

Comparison of Neurological Manifestations in the Two Waves of COVID-19 Infection: A Cross-Sectional Study

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Abstract

Introduction: Coronavirus Disease-19 (COVID-19) is an ongoing pandemic caused by highly contagious virus severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) that has infected millions of people across the world. Most of the countries have seen two wave patterns of the pandemic. The second wave is potentially more challenging due to high influx of cases, differing properties of the emerging mutants, and other dynamics of the evolving pandemic. Neurological manifestations are common among COVID-19 positive patients. In this context, the present study attempts to compare the neurological manifestation in the first and second waves of COVID-19. **Methodology:** A single-center retrospective observational study was undertaken to compare neurological manifestations in the first and second waves of COVID-19. A sample of 1500 patients in the second wave admitted with COVID-19 were included in this study and the findings were compared with 1700 patients in the first wave (data derived from a former study in the same center). A detailed questionnaire addressing co-morbidities, admission details, and clinical features was employed to collect data from the hospital records. **Results:** Out of 1500 COVID-19 patients in the second wave of COVID-19, 355 (23.7%) of them had one or more neurological manifestations during their in-patient stay. The most common neurological symptom in the 2nd wave of COVID-19 was headache reported in 216 (14.4%) of patients followed by fatigue in 130 (8.7%), myalgia in 120 (8.0%), smell and taste disorders (STD) in 90 (6.0%), altered sensorium in 40 (2.7%), dizziness in 24 (1.6%), seizures in 34 (2.3%), encephalopathy in 26 (1.7%), strokes in 13 (0.9%), etc., Compared to the first wave of COVID-19, dizziness ($P < 0.001$), myalgia ($P = 0.001$), headache ($P < 0.001$) and meningoencephalitis ($P = 0.01$) were more common while cerebrovascular syndromes ($P = 0.001$) were less common in the second wave. The mortality in the 2nd wave neurological subgroup was higher [66 (18.6%)] than 1st wave neurological subgroup [23 (10%)]. **Conclusion:** Meningoencephalitis, headache, and seizures were found to be more common in second wave as compared to first wave. The severity and mortality rate were higher in the second wave.

Keywords: Altered sensorium, COVID-19, dizziness, encephalopathy, headache, neurological, SARS CoV-2, seizure

INTRODUCTION

COVID-19 is an ongoing pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), which was first reported in Wuhan China on December 2019.^[1] As of August 2021, around 200 million confirmed cases of COVID-19 have been reported including 4.3 million deaths globally and 32 million confirmed cases, and 430 thousand deaths in India.^[2] The second wave of COVID-19, which began in 11 February 2021,^[3] and peaked in May 2021 has hit India very hard with the daily cases reaching nearly three times that of the first peak. The first wave peaked at the end of March 2021 and the second wave in mid-October 2021 in European countries. Studies showed that the proportion of severe cases to be less in the second wave compared to the first wave in European countries, probably because of the experience gained during the first wave leading to better preparedness and streamlined clinical management protocols during the second wave.^[4,5] However, a different trend has been observed in low- and middle-income countries like India. The infection rate and the proportion of young individuals with symptomatic infection have increased during the second wave, probably because of most of the vulnerable groups getting vaccinated on priority and young individuals being

more mobile for economic activities. The disease spread and test positivity rate are much higher in India during the second wave, which has led to increased requirements for oxygen and mechanical ventilation.^[3,6] However, a study from France showed that a lower proportion of patients required mechanical ventilation and a smaller number of thrombotic events occurred in the second wave compared to the first.^[4] Another key determinant of the clinical impact of the second wave is the emergence of viral mutants like “delta,” which are considered to be highly infectious and resistant to treatment measures and vaccines.^[7] Neurological manifestations have

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Submitted: 07-Dec-2021 **Revised:** 23-Feb-2022 **Accepted:** 05-Mar-2022

Published: 04-Aug-2022

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DOI: 10.4103/aian.aian_1048_21

been an important component of the clinical spectrum of the pandemic. Given this scenario, the neurological presentations of SARS-CoV2 could potentially show clinically relevant differences between the two waves, which have not been specifically addressed in medical literature till date.

The dynamic nature of the clinical presentations needs to be studied to understand the clinical impact of several factors, which has emerged over time like new viral mutants, vaccination, and readiness of health care sector. The neurotropism of the virus and the inflammatory response to infection could also undergo significant change over time. The study attempts to indirectly understand the impact of these changes by evaluating the difference in neurological presentations of the first two waves of the pandemic in the state of Kerala. This understanding could be potentially useful for constructing future strategies and policies.

METHODOLOGY

This was a single-center retrospective observational study comparing neurological manifestations in the first and second waves of COVID-19 conducted at Aster Malabar institute of medical sciences and research center (Aster MIMS) Hospital. The hospital is a National Accreditation Board for Hospitals and Healthcare Providers (NABH) accredited tertiary care center located in North Kerala. The purpose of the study was to determine the most common neurological features of COVID-19 infection in the second wave and compare it with the first wave. A confirmed case of COVID-19 was defined based on the result of reverse transcriptase PCR (RT-PCR), TrueNat or reverse transcriptase LAMP (RT-LAMP) assay on a nasopharyngeal sample. All the patients admitted to the hospital satisfying this criterion during the period from April 2021 to May 2021 when the second wave of COVID-19 was at its peak in the state were included in the study. A detailed questionnaire (data extraction tool) was used to collect the information provided in inpatient records. This questionnaire was divided into different sections to cover patients' socio-demographic data, systemic manifestations as well as details about inpatient stay, co-morbidities, and finally neurological manifestations. The inclusion criterion of this study was confirmed COVID-19 infection with one or more neurological symptoms during hospital admission.

The study protocol was approved by the institutional ethics committee (Registration no: EC/NEW/INST/2019/406 & ECR/301/inst/KL/2013/RR-19). The individual neurological phenomena and their frequencies were determined as a proportion of the total sample (1500 patients) and the neurological subgroup (355 patients). Second wave of COVID-19 was compared with first wave with respect to the frequency of neurological manifestations. The data for the latter was derived from a previous study of the author, which has been submitted for publication in a peer-reviewed journal. This data was composed of 230 patients with neurological manifestations identified from a total of 1700

consecutive patients with COVID-19 infection admitted to the same center during the period from June 2020 to January 2021.

Statistical analysis

Data was entered in Microsoft Excel, analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics (frequency, percentage, mean, standard deviation) was used to summarize baseline characteristics of the study subjects. Socio-demographic variables have been denoted by frequency tables. An association between two categorical variables was analyzed using Pearson's Chi-square test. If any cell's expected count was less than 5, Fisher Exact test was followed. P value < 0.05 was considered as statistically significant.

RESULTS

Out of 1500 patients [mean age (standard deviation (SD)): 52.3 (20.5); M: F ratio of 0.9:1], one or more neurological symptoms were encountered during their in-patient stay in 355 (23.7%). The mean age (SD) of participants with neurological manifestations was 49.8 years (20.56) and half of them were (50.7%) male. Socio-demographic data and clinical features of COVID-19 patients with neurological manifestations are summarized in Table 1. In the neurologically symptomatic group, 189 patients (53.2%) had history of one or more co-morbidities during the second wave of COVID-19 infections.

Table 2 shows the neurological manifestations of COVID-19 patients who were admitted in the hospital during the second wave. Out of 1500 COVID-19 patients included in the study, 209 (13.9%) had died during illness. Among the 355 patients with neurological manifestations, sixty-six (18.6%) patients died. Table 3 shows the comparison of neurological manifestations in the two waves of COVID-19. Significant differences were observed between the two waves of COVID-19 infection for the following neurological symptoms: dizziness ($P < 0.001$), myalgia ($p = 0.001$), headache ($P < 0.001$), meningoencephalitis ($P = 0.01$), and acute cerebrovascular syndromes ($P = 0.001$). The disease severity was also considerably higher in the second wave with higher incidence of pneumonia ($P < 0.001$), requirement for oxygen support ($P < 0.001$), ICU admission ($P = 0.01$), and mortality ($P = 0.004$). Regarding systemic features of patients with neurological manifestation, in the second wave, breathlessness was reported in 39.4% of patients while the percentage was lower in the first wave (27%). Pneumonia was diagnosed in 60 (26.1%) patients in the first wave and 172 (48.5%) patients in the second wave. The ICU admission and oxygen support increased during the second wave. During the second wave, 89 (25.1%) patients with neurological issues were admitted in ICU and 100 (28.2%) required oxygen support. During the first wave, 38 patients (16.5%) were admitted to ICU and 36 patients (15.7%) required oxygen support.

Table 1: Comorbidities, associated systemic features, and details of hospital stay in patients with neurological symptoms in first and second waves of COVID-19

Variables	First Wave (n=230) (%)	Second Wave (n=355) (%)	P
Death	23 (10)	66 (18.6)	0.004
Gender (Male)	114 (49.6)	180 (50.7)	0.787
Co-morbidities 189 (53.2%)			
Diabetes	79 (34.3)	110 (31)	0.395
Hypertension	64 (27.8)	104 (29.3)	0.701
Coronary artery disease	24 (10.4)	47 (13.2)	0.310
Asthma	24 (10.4)	21 (5.9)	0.045
Thyroid Disorder	18 (7.8)	18 (5.1)	0.176
Chronic kidney disease	3 (1.3)	14 (3.9)	0.078
Past history of stroke	8 (3.5)	12 (3.4)	0.949
Chronic Obstructive Pulmonary Disease	7 (3)	9 (2.5)	0.713
Cancer	3 (1.3)	3 (0.8)	0.684
Systemic features			
Fever	181 (78.7)	275 (77.5)	0.725
Cough	107 (46.5)	171 (48.2)	0.696
Breathlessness	62 (27)	140 (39.4)	0.002
Vomiting	49 (21.3)	46 (13.0)	0.008
Sore throat	34 (14.8)	42 (11.8)	0.299
Diarrhoea	33 (14.3)	43 (12.1)	0.432
Joint pain	22 (9.6)	11 (3.1)	0.001
Nausea	16 (7)	13 (3.7)	0.073
ICU Admission	38 (16.5)	89 (25.1)	0.014
Oxygen Support	36 (15.7)	100 (28.2)	0.001
Noninvasive Ventilation	11 (4.7)	15 (4.2)	0.749
Mechanical Ventilation	13 (5.6)	10 (2.8)	0.085
Smoking/Alcohol	16 (7)	19 (5.4)	0.424
If Yes, Active	11 (4.8)	11 (57.9)	0.296
Exercise	39 (17)	55 (15.5)	0.638
Pneumonia	60 (26.1)	172 (48.5)	<0.001
Investigation			
CT	52 (22.6)	50 (14.1)	0.008
MRI	35 (15.2)	26 (7.3)	0.002
EEG	12 (5.2)	2 (0.6)	<0.001

DISCUSSION

The neurotropism of the SARS-CoV 2 virus coupled with the immunological responses, hyper coagulable state, endotheliopathy, and a host of other factors have been implicated in the neurological presentations of infection.^[8] The virus enters the central nervous system (CNS) by vascular dissemination and locally across the cribriform plate of the ethmoid. The spectrum of clinical presentations includes headache, dizziness, myalgia, reduced cognition, anosmia, confusion, seizure, stroke, peripheral neuropathy, cranial nerve palsy, etc., Neurological manifestations of COVID-19 can be broadly classified into those involving the CNS and Peripheral nervous system (PNS).^[9] The Wuhan study was the first to highlight the importance of the neurological manifestations with about 36% of their patients exhibiting one or the other neurological symptoms with varying degrees

Table 2: Frequency of neurological manifestations in patients admitted with COVID-19 in the second wave

Variables	(n=1500) (%)
Headache	216 (14.4)
Fatigue	130 (8.7)
Myalgia	120 (8.0)
Smell and taste Disorder	90 (6.0)
Altered sensorium	40 (2.7)
Seizure	34 (2.3)
Dizziness	24 (1.6)
Encephalopathy	26 (1.7)
Acute cerebrovascular syndromes	13 (0.9)
Meningoencephalitis	5 (0.3)
Neuropathy	3 (0.2)
Myopathy	3 (0.2)
Visual Impairment	2 (0.1)
Facial Palsy	1 (0.1)
Central Nervous System (CNS) Vasculitis	1 (0.1)

NB: The term encephalopathy was used when the altered sensorium could not be attributed to a neurological cause like meningoencephalitis or stroke

of severity. Similar studies also observed that one-third of the patients had some neurological phenomena. Headache (17%) and dizziness (13%) were the most common. Cerebrovascular accidents (3%) and seizures (0.5%) were also observed in a subset of them. Studies showed that those with severe COVID-19 infection have more chances of neurological complications.^[10]

Neurological manifestations are seen in a significant proportion of patients in both first as well as the second waves. This study attempted to compare the neurological symptoms in first and second waves of COVID-19. Among 1500 patients in the second wave, 23.7% showed COVID-19 associated neurological symptoms, whereas in the first wave (1700 patients), 13.5% of patients reported the same. Headache was the most common neurological symptom in both the first and second waves. The prevalence of headache in other studies was between 6% and 45%.^[11-16] smell and taste disturbances (STD), which is an important PNS presentation among COVID-19 patients, also showed the same trend in both the first and second waves (3.6% and 6.0%, respectively). This is considerably low when compared to other studies where 36%–86% have been observed to have some form of STD.^[17-19] This disparity could be because of the retrospective design of our case series where there was inadequate mention of minor clinical symptoms in the case records probably owing to their low prognostic value.

Acute stroke has been a well-recognized complication of COVID-19 across clinical studies. Studies showed that the incidence of ischemic stroke in COVID-19 varies from 1.6% to 6%.^[20-22] In a retrospective review of 221 patients, around 6% had an acute cerebrovascular accident.^[23] Connors and Levy^[22] proposed a correlation between inflammation and subsequent coagulopathy. They noted that the level of

fibrinogen, platelet, and D-dimer and interleukins-6 levels increased in severely ill COVID-19 patients. Production of procoagulative factors and damage of capillary endothelium further potentiate microvascular thrombosis.^[3] In our analysis, we observed that 1.5% had a stroke in the first wave of COVID-19. In the second wave, the incidence of stroke (0.9%) was comparatively less. The neurological features of the 2nd wave of COVID-19 infection are compared with those of other studies in Table 4.

Regarding systemic features of patients with neurological manifestation, in the second wave, the proportion of patients with severe illness was considerably higher as indicated by higher incidence of pneumonia, oxygen requirement, and intensive care admissions. Furthermore, mortality was also significantly higher. This is a cause of concern owing to the emergence of new viral mutants. Global variants of concern, which have also been reported in India, include B.1.1.7 UK, P. 1 from Brazil, and B.1351 from South Africa.^[23,26] The Delta variant (B.1.617.2) was detected in India in the latter half of 2020 and involves spike proteins (this pathogenic variant has

been linked with the possibility of increased transmissibility and higher incidence of serious and complicated disease). Delta variant has the primary reason for the second wave in India. The Delta plus Variant (AY.1) is another mutated form of the Delta virus, which was reported in nine countries including India.

The strength of the study is the large sample size and the emphasis placed on the identification of the full spectrum of neurological manifestations. Also, because all patients are from a single center, the patient treatment protocol and record-keeping were uniform and meticulous. This allowed for a meaningful comparison between the two waves. Our study is limited by the retrospective design and the fact that all patients were selected from a single tertiary care center. The latter would have resulted in the selection of more severe cases. Other limitations include lack of follow up and nonavailability of biomarkers and information on the effect of management protocols on the clinical outcomes. The effects of vaccination status on the clinical presentations also were not determined in the present study.

Table 3: Association between neurological manifestations of first and second waves of COVID-19

Variables	n	1 st Wave (n=230) (%)	2 nd Wave (n=355) (%)	Chi-square value (df=1)	P
Headache	402	186 (80.9)	216 (60.8)	26.04	<0.001
Myalgia	168	44 (19.1)	120 (33.8)	14.89	0.001
Dizziness	78	54 (23.5)	24 (6.8)	33.76	<0.001
Acute cerebrovascular syndromes	41	26 (11.3)	13 (3.7)	10.73	<0.001
Meningoencephalitis	16	11 (4.8)	5 (1.4)	5.97	0.01

Table 4: Comparison of clinical spectrum across studies

	Sachin Sureshbabu et al. ^[27] (1 st wave)	Sachin Sureshbabu et al. (2 nd wave)	Romero-Sánchez CM et al. ^[24]	Mao L et al. ^[18]	Thanagaraj et al. ^[25]
Total No of Patients	1700	1500	841	214	600
Age (mean (SD))	43 (19.3)	55 (20.2)	66.42 (14.96)	52.7 (15.5)	40-60
Sex (Male) (%)	114 (6.7)	180 (12.0)	473 (56.2)	87 (40.7)	397 (66.2)
Headache (%)	186 (10.9)	216 (14.6)	119 (14.1)	28 (13.1)	245 (40.8)
Myalgia (%)	44 (2.6)	120 (8.0)	145 (17.2)	23 (10.7)	72 (12)
Dizziness (%)	54 (3.2)	24 (1.6)	51 (6.1)	36 (16.8)	46 (7.7)
Seizure (%)	29 (1.7)	34 (2.3)	6 (0.7)	1 (0.5)	36 (6)
Acute Cerebrovascular syndromes (%)	24 (1.4)	13 (0.9)	14 (1.7)	6 (2.8)	43 (7.1)
Ischemia (%)	19 (1.1)	13 (0.9)	11 (1.3)	NA	NA
Hemorrhage (%)	4 (0.2)	0	3 (0.4)	NA	2 (4.7)
Cerebral venous thrombosis (%)	2 (0.1)	0	0	NA	NA
Smell and taste disorders (%)	61 (3.6)	90 (6.0)	NA	NA	NA
Smell (%)	NA	NA	41 (4.9)	11 (5.1)	172 (28.7)
Taste (%)	NA	NA	52 (6.2)	12 (5.6)	NA
Visual Impairment (%)	5 (0.3)	2 (0.1)	1 (0.1)	3 (1.4)	NA
Facial Palsy (%)	1 (0.1)	1 (0.1)	NA	NA	NA
Altered Sensorium (%)	35 (2.1)	40 (2.7)	165 (19.6)	16 (7.5)	NA
Meningitis (%)	5 (0.3)	2 (0.1)	NA	NA	4 (0.4)
Encephalitis (%)	6 (0.4)	3 (0.2)	1 (0.1%)	NA	NA
Encephalopathy (%)	6 (0.4)	22 (1.5)	NA	NA	60 (10)
Neuropsychiatric (%)	8 (0.5)	4 (2.7)	167 (19.9)	NA	NA
Neuropathy /PNS involvement (%)	4 (0.2)	3 (0.2)	22 (2.6)	19 (8.9)	NA

CONCLUSION

In conclusion, the two waves were not much different in terms of the clinical spectrum of neurological manifestations. A higher incidence of encephalopathy in the second wave could be attributed to more severe cases being included in the study. This could indirectly reflect a change in the strategy of management wherein the milder cases are directed to first-line treatment centers due to an increase in demand for hospital beds. Nevertheless, the higher mortality and severity of the second wave deserves special mention, especially in the context of emerging mutants implicated in recent waves of the pandemic.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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