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Original Research Article

Neurological Complications of COVID-19: A Prospective Study in Tertiary Care Centre, India.

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus-2, viruses primarily affects respiratory system but now it is well known to have direct neurological involvement. Our aim was to describe the neurological manifestations of corona virus disease 2019 pandemic.

Methods: This was a prospective tertiary centre study to investigate the neurological manifestations of COVID-19 infection among in patients from a tertiary care centre, India from March 2020 to September 2021.

Results: Out of 488 patients admitted with COVID-19, 385 (79.5%) had neurological manifestations. Neurological manifestations commonly seen were headache (49%), encephalopathy (32.4%) and dizziness (28.7%). A statistically significant relationship was found between the presence of CNS manifestations and death ($p < 0.0001$).

Conclusion: Severe acute respiratory syndrome coronavirus-2 induce many central and peripheral nervous system manifestations. Encephalopathy and stroke were the commonest neurological manifestation with progressively higher mortality in young patients. Research needs to be undertaken to study the pathogenesis of neurological manifestations which may further help to improve the treatment regime.

Keywords: Covid-19, neurological manifestations, encephalopathy.

Introduction

Corona virus disease 2019 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most of the manifestations by SARS-CoV-2 are presented with upper respiratory tract infections and flu-like symptoms of varying severity [1]. However, Covid-19 has significant effect on multi-organs including the central and peripheral nervous system in some patients. A wide range affecting central (CNS) as well as peripheral nervous system (PNS) with varying severity of neurologic manifestations of SARS-CoV-2 infection has been recognized [2-5]. CNS manifestations such as Encephalopathy, stroke, seizure, headache, dizziness, dysgeusia , anosmia , movement disorders,

ataxia and myelitis, have been reported with a higher incidence in those with a more severe course of COVID-19 [5,6]. Generalized fatigue, myalgia, focal motor deficits, focal sensory deficits, rhabdomyolysis, Guillain-Barré syndrome (GBS) and polyneuropathy type of PNS manifestations are also seen with lower incidence [7,8]. These manifestations not only occur due to direct infection of the nervous system by SARS-CoV-2 but also secondary to a severe systemic reaction in response to a viral infection outside the nervous system [7].

However, as the frequency of these manifestations remain unclear in India, so we sought to characterize the prevelance of neurologic manifestations in patients with confirmed Covid-19 positivity at some point during their disease course in tertiary care center of south Rajasthan, India.

Material and Methods

Study population

A hospital-based prospective cohort study, conducted in the medicine and neurology department of Geetanjali medical college and hospital, a tertiary care center, from March 2020 to September 2021. It has been considered to be a period of second wave of SARS-COV-2 pandemic in India.

Case definition, registrations, and patient consents.

We prospectively analyzed the consecutive patients admitted or outpatient to the departments of neurology and medicine, with Covid -19 clinically suspected and were confirmed by SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab or broncho-alveolar lavage fluid. This study was approved by our institutional review committee. We obtained written informed consent from all study participants. We excluded patients with co-infection with other possible organism endemic to local area.

Data collection.

The number of patients enrolled during the study period determined the sample size. Demographic data collected included age, sex, and locality (urban / rural). Baseline investigations were performed at the time of admission. All patients underwent clinical evaluation regardless of whether they presented with neurologic symptoms. Laboratory data were collected by automated electronic query. Neurologic manifestations were identified by detailed history and clinical examination, diagnostic studies, and physician-documented diagnoses. We prospectively analyzed data for the presence or emergence of neurologic complications during the clinical course and included follow-up for 3 months after hospital discharge. Patients were contacted periodically by telephone or mail to minimize loss to follow-up, and they were excluded if lost to follow-up before study completion.

Categorization of cases and laboratory assay.

Confirmed COVID-19 positive patients identified by RT-PCR assay of nasopharyngeal swab or broncho-alveolar lavage fluid samples used for SARS-CoV-2 testing were categorize into 3 broad groups - group A comprise of absence of neurologic complications, group B having neurologic symptoms admitted in ward or outpatients and group C admitted in intensive care unit (ICU). CNS complications included encephalopathy, stroke, seizure, headache, dizziness, dysgeusia , anosmia , movement disorders and ataxia. PNS complications included generalized fatigue, myalgia, focal motor deficits, focal sensory deficits, rhabdomyolysis, Guillain-Barré syndrome (GBS) and polyneuropathy . We evaluated these cases using study profiles, subjecting them to specific investigations. The patients were reviewed by 2 neurophysician who were blinded to clinical data, and a consensus review was

obtained. Patients in group B underwent neuroimaging and CSF analysis, and those in group C underwent electrophysiologic evaluation including nerve conduction studies and electromyography (EMG). Baseline investigations included total and differential leukocyte count, platelet count, hematocrit level, blood sugar, serum electrolytes, serum creatinine, and liver function tests, D-dimer , IL-6, ferritin ,C-reactive protein (CRP), and creatine kinase (CK) for all enrolled patients. For all patients having CNS symptoms, we ordered laboratory testing of CSF and serum samples for Dengue, HIV-1 and 2, human T-cell lymphotropic virus I, herpes simplex, and cytomegalovirus; in addition, the study included Gram and India ink staining of CSF as well as staining for acid-fast bacilli to exclude common bacterial or fungal infections. We analyzed the CSF cell count as well as protein and glucose levels in patients with CNS complications. All patients were managed by symptomatic and supportive treatment. Symptomatic treatment was given in patients with neurologic complications as per clinical presentation. All cases were followed up at 3 months after hospital discharge, and outcomes analyzed using the modified Rankin Scale (mRS) and the GBS Disability Score [9].

Statistical analysis

During the evaluation of this study, frequency, percentage, arithmetic mean and standard deviation were used as descriptive statistics. The Pearson's chi-squared test was used for evaluation of categorical data and the Mann-Whitney test was used for the evaluation of quantitative data. For nonparametric data, we used univariate analysis with x2 test and Student t test for parametric data. We ascertained relative risks with a 95% confidence interval. p value of < 0.05 was considered statistically significant. Analyses were performed using the SPSS 20.1 software program.

Results

Baseline characteristics

This study included 488 consecutive patients with laboratory-confirmed Covid-19 infection. Four patients were lost to follow-up and excluded (figure 1).

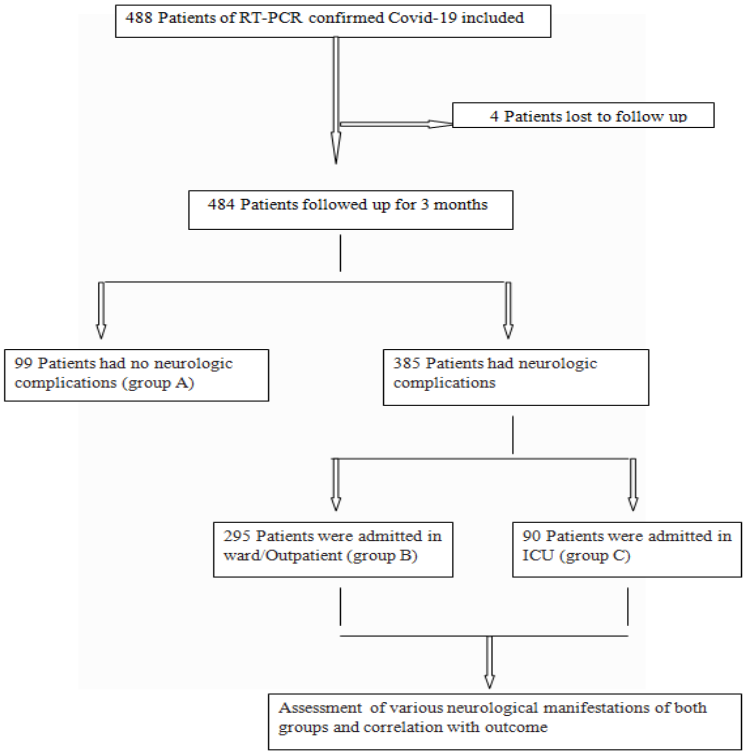

Figure1: Flow chart of study

The frequency of at least one neurologic symptom during the hospital course till at three month follow up was in 385(79.5%) patients. The remainder, 99 cases, had no neurologic complications (group A). The mean age of these 385 patients was 45 ± 18.23 years, ranging from 18 to 80 years. The male to female ratio was approximately 2:1 and 65% of patients resided in urban areas. The number of male patients was significantly higher than the number of female patients ($p < 0.05$). The mean age of patients hospitalized in the ICU was significantly higher ($p < 0.05$). A large number of patients (42%) were 40 years of age or younger.

The incidence of neurologic complications with Covid-19 found to be 79.54%. Out of 385 patients with neurologic complications, 295 were admitted in ward/outpatients (group B) and 90 were admitted in ICU (group C). There were various clinical manifestations of neurologic complications, as shown in table1. The most common CNS manifestation were headache (49%), encephalopathy (32.4%) and dizziness (28.7%).Rare but important CNS symptoms were stroke (9%), seizure (8.4%), hyper or hyokinetic movement disorders (2.2%), ataxia (1.5%) and myelitis (0.8%).

Common PNS involvement were generalized fatigue (43.9%), myalgia (38.5%) anosmia (16.4%) and dysgeusia (15.4%). Rare PNS manifestations were focal motor deficits (9.5%), focal sensory deficits (8.2%), rhabdomyolysis (4.7%), GBS (2.08%) and polyneuropathy (1.9%)

Clinical outcome

Out of 385 patients with neurologic complications, 60 (15.58%) died, all were admitted in intensive care unit and had encephalopathy or large stroke. A statistically significant relationship was found between the presence of CNS manifestations and death ($p < 0.0001$).

We also analyzed mRS disability scores at the time of admission and at 3-month follow-up. In the ICU group, at the time of admission, 27 (30%) patients had mRS scores ≤3, and 63 (70%) cases had mRS scores between 4 and 5. Out of these, 60 (66.66%) died during hospital course or at 3-month follow-up. Most of deceased cases had high mRS scoring at admission. Remaining 30 cases (33.33%) recovered, as seen by mRS≤3. Using the GBS disability score for the ward/outpatients group, we found 192 (65.08%) patients with GBS scores ≤3 and 103 (34.92%) with scores between 4 and 5 at the time of discharge. The GBS score was ≤3 for all PNS patients at the 3-month follow-up.

Table 1: Demographic parameters in Covid-19 patients.

Parameters		Ward/Outpatients (n=295)	ICU Patients (n=90)	Total (n=385)
Age, mean ± SD		32 ± 12.5	56 ± 14.3	45 ± 18.23
Sex	Male	192 (65.08%)	58 (64.44%)	250 (64.94%)
	Female	103 (34.92%)	32(35.56%)	135(35.06%)

Table 2: Neurological manifestations in Covid-19 patients

Neurological manifestations	Ward & outpatients (group B) (n=295)	ICU patients (group C) (n=90)	Total patients (n=385)
Headache	119(40.33%)	70(77.77%)	189 (49.09%)
Encephalopathy	38 (12.88%)	85(94.44%)	123 (32.4%)
Dizziness	75 (25.42%)	35(38.88%)	110 (28.57%)
Anosmia	50 (16.94%)	13(14.44%)	63 (16.36%)
Dysgeusia	48(16.27%)	12(13.33%)	60 (15.58%)
Stroke	12(4.07%)	22(24.44%)	34(8.83%)
Seizure	02(0.7%)	30(33.33%)	32(8.31%)
Movement disorders	06(2.03%)	02(2.22%)	8(2.08%)
Ataxia	03(1.02%)	02(2.22%)	5(1.3%)
Myelitis	02(0.7%)	01(1.11%)	3(0.78%)
Generalized fatigue	101(34.24%)	68(75.55%)	169(43.9%)
Myalgia	90(30.51%)	58(64.44%)	148(38.44%).
Focal motor deficits	30(10.17%)	06(6.66%)	36(9.35%)
Focal sensory deficits	28(9.49%)	03(3.33%)	31(8.05%)
Rhabdomyolysis	16(5.42%)	02(2.22%)	18(4.68%)
GBS	06(2.03%)	02(2.22%)	8 (2.08%)
Polyneuropathy	06(2.03%)	01(1.11%)	7(1.82%)

Discussion

Neurologic manifestations are common in COVID-19 infection. The exact incidence of these manifestations is very difficult to determine because of the differences in which neurological conditions were defined, recording system, method of data collection and bias in notifying. Incidence rate also varies in a primary care hospital and tertiary referral center. We found a high prevalence of neurological cases (79.5%) with various types of CNS and PNS complications. Neurological involvement due to SARS-CoV-2 occurs due to direct viral invasion, inflammation/demyelination or development of prothrombotic state [10].

In a retrospective study of 214 patients in China, neurologic manifestations were found in 36.4% of patients [7]. In our study, much higher rate was seen, which may be due to the prospective nature of study, detailed questioning and neurological examination of patients. In a large multicenter retrospective cohort study conducted in China, the frequency of neurological manifestations was found to be 3.5% [11]. This lower rate may be explained by the fact that patients with headache, dizziness, fatigue and myalgia types of nonspecific symptoms were excluded from the study according to the protocol. In our study, headache and generalized fatigue were among most common symptoms as recorded. Differences in frequencies may be due to SARS-CoV-2 strain variations or genetic factors including polymorphism in expression of the viral receptor angiotensin-converting enzyme 2 (ACE 2) in the human nervous system [12].

Since April 2020 on the European Academy of Neurology(EAN) website, an online questionnaire is available, about a large study conducted by the EAN, approved and presented to EAN members and other physicians worldwide [13]. All patients with a diagnosis of COVID-19 were included in this study and the most frequent neurological symptoms were headache (61.9%), myalgia (50.4%), and anosmia (49.2%) [13]. In our study, we

also observed similar and most frequent symptoms, although the order was different, with different percentage as shown in the results. In our study more young population was affected and any neurologic manifestations as a whole were more likely to occur in younger people, which are surprising and could be potentially explained by greater clinical emphasis on the risk of respiratory failure than other symptoms. Alternatively, early neurologic manifestations such as headache, generalized fatigue, myalgia, or dizziness may have prompted earlier medical care. In our study, high mortality associated with encephalopathy, independent of respiratory severity, parallels previous literature in sepsis and delirium associated encephalopathy and mortality [14,15] and emphasizes its relevance in Covid-19 [15]. Factors attributed to the pathogenesis of encephalopathy include metabolic impairment, hypoxia, electrolyte disturbances, sepsis, inflammation or cytokines storm, endothelial damage, recurrent seizures, and direct viral tropism. Early recognition and screening for encephalopathy in Covid-19 may have utility in resource allocation and great potential to improve patient outcomes. Furthermore, our findings emphasize the broader need to develop interventions that target encephalopathy as a component of multi-organ system medical illness.

In a systematic review, cerebrovascular disease was reported at a rate of 1.8% in COVID-19 patients [16]. In our study, the incidence of cerebrovascular disease was found to be 9%. Higher rate may be due to different study design, viral strain variations or different ethnicity. It is thought that there may be several reasons for the occurrence of cerebrovascular disease in COVID-19 infections. One is the severe inflammatory response elicited by SARS-CoV-2, upregulating pro-coagulative factors [17]. Another cause may be the injury in vascular wall, leading to the release of tissue factors and cytokines. Yet another reason is that the cytokine storm precipitates and aggravates microthrombosis [18].

We found seizures in 8.4% of patient in our study. The incidence of seizures reported in literature varies from 0.3-6.7% [19,20]. Cause of seizure in COVID-19 may be secondary to encephalitis, encephalopathy, cerebrovascular events, metabolic and electrolyte derangement or acute symptomatic seizures.

Peripheral nervous system involvement.

We saw many patients with various neuromuscular involvements in our study. It may be isolated or associated with other neurological manifestations. Generalized fatigue (43.9%) and myalgia (38.5%) were the most frequent symptoms in our study similar to Moro *et al* [13], although the order is different. Anosmia (16.4%) and dysgeusia (15.4%) are commonest cranial nerves involved in our study similar to Mao *et al.* [7] Other cranial nerves are also involved in isolation or as part of GBS.

We observed around 20% case of peripheral nerve involvement in the form of focal motor deficits, focal sensory deficits and polyneuropathy. Garcia *et al.* [20] had also reported neuropathy in 5.4% while Khedr *et al.* [19] reported 3/439 patients having neuropathy other than GBS.

We reported eight patients with GBS (2.08%). The reported incidence of GBS has been 0.67%, 0.05%, and 0.91% in Italian, Philippine, and Egyptian studies, respectively [19-22]. The pathogenesis of neuro-muscular manifestation has been speculated to be immune mechanisms or direct neurotropic effects of the virus [19, 20].

Limitations

As COVID-19 is highly infectious in nature so detailed history, repeated examination and investigations (cranial imaging, electroencephalography, electromyoneurography, and CSF

analysis) were not possible in all patients admitted with COVID-19. This limited a more complete neurologic work up in many Covid-19 patients. Only limited months into the pandemic, the long-term effects of Covid-19 on the nervous system remain uncertain. Long-term follow-up is necessary to assess the true burden of neurological complications. However, this study provided with a more generalized view of the neurologic manifestations in Covid-19 patients and could identify opportunities for regionalized resource allocation and preparedness protocols in a large hospital network system.

Conclusions

SARS-CoV-2 produces different neurological manifestations including central and peripheral nervous system involvement. Encephalopathy and stroke were the commonest neurological manifestation with progressively higher mortality in young patients from this wave. Research needs to be undertaken to study the pathogenesis of neurological manifestations which may help us to improve the treatment of these complications and reduce mortality. Prospective cognitive and neurologic-focused evaluations through specialized clinics dedicated to further diagnostic assessment and tailored rehabilitation needs, could play a significant role in recovery from this pandemic.

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