**Original Article**

# Neurological presentation of COVID-19: experience from a tertiary care hospital of Bangladesh

**Islam MR[a], Rahman T[b], Ahmed SM[c], Khan MSH[d], Azad MR[e], Alam D[f], Habib R[g]**


## ABSTRACT

***Background:*** *Neurological manifestations of COVID-19 are being recognized day by day although predominant presentation is of respiratory illness. Understanding of impact of the virus on nervous system is important for selection and evolution of treatment now and in the future. The aim of the study was to describe the manifestations of COVID-19 affecting nervous system in a tertiary care hospital of Bangladesh*

***Methods:*** *This cross-sectional study was carried out in Department of Neurology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital from March, 2020 to October, 2020. Total forty patients who were admitted under neurology department were included in the study. Evidence of SARS-CoV-2 infection was confirmed in all the patients if RT-PCR of respiratory samples (eg, nasal or throat swab) was positive for viral ribonucleic acid (RNA). Clinical syndromes associated with COVID-19 were classified broadly as a cerebrovascular event, altered mental status and peripheral nervous system disorders. Data were collected on the basis of specific clinical case definitions.*

***Results:*** *Median age of the patients was 58.6 years (range 22–73). Among those, 26 (65%) were male and 14 (35%) were female. Twenty two (55%) of 40 patients presented with cerebrovascular event, of whom 15 (68%) had an ischaemic stroke, 5 (23%) an intracerebral haemorrhage. Two (9%) patients were diagnosed as cerebral venous sinus thrombosis on the basis of clinical presentation and magnetic resonance venography (MRV) finding. Apart from cerebrovascular events, 14 (35%) of 40 patients presented with altered mental status, comprising 9 (64%) patients with unspecified encephalopathy and 5 (36%) patients with encephalitis. Four (10%) patients were diagnosed as peripheral nervous system disorder among those 2 (50%) as* Guillain-Barré syndrome *(GBS) and 2 (50%) as Bell's palsy. If we analyze the presenting features of the 40 patients, it is found that, 22 (55%) patients presented with headache, 20 (5%) with hemiparesis, 20 (50%) with speech problems, 19 (48%) with altered mental status, 10(25%) with facial asymmetry, 4 (10%) with seizure. Few percentages of patients presented with anosmia (10%), ageusia (5%) and quadriparesis (5%).*

***Conclusion:*** *Neurological involvement in COVID-19 is one of the major focuses of neurologist now a day. We have found cerebrovascular disese, encephalopathy and peripheral nervous system disorder as presentation of COVID-19 in our study. Prompt recognition of cases and early initiation of therapy will hasten better outcome of the patients. Neurological complications can cause permanent disability that will cost large scale health and economic burden. Further nationwide study is needed to quantify the association and disease burden.*


***Key words:*** *COVID-19, neurological presentation.*

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**Author information**

a. Md. Rashedul Islam, Assistant Professor, Department of Neurology, BIRDEM General Hospital, Dhaka, Bangladesh.

b. Tanbin Rahman, MD Thesis part student (Hematology), Dhaka Medical College, Dhaka, Bangladesh.

c. Syed Mohaimeen Ahmed, Resident Medical Officer, Department of Neurology, BIRDEM General Hospital, Dhaka, Bangladesh.

d. Mohammad Sakhawat Hossen Khan, Registrar, Department of Neurology, BIRDEM General Hospital, Dhaka, Bangladesh.

e. Md. Rihan Azad, Assistant Registrar, Department of Neurology, BIRDEM General Hospital, Dhaka, Bangladesh.

f. Dilruba Alam, Registrar, Department of Neurology, BIRDEM General Hospital, Dhaka, Bangladesh.

g. Rumana Habib, Associate professor, Department of Neurology, BIRDEM General Hospital, Dhaka, Bangladesh.

**Address of correspondence:** Md. Rashedul Islam, Assistant Professor, Department of Neurology, Room-1420, 13th Floor, BIRDEM General Hospital, Shahbag, Dhaka-1000, Dhaka, Bangladesh. Email: rashed2k2001@yahoo.com

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## INTRODUCTION

Clinicians of Wuhan, China notified World Health Organization (WHO) on 31st December, 2019 about a novel and severe respiratory virus which was named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) later on. Disease caused by SARS-CoV-2 is named as Corona Virus Disease 2019 (COVID-19) which is considered as global public health emergency. WHO declared SARS-CoV-2 as a public health emergency on 11th March, 2020. Most of the patients presented with mild symptoms like fever, cough etc and recovered without any specific treatment. Acute respiratory distress syndrome (ARDS), sepsis, cardiac failure, acute renal failure, metabolic derangements have been reported particularly in patients with advanced age and comorbidity.[1,2,3] Neuropsychiatric and psychiatric manifestations have also been reported in severe cases.[4] These complications are relatively uncommon, but such patients often affected severely necessitating intensive care admission resulting in poor outcomes.[5] Initial studies featured that, there were some nonspecific neurological symptoms in COVID-19 like headache, dizziness, myalgia etc. Symptoms like anosmia and dysgeusia published in early case reports were a concern for neurologists.[6,7,8] There was a Japanese patient who was diagnosed as encephalitis caused by SARS-CoV-2 which was identified in cerebrospinal fluid (CSF).[9] Later on, there was a case report published on acute necrotizing encephalopathy associated with COVID-19.[10] With time, more reported cases of cerebrovascular disease in COVID-19 patients pointed to severe neurological manifestations with SARS-CoV-2.[11] Neurological manifestations can occur due to direct viral cytopathy, para-infectious cytokine storm, post-infectious immune-mediated disease or systemic effects of COVID-19. [11] Central nervous system (CNS) presentations are headache, encephalopathy, ischemic stroke, intracerebral hemorrhage, encephalitis and encephalomyelitis, acute myelitis etc. Established peripheral nervous system manifestations are loss of smell/taste sensation, Bell's palsy, Guillain-Barré syndrome (GBS) and its variants. Apart from that, myalgia, myositis and rhabdomyolysis has been reported in different studies.[12]

Globally, upto 12th October 2020, there have been 37,326,080 confirmed cases of COVID-19, including 1,073,973 deaths, reported to WHO. Between 8th March and 12th October 2020, there were three hundred seventy-nine thousand seven hundred thirty-eight (379,738) COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR), including five thousand five hundred fifty-five (5,555) related deaths (Infection fatality rate 1.46%) in Bangladesh. Bangladesh is the top 16th country with regards to COVID-19 cases in the world and accounts for 1% of the cases in the world.[13]

As COVID-19 cases are increasing in number with time, there are growing concerns for the neurologists regarding some matter of neurological manifestations of SARS-CoV-2. Several studies have already been published in Bangladesh stating neurological manifestations of COVID-19 and clinico-pathological findings of Bangladeshi COVID-19 patients with their clinical outcome.[14, 15] In this study, we tried to identify the neurological manifestations and complications of patients with COVID-19 attended in a tertiary care hospital of Bangladesh with an aim to update the knowledge of the clinicians and researchers.

## METHODS

### Study design

It was cross-sectional study.

### Study population

This study was carried out in Department of Neurology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital from March, 2020-October, 2020.Forty patients participated in the study. All the patients who were admitted under neurology department and diagnosed as COVID-19 later on were included in the study. Patients were given option to be transferred to designated COVID hospitals and some patients were transferred out.

### Evidence of COVID-19

Evidence of SARS-CoV-2 infection was defined as confirmed COVID-19 if RT-PCR of respiratory samples (eg, nasal or throat swab) was positive for viral ribonucleic acid (RNA).

### Clinical case definitions

Clinical syndromes associated with COVID-19 were classified broadly as a cerebrovascular event (defined as an acute ischaemic stroke, haemorrhagic stroke, thrombotic vascular event), altered mental status

(defined as an acute alteration in personality, behaviour, cognition, or consciousness), peripheral nervous system disorders (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle). Data were collected on the specific clinical case definitions within these broad presentations, as follows: a cerebrovascular event (ischaemic stroke, intracerebral or subarachnoid haemorrhage, cerebral venous sinus thrombosis); altered mental status (encephalopathy, encephalitis—defined as encephalopathy with evidence of inflammation in the CNS [CSF white cell count >5 cells per iL, protein >0·45 g/dL, or MRI consistent with inflammation], seizures [clinical or electroencephalographic (EEG) evidence] and peripheral nervous system disorder (GBS and other peripheral neuropathy).[6]

## RESULTS

Mean age of the patients was 58.6 years (range 22–73). Among those 26 (65%) were male and 14(35%) were female. Data on the sex and age of the patients are reported in the Table I. Age distribution of the study population is described in Figure 1. Number of clinical case according to clinical case definitions has been described in Figure 2. Twenty two (55%) of 40 patients presented with cerebrovascular event, of whom 15 (68%) had an ischaemic stroke, 5 (23%) an intracerebral haemorrhage. A magnetic resonance imaging (MRI) of a patient with ischemic stroke is shown in Figure 3. Two (9%) patients were diagnosed as cerebral venous sinus thrombosis on the basis of clinical presentation and Magnetic resonance venography (MRV) finding. Neuro imaging of a patient with cerebral venous sinus thrombosis is shown in Figure 4. Apart from cerebrovascular events, 14 (35%) of 40 patients presented with altered mental status, comprising 9 (64%) patients with unspecified encephalopathy and 5 (36%) patients with encephalitis. MRI brain of a case of encephalitis is shown in Figure 5. Four (10%) patients were diagnosed as peripheral nervous system disorder among those 2 (50%) as GBS and 2 (50%) as Bell's palsy. Presenting feature of the study population is shown in Table II. If we analyze the presenting features of the 40 patients, it is found that, 22 (55%) patients presented with headache, 20 (5%) with hemiparesis, 20 (50%) with speech problems, 19 (48%) with altered mental status, 10 (25%) with facial asymmetry, 4 (10%) with seizure. Few percentages of patients presented with anosmia (10%), ageusia (5%) and quadriparesis (5%).

**Table I** Age and sex data of patients (N=40)

| | All cases (n=40) | Cerebrovascular (n=22) | Altered mental status (n=14) | Peripheral nervous system involvement (n=4) |
|---|---|---|---|---|
| Male | 26 (65%) | 14 (64%) | 10 (71%) | 2 (50%) |
| Female | 14 (35%) | 8 (36%) | 4 (29%) | 2 (50%) |
| 21–30 | 5 (13%) | 2 (9%) | 2 (14%) | 1(25%) |
| 31–40 | 7 (18%) | 2 (9%) | 3 (21%) | 2 (50%) |
| 41–50 | 8 (20%) | 4 (18%) | 3 (21%) | 1 (25%) |
| 51–60 | 11 (28%) | 9 (41%) | 2 (14%) | - |
| 61–70 | 8 (20%) | 4 (18%) | 4 (29%) | - |
| 71–80 | 1 (3%) | 1 (5%) | - | - |

**Table II** Presenting neurological feature (N=40)

| | |
|---|---|
| Presenting symptom | Headache [22 (55%)] |
| | Hemiparesis [20 (50%)] |
| | Speech problem [20 (50%)] |
| | Altered mental status [19 (48%)] |
| | Facial asymmetry [10 (25%)] |
| | Seizure [4 (10%)] |
| | Anosmia [4 (10%)] |
| | Ageusia [2 (5%)] |
| | Weakness of all four limbs [2 (5%)] |

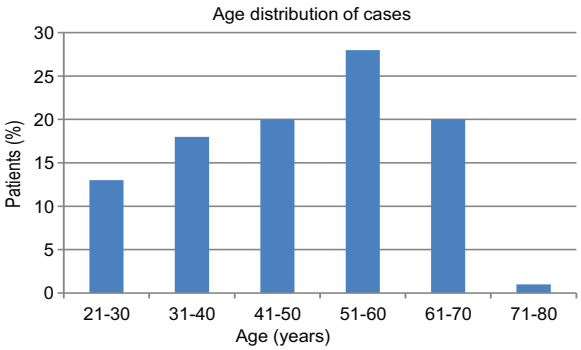


**Figure 1** Age distribution of cases

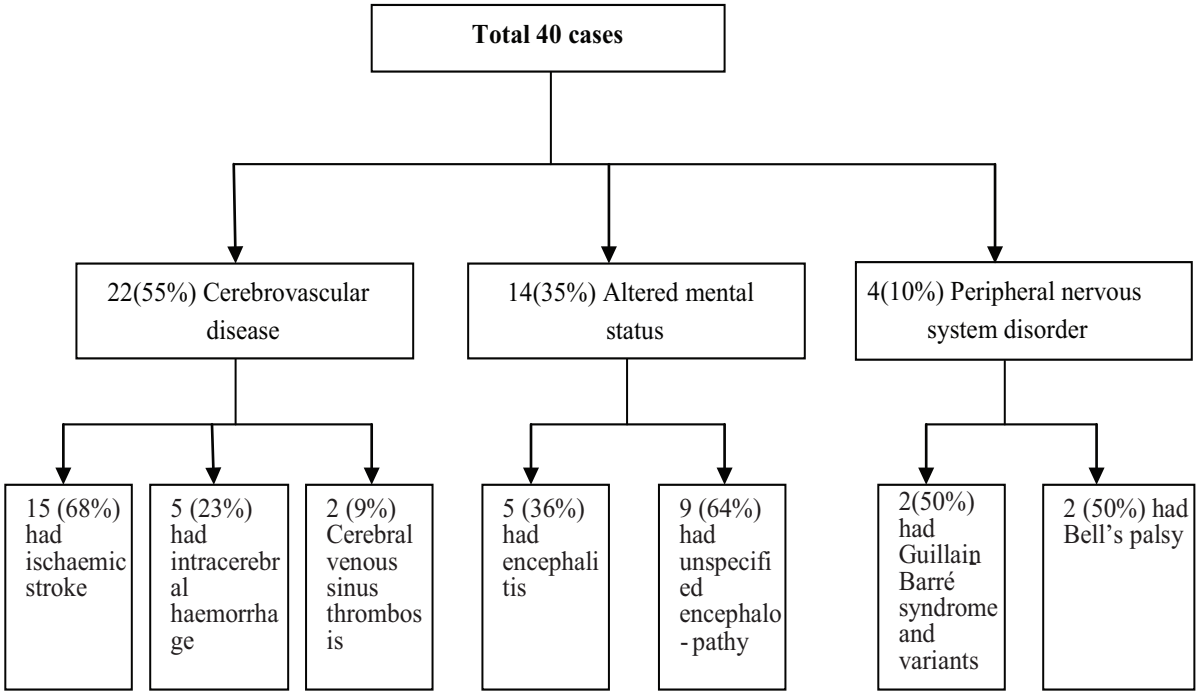


**Figure 2** Number of clinical case according to clinical case definitions

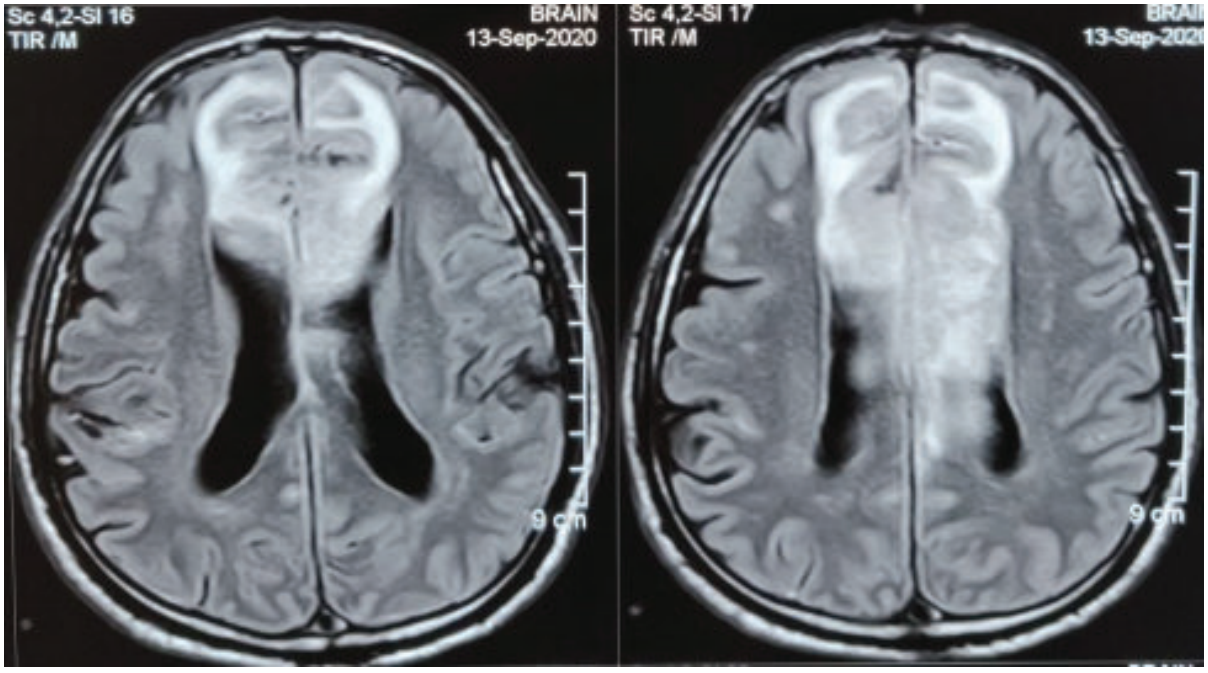


**Figure 3** MRI of brain fluid-attenuated inversion recovery (FLAIR) sequence showing bilateral cerebral infarction involving anterior cerebral artery territory

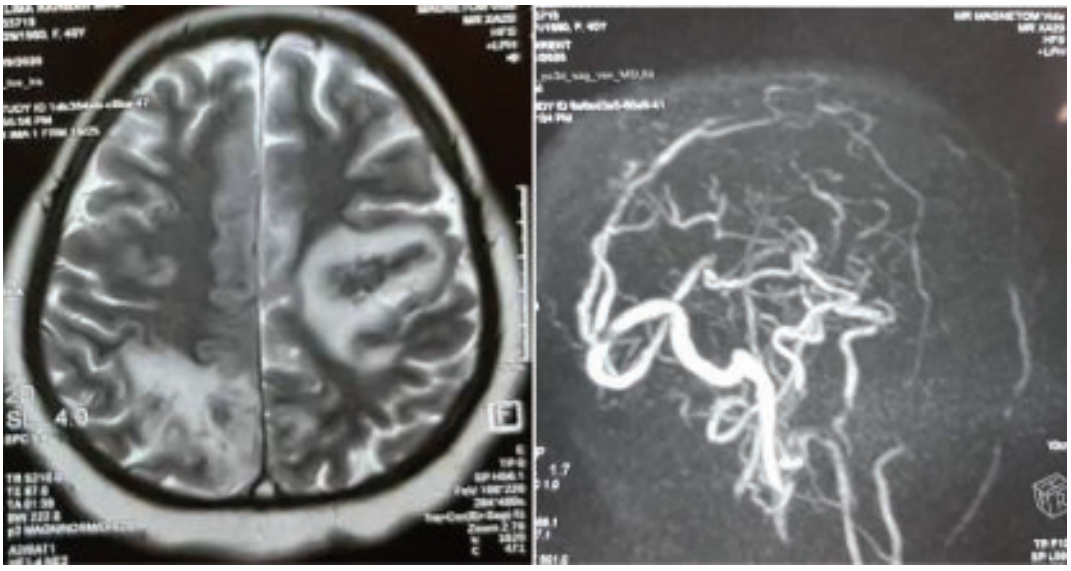

**Figure 4** MRI and MRV showing venous infarction and cerebral venous sinus thrombosis

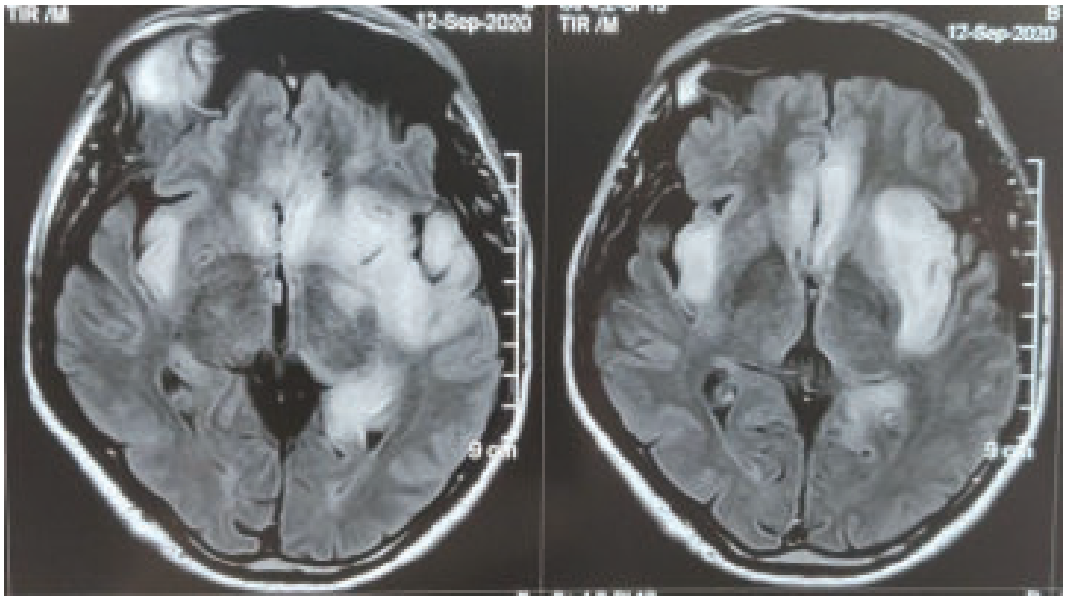


**Figure 5** MRI of brain FLAIR sequence showing bilateral hyperintense signal change involving frontotemoral lobes with cerebral edema suggestive of encephalitis

## DISCUSSION

We tried to study systematically the neurological presentation of COVID-19 in this study. Evidence is found to see the association with cerebrovascular disease, as well as with other forms of vascular disease.[16, 17] Cerebrovascular events are identified as major group in our study. We have found that, 22 (55%) of 40 patients presented with cerebrovascular event. Among those 22 patients, 15 (68%) had an ischaemic stroke, 5 (23%) an intracerebral haemorrhage. Two (9%) patients were diagnosed as cerebral venous sinus thrombosis. Cerebrovascular events were reported for 13 (6%) of 221 COVID-19 patients in an early study from Wuhan[18] 11 (5%) patients developed ischaemic stroke, one (<1%) had intracerebral haemorrhage, and one (<1%) had cerebral venous sinus thrombosis. Another study from

Italy reported that 43 of 56 SARS-CoV-2 positive patients admitted to their neurology unit had cerebrovascular disease. Among those 35 had ischaemic stroke and three haemorrhagic stroke, and five had transient ischaemic attacks.[19] A study conducted in UK reported that 77 (62%) of 125 patients presented with a cerebrovascular event, of whom 57 (74%) had ischaemic stroke, 9 (12%) had intracerebral haemorrhage, and 1 (1%) had CNS vasculitis.[20] Most of the patients described in different studies had known risk factors for cerebrovascular disease, especially hypertension, diabetes, dyslipidaemia, and other vascular disease.[18,21,22,]Younger stroke patients have also been reported.[21,22] Blood D-dimer concentration was raised in many patients with COVID-19 which is consistent with a pro-inflammatory, coagulopathic state in the setting of critical illness.[18,22,23] Immediate anticoagulation with low-molecular-weight heparin has been recommended for patients with, to reduce the risk of thrombotic disease.[23] This may reduce COVID-19-associated ischaemic stroke, but the risk of intracranial haemorrhage, especially haemorrhagic transformation of an acute infarct must be considered. Early studies suggest that cerebrovascular disease in COVID-19 might be due to a coagulopathy. SARS-CoV-2 can cause damage to endothelial cells, activating inflammatory and thrombotic pathways.[24] Endothelial cell infection or monocyte activation, upregulation of tissue factors, and the release of microparticles, which activate the thrombotic pathway and cause microangiopathy, might occur for SARS-CoV-2 as for other viruses.[25,26] Thrombocytopenia with elevated D-dimer and C-reactive protein in severe COVID-19 and stroke are consistent with a virus-associated microangiopathic process.[18] Endothelial dysfunction can potentially lead to microvascular and macrovascular complications in the brain. Endothelial infection by SARS-CoV-2 with inflammation and apoptosis of endothelial cells has been shown in kidney, heart, bowel, and lung at autopsy, [24] but cerebral vessels have not yet been investigated.

We also identified 14 (35%) of 40 with altered mental status comprising neurological diagnosis like encephalopathy and encephalitis. These 14 patients presented with altered mental status, comprising 9 (64%) patients with unspecified encephalopathy and 5 (36%) patients with encephalitis. A study conducted in United Kingdom described that, 39(31%) of their 125 patients presented with altered mental status among these 9(23%) patients had unspecified encephalopathy and 7(18%) had evidence of CNS inflammation meeting the clinical case definition for encephalitis.[20]

Encephalitis is the inflammation of brain parenchyma. Clinical evidence of brain inflammation is obtained by CSF pleocytosis, neuroimaging abnormalities or changes in EEG. We diagnosed our encephalitis cases on the basis of CSF findings and MRI of brain abnormalities. No specific treatment exists for SARS-CoV-2 encephalitis. We treated our patients with high dose steroids and antiviral therapy. Like other forms of encephalitis, burning question arises concerning the relative contributions of viral damage and host inflammatory response, and whether corticosteroids might be useful. Encephalopathy is a pathobiological process in the brain that usually develops over hours to days and can manifest as changed personality, behavior, cognition, or consciousness (including clinical presentations of delirium or coma).[27] Various factors are considered in patients with encephalopathy and COVID-19 which includes hypoxia, drugs, metabolic abnormalities etc.[23]A study from Wuhan, China described impaired consciousness in 16(7%) of their studied 214 patients.[28] In a French series of intensive care patients with COVID-19 had neurological complications including 40(69%) with encephalopathy. MRI of their 13 patients showed leptomeningeal enhancement.[29] Acute disseminated encephalomyelitis is a demyelination disease of central nervous system, typically occurring weeks after an infection or vaccination, usually presents with focal neurological symptoms, often with encephalopathy.[30] Two case reports were described in women with acute disseminated encephalomyelitis and SARS-CoV-2 detected.[31,32]

In our study, 4(10%) patients were diagnosed as peripheral nervous system disorder among those 2(50%) as GBS and 2(50%) as Bell's palsy. A study done in UK described 6(5%) of their patient presented as peripheral nervous system disorder among those 4(67%) patients were diagnosed as GBS and variants, 2(33%) as other peripheral nervous system disorder.[20] GBS is an acute polyradiculopathy which is characterised by rapidly progressive, symmetrical limb weakness, areflexia, sensory symptoms and facial weakness in some cases. Bell's palsy was found in patients with COVID-19 in

some studies done in China.[33] In our study, 22(55%) patients presented with headache, 20 (5%) with hemiparesis, 20 (50%) with speech problems, 19 (48%) with altered mental status, 10 (25%) with facial asymmetry, 4 (10%) with seizure. Few percentages of patients presented with anosmia (10%), ageusia (5%) and quadriparesis (5%). A study conducted in National institute of Neuroscience described 30 (56.60%) of their patients presented with hemiplegia, 7 (13.20%) with altered mental state, 2 (3.77%) had quadriparesis, 1 (1.88%) had paraparesis and 1 (1.88%) patient presented with seizure.[34] Several reports have described seizures especially in children with SARS-CoV-2 infection. In one series of 168 children hospitalised with COVID-19, seizures were described for five (3%) children, of whom three had pre-existing epilepsy.[34] Anosmia) and ageusia have been considered as symptoms of COVID-19. A study of 259 patients[22] including 68 who were positive for SARS-CoV-2, found that abnormal smell and taste were both strongly associated with COVID-19. Olfactory dysfunction was reported for 357 (86%) of 417 COVID-19 patients; 342 (82%) reported gustatory disorders in a European study.[35]

Confirmation of the link between COVID-19 neurological complications will require detailed prospective longitudinal studies. Systematic participant evaluation, comparison with appropriate control group will be needed to understand this association. Altered mental status is a common problem in hospitalized patients with severe infection especially in ICU setting. This problem is particularly important for elder group. Exclusion of iatrogenic factors particularly sedatives, anti psychotics should be considered as factor for future studies.

Our study represents a group of patients who attended OPD of neurology department and also hospitalized patients with neurological complications associated with COVID-19. Larger scale prospective studies will identify broader cohort of COVID-19 patients and estimate the prevalence of these complications and identify patients at risk. Community studies will identify high risk patients more thoroughly although widespread serological testing will be required for that. This study will provide valuable information that is urgently needed by the clinicians, researchers to formulate policy and management plans for COVID-19 patients.

## Conclusion

Central and peripheral neurological association of COVID-19 is one of the major focuses of recent studies. Further case-control studies will be needed to establish whether this association is causal or coincidental. It is expected that, the overall number of neurological disorders associated with COVID-19 will be larger day by day in this current pandemic situation. Complications particularly stroke and encephalitis can cause long term disability to the patients that had potential to have large heath and economic burden. Large scale clinical and epidemiological studies are needed to quantify these associations and disease burden.

**Authors' contributions:** MRI drafted the protocol, collected data, did literature search and drafted the manuscript. TR performed the literature search and did statistical analysis. SMA, MSHK, MRA, DA collected data. RH helped in preparation of manuscript and did literature search. All authors read and approved the final manuscript.

**Conflict of interest:** Nothing to declare.

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