

ORIGINAL ARTICLE

Neurological manifestations as primary presentation of COVID-19 in hospitalized patients

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Objective: To characterize patients with coronavirus disease 2019 (COVID-19) who presented primarily with neurologic symptoms without typical COVID-19 symptoms of fever, cough, and dyspnea.

Methods: We retrospectively identified COVID-19-positive patients 18 years and older that had neurology symptoms on presentation requiring neurology consultation between March 14, 2020 and May 18, 2020. The patients were then classified into those with typical COVID-19 symptoms and those without. Demographic, clinical symptoms, laboratory result, and clinical outcomes were collected.

Results: Out of 282 patients who had neurology consult during this period, we identified 56 (mean age 69.2 years, 57% women) who tested COVID-19-positive and had neurologic symptoms on initial presentation. Of these, 23 patients (mean age 65.2 years, 52% women) had no typical COVID-19 symptoms while 33 did (mean age 72.2 years, 60% woman). In both groups, impaired consciousness was the most common initial neurologic symptom, followed by stroke, unsteady gait, headache, seizure, syncopal event, acute vision changes, and intracranial hemorrhage. Out of the 23 patients without typical COVID-19 symptoms on presentation, 10 went on to develop typical symptoms with 8 needing supplemental oxygen and one requiring mechanical ventilation.

Conclusion: Patients who have COVID-19 can present with serious neurologic symptoms such as impaired consciousness and stroke even without typical COVID-19 symptoms. Those without typical COVID-19 symptoms can later develop typical symptoms severe enough to need respiratory support.

KEYWORDS

COVID-19, neurological, presentation, SARS-CoV-2, symptom

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first described in Wuhan, China, in 2019 causes a disease subsequently named coronavirus disease 2019 (COVID-19).^{1,2} Early on, the Center for Disease Control (CDC) found that 96% of

symptomatic COVID-19 patients had symptoms of fever, cough, and shortness of breath.^{3,4} Neurological symptoms have also been described extensively in patients with COVID-19, including headaches, dizziness, encephalopathy, meningoencephalitis, ischemic and hemorrhagic stroke, Guillain-Barre Syndrome, smell/taste dysfunction, and seizures.⁵⁻¹³ Of these, the commonly

found neurologic symptoms included impaired consciousness, dizziness, and headaches.^{5,6,8-14}

We report on neurologic symptoms found in COVID-19 patients at an academic community hospital in Queens, New York. New York City's borough of Queens was particularly hit hard being one of the top county by death toll in the whole USA.¹⁵ We focused on neurologic symptoms on presentation in COVID-19-positive patients, specifically those without any typical symptoms, as these patients would raise less concern for COVID-19 and be easily missed.

2 | METHODS

2.1 | Patients

This is a single-center retrospective study with data from New York Presbyterian Queens, a tertiary care community hospital serving a racial and ethnic diverse population of over 2 million in Queens, New York.¹⁶ The time period of this study was between March 14, 2020 and May 18, 2020, at the peak of the COVID-19 epidemic in Queens.¹⁷ All charts for admitted patients older than 18 years old that had neurology consultations during the study period were reviewed for those that tested positive for SARS-CoV-2 based on high-throughput sequencing or real-time reverse-transcription polymerase chain reaction (RT-PCR) analysis of upper respiratory tract specimens.

From this group, we identified those that had neurologic symptoms on presentation. Of the patients who had symptoms on initial presentation, we divided them into those who had typical COVID-19 viral symptoms and those that did not. We used the CDC's definition of typical COVID-19 symptoms, which are fever, cough, and dyspnea.^{3,4} The presence of fever as a symptom was included if subjectively reported by the patient or if the temperature was elevated above 38.0° Celsius. All patients included in the study were followed until discharge or death. For patients who never had typical COVID-19 symptoms, we checked to see if they returned to the emergency room within a month after discharge for typical COVID-19 symptoms.

We classified the neurologic symptoms as impaired consciousness, stroke (acute and subacute), seizure, headache, intracranial hemorrhage, unsteady gait, syncopal event (including pre-syncopal symptom such as dizziness), and acute vision changes. The symptoms were recorded based on clinician notes from the electronic medical records. The diagnosis of stroke and intracranial hemorrhage was based on neuroimaging.

2.2 | Ethics

This study was approved by New York Presbyterian Queens Institutional Review Board and need for informed consent was waived as study was minimal risk and not practical to conduct without waiver.

2.3 | Data Collection

For each SARS-CoV-2-positive patient with neurologic symptoms on initial presentation, data were collected which includes demographics, radiology results (including MRI, CT and chest X-ray), laboratory values, clinical symptoms, length of stay, and overall in-hospital mortality.

2.4 | Statistical analysis

Comparison was made between the group that had typical COVID-19 symptoms versus the group that did not. Mann-Whitney *U* test was used to analyze continuous variable. For comparison of categorical variables, chi-square was used. When sample size of categorical variable is small, Fisher's exact test was used. Statistical analysis was performed using GraphPad Prism 8.4.3 (GraphPad). Significance was set at 2-sided *p*-value of less than .05.

3 | RESULTS

During our study period, there were a total of 282 neurology consults, of which 107 tested positive for SARS-CoV-2. These 107 patients represent 4.4% of the 2,414 COVID-19 patients admitted during the study period (Figure 1). Of the 107 patients, 56 patients (52%) had neurological symptoms on initial presentation. The remaining 51 patients (48%) developed neurological symptoms later during their hospital course. Of the 56 patients that had neurological symptoms on initial presentation, 33 (59%) patients had concurrent typical symptoms of COVID-19 on presentation. The remaining 23 patients (41%) presented without any typical COVID-19 symptoms.

Of the 23 COVID-19 patients who had neurologic symptoms without typical COVID-19 symptoms on presentation, 8 later developed dyspnea and needed supplemental oxygen, one developed fever and required mechanical ventilation, and one developed fever without any other typical symptoms. The mean length of stay for the 23 patients was 8.8 (SD ± 8.7) days. For the 13 that did not develop typical COVID-19 symptoms during hospitalization, their mean length of stay was 5.6 (SD ± 4.1) days. None of these 13 returned to the hospital with typical COVID-19 symptoms within a month after discharge. There was no significant difference in demographic between the group that developed typical COVID-19 symptoms and the group that did not.

The demographics and comorbidities of the 56 patients who had neurologic manifestation on COVID-19 presentation are summarized in Table 1. Their mean age was 69.2 years old (standard deviation of 17.1), and 57 percent were female. Racial breakdown was 23% Asian, 21% White, 20% Black, and 36% others (which included Hispanic). Hypertension was the most common comorbidity at 82.1%, followed by hyperlipidemia (60.7%), diabetes (50%), history of stroke (29%), coronary artery disease (27%), chronic kidney disease (21%), obesity with BMI > 30 kg/m² (21%), and COPD/Asthma (7%).

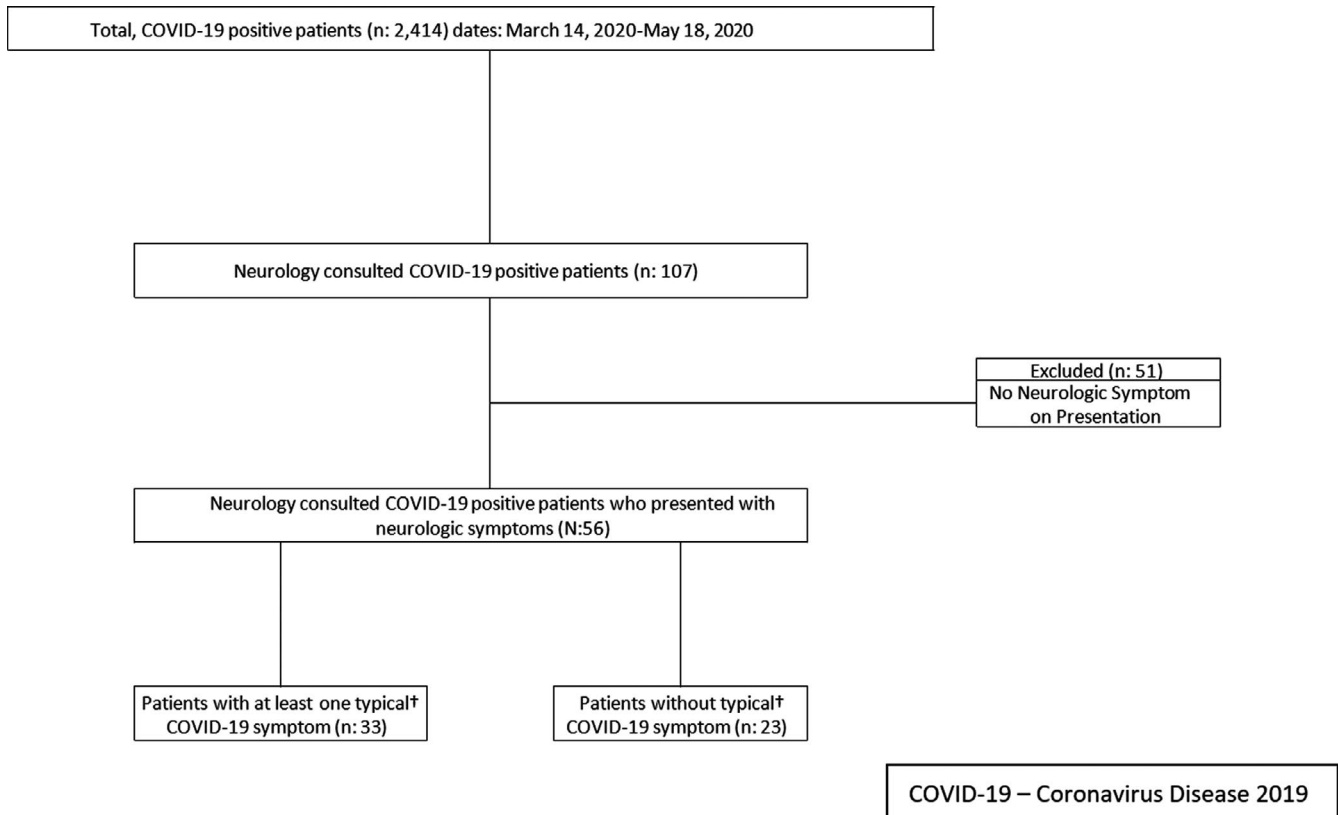


FIGURE 1 Flow chart of study enrollment. †Typical COVID-19 symptoms are fever, cough and shortness of breath

In our 56 COVID-19 patients who had neurologic symptoms on presentation, impaired consciousness was the most common (45%), followed by stroke (18/56 [32%]–13 [23%] with acute stroke, 5 [9%] with subacute stroke), unsteady gait (20%), headache (13%), seizure (11%), syncopal event (9%), acute vision changes (5%), and intracranial hemorrhage (4%). The overall in-hospital mortality rate was 21%, and the median length of stay was 8 ± 3.2 –14 days.

Of the patients with neurologic and typical COVID-19 symptoms on presentation ($n = 33$), the most common neurologic symptom was impaired consciousness (45%), followed by stroke (10/33 [30%]–6 [18%] with acute stroke, –4 [12%] with subacute stroke), unsteady gait (18%), syncopal event (12%), headache (3%), seizure (3%), and acute vision change (3%). Of the patients with neurologic symptoms on presentation without typical COVID-19 symptoms ($n = 23$), the most common neurologic symptom was impaired consciousness (43%), followed by stroke (8/23 [34%]–7 [30%] with acute stroke, –1 [4%] with subacute stroke), unsteady gait (22%), headache (17%), seizure (13%), acute vision changes (9%), syncopal event (4%), and intracranial hemorrhage (4%).

The laboratory results of our patient group are summarized in Table 1. The group without typical COVID-19 symptom was noted to have significantly lower median serum creatinine (0.86 vs. 1.04 mg/dl, $p = .04$). The markers of inflammation were noted to be higher in the group with typical COVID-19 symptoms, but no statistical significance was reached. When we looked at the total number of stroke patients who had D-dimers checked ($n = 8$, mean = 14,686 ng/ml) versus non-stroke patients who had D-dimer checked ($n = 23$,

mean = 2,000 ng/ml), we found that stroke patients had significantly higher D-dimer ($p = .015$). The subgroup of patients who had stroke without typical COVID-19 symptoms and had D-dimer tested were too small to draw a conclusion regarding whether D-dimer is elevated in this subset of patients.

There was no statistical difference in demographics and comorbidities between the group with typical COVID-19 symptoms and the group without (Table 1). There was also no statistical difference in neurologic symptomatology, overall in-hospital mortality, and length of stay between the two groups.

4 | DISCUSSION

The neurological manifestations associated with COVID-19 have been well described, but few studies have looked at neurological manifestations as primary presenting symptoms without the typical COVID-19 symptoms of fever, cough, and shortness of breath. To our knowledge, this is the largest retrospective dataset (23 patients) looking at SARS-CoV-2-positive patients presenting with neurologic manifestations without typical COVID-19 symptoms as Mao et al. had 2 patients presenting with acute stroke⁵ and Frontera et al. reported 10 patients.¹¹ In contrast to our study, neither of these two studies provided additional details on this subset of patients. Other earlier studies had mentioned neurologic symptoms on presentation but did not stratify findings based on presence or absence of typical COVID-19 symptoms.^{8,10,12,13}

TABLE 1 Clinical variables and demographics of patients with typical symptoms vs without typical symptoms^a

	Total	At least One Typical Symptom ^a	Without Any Typical Symptoms	p-value
	n (%)	n (%)	n (%)	
All Patients				
Total	56 (100)	33 (59)	23 (41)	
Age, mean (±SD)	69.2 (±17.1)	72 (±15.2)	65.2 (±19.2)	.16
Female	32 (57)	20 (60)	12 (52)	.59
Race				.29
African American	11 (20)	6 (18)	5 (22)	
Asian	13 (23)	10 (30)	3 (13)	
White	12 (21)	8 (24)	3 (17)	
Other	20 (36)	9 (27)	11 (48)	
Mortality/Total (%)	12/56 (21)	9/33 (27)	3/23 (13)	.32
ICU Stay	4 (7)	3 (9)	1 (4)	.63
Intubation	4 (7)	3 (9)	1 (4)	.63
Length of Stay, median (IQR)	8 (3.2–14)	9 (4.5–14.5)	7 (3–11)	.20
Neurological Symptoms or Syndromes				
Impaired consciousness	25 (45)	15 (45)	10 (43)	1
Stroke	18 (32)	10 (30)	8 (35)	.78
Acute	13 (23)	6 (18)	7 (30)	.34
Subacute	5 (9)	4 (12)	1 (4)	.64
Seizure	6 (11)	3 (9)	3 (13)	.68
Headache	7 (13)	3 (9)	4 (17)	.42
Intracranial Hemorrhage	2 (4)	1 (3)	1 (4)	1
Unsteady Gait	11 (20)	6 (18)	5 (22)	.75
Syncopal Event	5 (9)	4 (12)	1 (4)	.64
Acute Vision Changes	3 (5)	1 (3)	2 (9)	.56
Comorbidities				
Chronic Kidney Disease	12 (21)	9 (27)	3 (13)	.32
COPD/Asthma	4 (7)	3 (9)	1 (4)	.64
Coronary Artery Disease	15 (27)	9 (27)	6 (26)	1
Current Smoker	2 (4)	1 (3)	1 (4)	1
Diabetes Mellitus	28 (50)	17 (52)	11 (48)	1
History of Stroke	16 (29)	11 (33)	5 (22)	.39
Hypertension	46 (82)	26 (79)	20 (87)	.5
Hyperlipidemia	34 (61)	21 (64)	13 (57)	.78
Obesity (BMI ≥ 30 kg/m ²)	12 (21)	6 (18)	6 (26)	.52
Initial laboratory values, median (IQR)				
GFR < 60 ml/min/1.73 m ²	22 (39)	14 (42)	8 (35)	.59
White Blood Cell Count (WBC), ×10 ⁹ /L	7.38 (5.14–10.4)	7.27 (5.24–10.0)	7.58 (4.94–11.0)	.9
Platelets, ×10 ⁹ /L	206 (147–269)	197 (147–241)	241 (147–349)	.1
Creatinine, mg/dl	1.01 (0–78–1.67)	1.04 (0.9–2.05)	0.86 (0.73–1.24)	.04
Aspartate Aminotransferase (AST), U/L	37 (20–54)	38 (26–52)	24 (18–57)	n:33 n:22 .08
Alanine Aminotransferase (ALT), U/L	19 (14–36)	19 (15–38)	17 (11–30)	n:33 n:22 .35
D-Dimer, ng/ml	902 (437–3660)	1985 (458–4604)	565 (375–1148)	n:20 n:11 .32
Fibrinogen, mg/dl	726 (459–900)	872 (622–932)	542 (410–630)	n:11 n:7 .19
Ferritin, ng/ml	630 (292–1424)	739 (309–1765)	478 (120–955)	n:20 n:15 .20

(Continues)

TABLE 1 (Continued)

	Total	At least One Typical Symptom ^a	Without Any Typical Symptoms		p-value	
	n (%)	n (%)	n (%)	n (%)		
Procalcitonin, ng/ml	0.12 (0.05–0.5)	0.12 (0.06–1.03)	n:32	0.14 (0.02–0.21)	n:13	.27
C-Reactive Protein (CRP), mg/dl	3.8 (1.6–16.5)	5.0 (1.95–21.3)	n:22	2.5 (1.17–12.3)	n:15	.19
Erythrocyte Sedimentation Rate (ESR), mm	66 (39–117)	71 (49–124)	n:16	62 (38–114)	n:11	.49
Lactate dehydrogenase (LDH), U/L	320 (235–471)	401 (246–574)	n:17	301 (225–365)	n:13	.16
Creatinine Phosphokinase (CPK)	176 (116–633)	176 (94–563)	n:13	225 (102–1161)	n:10	.83

Bold value indicates significant difference.

^aTypical symptoms are fever, cough, and shortness of breath.

There was no significant difference in rate of presentation with neurologic symptoms between those with typical COVID-19 symptoms and those without, including for more serious neurologic manifestations such as impaired consciousness and stroke. We also did not find significant difference in overall mortality and length of stay between these two groups. This is not surprising given our small sample size.

Impairment of consciousness was the most common neurological symptom on presentation in both the typical COVID-19 symptom group and the group without typical COVID-19 symptoms (45% vs. 43%, $p = 1$). With exception of Frontera et al., other studies did not find impaired consciousness to be the most common at presentation but did find it to be common during course of COVID-19.^{8,10–13} The discrepancy may be due to this study's inclusion criteria of patients who had a neurology consultation, thus likely excluding less severe neurologic symptoms that did not need neurology consultation. Frontera et al. also used neurology consultation in their inclusion criteria, which may explain why they also found impaired consciousness as the most common presenting neurologic symptom.

Among the other neurologic manifestations seen on presentation, we found stroke to be second most common in the group with typical COVID-19 symptoms and the group without (30% vs 35%, $p = .78$). The number of stroke patients may have been underreported due to our inclusion criteria of acute stroke on brain imaging. Some patients may have been too ill to leave the intensive care unit for MRI. The surge in patients from COVID-19 also severely strained hospital resources and when combined with efforts to prevent COVID-19 transmission may have hampered radiologic stroke diagnosis. The increased risk of stroke associated with COVID-19 has been attributed to endovascular injury and a prothrombotic state.^{18,19} It has also been found that COVID-19 is more likely to cause stroke than other viral illness such as influenza.¹⁸ We found those who had stroke had higher D-dimer levels consistent with prior reports.^{14,18} The existing literature is mixed on stroke occurrence at COVID-19 onset. One study found no stroke at COVID-19 presentation,¹³ whereas others found varied rate from less than what we found to rates closer to ours.^{5,11,21}

Overall, it was rare for COVID-19 patients admitted to our hospital to have a neurology consult. In our series, only 107 out of

2,414 (4.4%) had a neurology consult. Rifino et al. reported a rate of 137/1760 (7.7%), but they also included patients who had neuroradiology and neuro-physiology studies without neurology consultation, thus their actual number of patients who had neurology consult may be closer to ours.¹² Frontera et al. at 606/3885 (13.5%), which is much higher¹¹ and possibly due to institutional difference in utilizing neurology consult since both our studies take place in New York City with similar demographics.

One of the challenges of this study is determining if the neurological symptoms were related to SARS-CoV-2 or a coincidental finding given that COVID-19 infection can be asymptomatic.²⁰ Many of the neurologic symptoms seen with COVID-19, such as headache and unsteadiness, are non-specific and seen in viral illness and other disease states. Despite that, many earlier studies have included non-specific neurologic symptoms.^{8–13} The benefit of our methodology is even if the neurologic symptom seems non-specific, they precipitated neurology consults.

The strength of our paper is that all included patients were evaluated by a neurologist which was not done with some of the earlier papers.^{5,8,10,13} All patients in the study were confirmed to have COVID-19 based on RT-PCR from nasopharyngeal swab, whereas some studies allowed for diagnosis of COVID-19 based on clinical and radiologic findings.^{5,8,12} Further, all patients in this study had neurologic symptoms severe enough to warrant neurologic evaluation and is thus a better reflection of what hospital neurologists may encounter.

There were many limitations of this study. First and foremost, this is a retrospective dataset with a small sample size. The number of SARS-CoV-2 patients presenting with neurologic manifestation is likely underestimated. Our data were collected only on COVID-19 patients that had neurology consultations, which as pointed out earlier, likely resulted in a smaller cohort as milder neurologic symptoms may not have triggered a consultation. Furthermore, clinicians may not have screened for neurologic symptoms if they did not feel it was pertinent to management during a pandemic when systems were at or above capacity. Patients also likely avoided coming to the hospital during this time; thus, many patients who had SARS-CoV-2 and milder neurologic symptoms likely stayed home if they were not severely ill. There were many patients that presented in critical condition requiring

intubation and sedation, and thus, many of their neurologic conditions would have been missed.

5 | CONCLUSIONS

Much attention is given to the presence of fever, cough, and dyspnea as symptoms of COVID-19, with neurologic symptoms also commonly seen on presentation. Our study shows COVID-19 patients can have neurologic manifestation severe enough to warrant neurology consultation in the absence of typical COVID-19 symptoms. This can include serious neurologic manifestations such as stroke and impaired awareness. Many of these patients can later deteriorate to need respiratory support. Thus, it is important to screen for SARS-CoV-2 in patients who present with neurologic symptoms even if without common typical symptoms.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest and no disclosures.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Chuang DT, Aydemir S, Magda P, Thomas C, Zarnegar R. Neurological manifestations as primary presentation of COVID-19 in hospitalized patients. *Acta Neurol Scand*. 2021;143:569–574. <https://doi.org/10.1111/ane.13399>