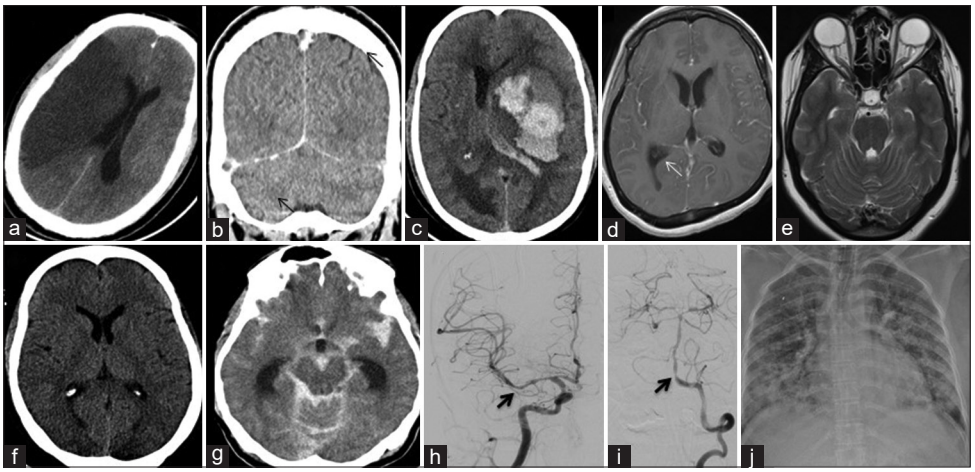

Figure 1: (a) Right middle cerebral artery territory infarct, (b) Superior sagittal sinus and right transverse sinus thrombosis; case of Cerebral venous sinus thrombosis. (c) Left basal ganglia bleed with variable densities suggestive of Cerebral venous sinus thrombosis. (d) T1 axial image with post contrast enhancement in a case of Meningitis. (e) T2 axial images of the Brain showing partial empty sella with tortuous optic nerves in a case of IIH (idiopathic intracranial hypertension). (f) Hypodensity in bilateral Occipital region suggestive of posterior reversible encephalopathy syndrome (PRES). (g) Hyperdensity of the sylvian fissure and all the basal subarachnoid spaces suggestive of Subarachnoid haemorrhage. (h and i) Digital substarction angiogram showing multifocal stenosis and ectasia of middle cerebral artery and posterior cerebral artery (Arrows). (j) X-Ray of patients showing diffuse (More in bilateral lower zone) pulmonary infiltrates

one each had basi-frontal bleed, intraventricular bleed and sub-arachnoid haemorrhage (SAH). CRP was increased in 5/6 patients (mean = 104 ± 95). Ferritin was elevated in 2/4 patients and D-dimer in a single patient in whom it was tested. Angiogram of patient with SAH showed multifocal stenosis and ectasia of middle and posterior cerebral artery suggestive of vasculitis. He underwent external ventricular drainage for hydrocephalus. One patient with basal ganglia bleed required decompressive craniectomy. Two patients were in addition treated with Remdesivir. The median mRs score was five patients (range: 5–6) and death occurred in three patients.

2. *Encephalopathy (n = 23):*
   Twenty-three (23%) patients had encephalopathy due to hypoxia, metabolic disturbances, sepsis or a combination of factors. Seven (30.4%) patients had delirium and seizures occurred in 4 (17.3%). The mean GCS was 10.5 ± 3.7. The mean age of the patients was 64.1 ± 10.1 (range: 47–79) with male predominance (15:8). The mean duration of symptoms was 4.4 ± 7.0 (range: 1–37) days. Seven patients had hypertension and 12 had diabetes. The median COVID-19 Reporting and Data System (CORADS) score was 4 (range: 1–5). CRP, D-dimer and IL-6 were elevated in all patients (n = 19) and ferritin was elevated in seven patients (n = 16). The mean CRP was 122.1 ± 122.4 mg/L (range: 33-495; normal <10), mean D-dimer was 2789 ± 2936 µg/L (range: 890-8656; normal <500), mean ferritin was 551.4 ± 586.4 µ/L (range: 45–1860; normal \: 12–300) and mean IL-6 was 178.1 ± 586.4 pg/mL (range: 15–1528; normal ≤1.8 pg/mL). Uremia was present in four patients. Computed tomography (CT) brain (n = 9) showed age-related cerebral atrophy. Brain MRI (n = 4) showed cerebral atrophy in two patients and cortical diffusion restriction suggestive of hypoxia in two patients. Fifteen patients received Remdesivir, four patients received plasma therapy and one patient received Tocilizumab. The median mRs score was 4 (range: 1–6) [similar in those with and without co-morbidities]. with poor outcome in 13 patients and death in five patients. A female patient, non-hypertensive, presented with headache, blurring of vision and altered sensorium. Blood pressure was 180/100 mm Hg. CT brain showed bilateral occipital lobe hypodensities suggestive of posterior reversible encephalopathy syndrome (PRES). She was treated with antihypertensive agents and had complete recovery.
3. *Meningo-encephalitis (n = 5):*
   Five patients presented with fever, cough, headache, and altered level of consciousness. Two had seizures. The mean age was 36.5 ± 15.9 years with male predominance (4). The median duration of symptoms was 3 days (range: 1–10).). One patient was diabetic. The mean GCS score was 11.2 ± 2.1. CRP and D-dimer were elevated in two patients. The mean CSF protein level was 61.2 ± 46.9 mg/dL (21–106), CSF glucose level was 62.6 ± 17.6 mg/dL (range: 42–94). The mean CSF cell count was 74.0 ± 228.9 (range: 8–620) with polymorphonuclear cells predominance in two patients. CSF-PCR for SARS-CoV-2 was not done. CSF analysis for other bacterial, viral and fungal infections were negative. They were classified as probable COVID-19 meningoencephalitis. Brain MRI showed leptomeningeal enhancement in four patients. Patients were treated with Remdesivir. Death occurred in one patient, while three had a poor outcome.
4. *New-onset seizures (n = 5):*
   Five (5%) patients presented with new-onset seizures; three presented with status epilepticus and two patients

had a single episode. Three patients were diabetic and one had hypertension. Four patients had COVID-19 symptoms. CRP, ferritin, D-dimer and IL-6 (done in 3) were elevated. MRI brain was normal in all. Two patients received Remdesivir. All the patients had a good outcome.

5. *New-onset headache (n = 7):*
   Seven (7%) patients presented with new-onset headache. None had history of migraine in the past. Female predominance (4) was noted. The mean age was 36.4 ± 8.3 years (range: 27-53). The mean duration of symptoms was 7.0 ± 9.0 (range: 3-20) days. Five patients had blurred vision and anosmia; three patients had raised intracranial pressure (ICP). The patients without raised ICP had recent onset holocranial headache, with fever and cough in three patients. CRP, D-dimer, ferritin and IL-6 was elevated in three patients. CSF analysis and MRI brain were normal. Three patients with raised intracranial pressure had recent onset holocranial headache, vomiting and blurred vision. They had papilloedema and reduced visual acuity. CSF opening pressure was greater than 30 cms. MRI brain showed empty sella with dilated peri-optic spaces. One patient underwent theco-peritoneal shunt while two responded well to medical management.
6. *Acute disseminated encephalomyelitis (ADEM) (n = 1):*
   A young girl (3 years) presented with fever of 1-day; blurred vision followed by progressive quadriparesis. MRI brain showed demyelinating lesions in bilateral subcortical and deep white matter of cerebral hemispheres. CSF analysis revealed raised protein (61 mg/dL) and normal cells (4 lymphocytes). She was started on systemic steroids.
6. *Anxiety disorder (n = 1):* A diabetic lady (43 years) had fever, cough, shortness of breath, anosmia. She was diagnosed as moderate COVID-19 and received steroids, remdesivir. She recovered well with treatment but presented after 2 weeks with anxiety and excessive fearfulness. She was managed with membrane stabilisers and counselling.

Peripheral nervous system involvement:

Guillain-Barre syndrome (GBS) (n = 10) and isolated cranial neuropathy (n = 2)

Ten (10%) patients presented with tetraplegia. The mean age of the patients was 46.8 ± 14.8 years (range: 33–74). Seven were males. The mean duration of symptoms was 7.8 ± 8.4 days (range: 2–30). Five patients had preceding fever with cough. Six patients (60%) had bifacial weakness Nerve conduction study (done in 6) showed features of demyelination in 1 patient and axonal pattern in 5. One patient was diagnosed as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), 2 as acute motor axonal neuropathy (AMAN) and 3 as acute motor-sensory axonal neuropathy (AMSAN) [Figure 2]. CSF (done in 5) showed albumino-cytological dissociation. Seven patients required ventilator assistance with ICU stay ranging from 8-30 days. One patient each had diabetes and hypertension. Inflammatory markers were increased in all the patients; two patients received remdesivir. The median mRs score at discharge was 5 with death of 1 patient.

2 patients presented with cranial neuropathy. An elderly diabetic (60 years) presented with pupil sparing right oculomotor nerve palsy of 3 days duration. There were no preceding COVID-19 symptoms. Glycosylated haemoglobin was 6.8%. MRI brain and CSF analysis were normal. The other patient, (48 years) without vascular risk factors, presented with diplopia of 2 days with fever and cough. He had isolated right abducens nerve palsy. MRI brain and CSF analysis were normal. Both patients responded to steroid therapy.

Critical-illness neuromyopathy in severe COVID-19 (n = 3):

3 patients (mean age-64 years) presented with severe COVID-19 with a median CORADS score of 5, while two patients were diabetic. CRP, ferritin, D-dimer and IL-6 were elevated. Serum creatine phosphokinase was normal. The median days on ventilator were 20 days. They later developed hypotonic, areflexic quadriparesis suggestive of critical-illness neuromyopathy. NCS and EMG were not done. CSF did not show albuminocytological dissociation. Three patients received Remdesivir while one each received Tocilizumab and plasma therapy. Two patients had poor outcome.

COVID in patients with pre-existing neurological disorders [Table 2]:

Relapse of Neuromyeltitis optica spectrum disorder (NMOSD) and myasthenic crisis:

Three patients with NMOSD presented with relapse: two had bilateral optic neuritis and one had opticomyelopathy. Two patients were on oral steroids and one on azathioprine. All three had mild COVID-19 and had good recovery with steroids and plasma exchange. Five patients of myasthenia gravis had severe COVID-19 [median CORADS (The coronavirus disease 2019 (COVID-19) Reporting and Data System)-5] and presented in myasthenic crisis. All patients received remdesivir and three patients also received tocilizumab. Death occurred in four patients and one patient had good outcome.

Other patients with pre-existing neurological disorder and COVID positive status: Three patients with the previous history of seizure presented with recurrence. One patient had unilateral hippocampal sclerosis while the other two had normal MRI. All of them were asymptomatic for SARS-COV2. A patient with the past history of ADEM presented with giddiness and MRI brain was normal. Patients with other pre-existing neurological disorders who presented with worsening/relapse were: Idiopathic Intracranial Hypertension (2), inflammatory myositis (1), brachial plexopathy (1), tubercular meningitis with hydrocephalus (1) and orbital apex syndrome (1).

Discussion

In this large hospital-based study from India, we report a wide range of neurological syndromes associated with confirmed

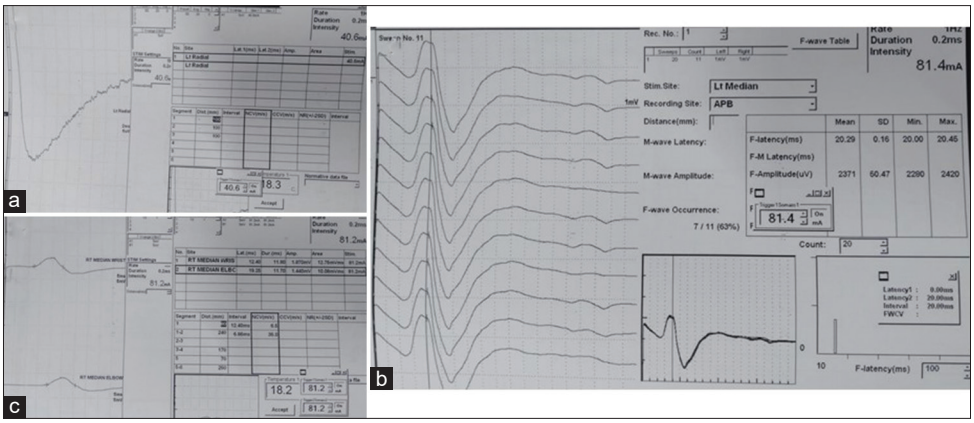

Figure 2: (a) Absent sensory conductions of the Radial nerve in patient of AMSAN variant of GBS. (b) Prolonged F-wave latency (20.3 ms) in a patient of AMAN variant of GBS. (c) Median nerve conductions showing prolonged latency (12.4 ms), decreased amplitude (1.8 mV) and reduced conduction velocity (35 m/s)

COVID-19 infection from two large tertiary neurology centres. Of the 120 patients in the cohort, 100 had new-onset neurological symptoms associated with COVID-19 infection and the commonest clinical manifestations were stroke, encephalopathy and GBS. The unusual clinical presentations were new-onset seizures, headache and ADEM. COVID-19 infection was also detected in 20 patients with pre-existing neurological illness and manifested typically as a relapse of the underlying disorder. Neurological symptoms have been reported to occur in a significant proportion of patients admitted with COVID-19 infection from various parts of the world,[4,5,6,7,9,10,14] majority relying on electronic databases. Our study was conducted in two large tertiary neurology referral services and reports a comprehensive range of neurological manifestations associated with COVID-19 infection.

Our study cohort of COVID-19 infection related neurological disease, is one of the largest reported so far. Earlier cohorts reported 78 patients with neurological manifestations from China,[5] 153 patients from UK reported from a nationwide survey using an electronic database,[8] 483 patients from Spain,[6] 83 patients from Turkey[7] 56 patients from Italy[9] and 43 patients from UK.[10] The range of neurological manifestations in our cohort was wide and the viral infection resulted in involvement of both central and peripheral nervous systems. Stroke (43%), encephalopathy (23%), GBS (10%) were the most common diseases. The profile of neurological manifestation is consistent with the earlier reported studies (summarised in Table 3).[14-17] Our study thereby confirms that COVID -19 infection can affect the nervous system in myriad ways and neurological manifestations of stroke, GBS and headache can be the sole manifestation or the presenting feature of COVID-19 infection, in more than 50% of patients.

Stroke was the most common neurological manifestation encountered in our study. Inflammation, endothelial dysfunction, platelet activation and thrombin generation cause arterial and venous thrombotic complications in COVID-19.[18] In the present study, patients with AIS were of younger age and nearly two-third of patients did not have conventional risk factors. The lower age of our COVID-19 related stroke cohort compared to a pooled analysis of 174 COVID-19 patients with AIS,[19] is probably reflective of the younger age of stroke in the Indian population.[20] Our cohort was characterised by greater stroke severity (NIHSS: 18.3 ± 9.2), with a majority demonstrating large artery involvement (81.8%) and nearly three-fourth had a poor stroke outcome, consistent with earlier reports.[18,19] A multicentre study of 60 stroke patients with COVID-19 infection from India showed stroke patients were younger with male predominance, without vascular risk factors in 26% patients and large artery territory stroke in 36.6% patients.[21]

We had 13 patients of CVST in our study which is larger compared to the number of cases reported in other case series. 14 patients with CVST in COVID-19 have been reported so far.[22] The larger numbers of patients with CVST (13) in our cohort is perhaps indicative of the higher prevalence of CVST in India compared to western populations.[23] The higher prevalence of hypercoagulable state due to chronic alcoholism, hyperhomocysteinemia, anemia, dehydration in the post-partum period probably predisposed COVID-19 patients towards developing CVST.[23] However, the severe COVID-19 form in our patients was lower that may have contributed to lower mortality in our study compared to previous reports.

Six patients had presented with intracerebral bleed in this series. Endothelial injury by viral invasion/inflammation and disruption of the renin-angiotensin system (RAS) leads to cerebral blood flow dysregulation and intracerebral bleed.[23] Our cases were younger compared to other cases reported worldwide. A meta-analysis of intracerebral haemorrhage in COVID-19 cases found that only 16% of bleeds occurred in less than 50 years of age.[24,25] None of our patients received anticoagulation prior to onset of disease, while the meta-analysis that included predominantly older cohorts from the west, revealed that 51% had received some form of anticoagulation prior to intracerebral bleed.[25]

Table 3: Comparison of our Study with that of previous large studies

	Mao L *et al*.[5] (China) (*n*=78)	Romero-Sanchez *et al*.[6] (Spain) (*n*=483)	Karadas *et al*.[7] (Turkey, *n*=83)	Varatharaj *et al*.[8] (UK) (*n*=153)	Paterson *et al*.[10] (UK) (*n*=43)	Benussi *et al*.[9] (Italy) (*n*=56)	Chen *et al*.[10]	Present study (India) (*n*=119)
Stroke	5 (4 AIS; 1 intracerebral bleed)	14	9	77 (57 AIS; 9 intracerebral bleed; 1 CNS vasculitis)	8 AIS	43 (35 AIS; 3 hemorrhagic stroke; 5 TIA)	NA	43 (24 AIS; 13 CVST; 5 intracerebral bleed; 1 CNS vasculitis)
Encephalopathy	16	165	23	9	10	NA	26	23
New onset psychosis	NA	167	NA	10	NA	NA	NA	NA
Neurocognitive (dementia-like) syndrome	NA	NA	NA	6	NA	NA	NA	NA
Encephalitis	NA	1	NA	7	2	NA	NA	5
Affective disorder	NA	NA	NA	4	NA	NA	NA	1
ADEM	NA	NA	NA	NA	9	NA	NA	1
New onset seizures	NA	6	NA	NA	NA	NA	NA	5
Isolated cranial neuropathy	NA	NA	NA	NA	NA	NA	NA	2
Headache	28	119	64	NA	NA	NA	31	7
Anosmia	12	41	18	NA	NA	NA	NA	17
Brachial plexopathy	NA	NA	NA	NA	1	NA	NA	NA
Critical-illness neuropathy	NA	NA	NA	NA	NA	NA	NA	3
GBS	NA	1	1	NA	7	NA	NA	10
Skeletal muscle injury	23	253	36	NA	NA	NA	NA	NA

AIS: Acute Ischemic stroke; CVST: Cerebral venous sinus thrombosis; ADEM: Acute demyelinating encephalomyelitis; GBS: Guillain barre syndrome; CNS: Central nervous system; NA: Not applicable

Encephalopathy is more common in severe and critical COVID-19 patients noted to occur in 7.5% to 74% of cases.[5,26] We found encephalopathy in 22% of patients mainly due to septic, hypoxic/metabolic causes. The inflammatory markers (C-reactive protein, interleukin-6, procalcitonin, D-dimer and ferritin) were raised in all patients as observed previously.[26] One patient of ours had features of PRES, hypertension and had good recovery with management of hypertension. There are only a few reports of PRES in COVID-19: this has been reported in patients who required prolonged mechanical ventilation or who received anti-IL6 treatment.[26-29]

Seizures as a presenting feature were seen in 5 of our patients and may occur due to neurotropism of SARS-CoV2, proinflammatory cytokines, or due to the proconvulsant effect of Angiotensin II.[30] Metabolic factors, hypoxia, and sepsis may contribute to the pathogenesis. Seizures as a presenting manifestation of COVID-19 is extremely rare, reported in 0.7% (7/1043) of cases from US.[30] All patients in this cohort had mild COVID-19 infection while 57% of the cases previously reported had severe COVID-19 infection and respiratory failure.[31]

Headache in COVID-19 patients occurs due to direct invasion of trigeminal nerve endings in the nasal cavity by the SARS-CoV-2, increase in the nociceptive calcitonin gene-related peptide level by angiotensin II, trigeminovascular activation by proinflammatory cytokines. The characteristics of headache related to COVID-19 infection include presence of bilateral headache, duration over 72 h, male gender, analgesic resistance, gastrointestinal symptoms, and anosmia/ageusia.[32,33,34] Interestingly, 71% of our patients also reported anosmia. There are few reports of headache due to intracranial hypertension associated with COVID-19. Inflammation and hyperviscosity may be contributing to venous congestion in these cases [35].

ADEM in the current cohort was observed in a child (3 years) with typical bilateral subcortical and deep white matter lesions. ADEM in association with COVID-19, has been reported in only few case reports in both adults and paediatric population, except for a series from UK, where 9/45 cases had ADEM.[10] Interestingly, four of them had hemorrhagic changes on MRI and one had necrosis with a poor response to steroids.

We recorded 10 cases of GBS with a mean age of 47 years. Direct cytotoxic effects of virus on peripheral nerves or immune-mediated mechanisms account for nerve damage.[36] Preceding respiratory symptoms were present only in 5 patients. Around 40 patients have been reported worldwide with COVID-19 infection and GBS so far.[36,37] The mean age of patients was 60.5 years. Bifacial weakness was present in 60% of our patients and all had tetraplegia as reported in other studies. However, ventilator assistance was required in 80% of our patients compared to 43.6% of reported cases.[27] Electrophysiological studies showed axonal pattern of neuropathy in more than 80% of cases (5/6), while demyelinating pattern is reported in 75%.[36] Only one of our patients expired and the remaining patients had a significant

disability at discharge with a median mRS of 5, in contrast to the good outcome in 65.8% of cases reported worldwide.[36,37]

Two patients had isolated cranial neuropathy involving oculomotor and abducens nerves in this series. Neuroimaging and CSF analysis were normal in both patients and both had good response to steroids. Dinkin *et al.*[38] reported two cases of ophthalmoparesis, one case of Miller-Fisher syndrome with hyperintensity and enhancement of oculomotor nerve on MRI and second patient had isolated abducens nerve palsy with enhancement of the optic nerve sheaths and posterior tenon capsules. Glossopharyngeal and vagal neuropathy has also been reported with COVID-19.[38]

Three elderly patients with severe COVID-19 with median duration on ventilator of 20 days developed critical-illness neuromyopathy in our series. Twelve patients with critical illness myopathy or neuropathy have been reported from Spain.[39,40] Average age was 65 years with a median duration of ICU stay of 24 days. 4 patients had sensorimotor axonal neuropathy and 7 had myopathy with a mild elevation of CK.

There were 20 patients with pre-existing neurological illness who presented with relapse, among whom were 3 cases of NMOSD and 5 cases of MG. All the NMOSD patients had good response to steroids and plasmapheresis. A retrospective series of 75 patients of NMOSD from France showed 5 patients with confirmed COVID-19. None of them had severe COVID-19 despite immunosuppressive therapy and none had relapse.[41] A study from Iran also reported 5 patients with NMOSD and COVID-19 and none had clinical relapse.[42]

Myasthenia gravis patients in the current cohort presented in crisis and all of them required mechanical ventilation and aggressive therapy including remdesivir and tocilizumab. Mortality rate was 80% despite adequate treatment. A retrospective study on 15 patients of MG with COVID-19 showed exacerbation of MG requiring mechanical ventilation due to COVID-19 in 13 patients.[43]

The strength of the current study is the detailed assessment of each patient by a neurologist, in comparison to many studies where data regarding neurological manifestations were derived from electronic databases and no detailed assessment was done. We acknowledge the limitations that this being a hospital-based chart review in a tertiary care centre, may not reflect the true prevalence and extent of neurological manifestations with COVID-19.

In Conclusion, We report a wide spectrum of neurological disorders associated with COVID-19 from India with a detailed evaluation of all patients by experienced neurologists, using appropriate investigations. Stroke, encephalopathy and GBS were the commonest neurological disorders associated with COVID-19. Less common manifestations were new-onset seizures, intracranial hypertension and SAH due to CNS vasculitis. Stroke, headache or GBS can be the sole or presenting feature of COVID-19 infection in more than 50 percent of patients. Our study emphasises the need to be aware of the various neurological syndromes associated with COVID-19 infection and diagnose early for adequate management. This will enable the institution of appropriate therapy early in the course of illness and reduce burden of neurological disability resulting from the COVID-19 pandemic.

Data availability

Data is available with the authors. Anonymised data will be shared if ethically indicated.

Ethics approval

Obtained from both the respective hospitals

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Conflicts of interest

There are no conflicts of interest.

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