Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline

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A B S T R A C T

Objective: To report neurological manifestations seen in patients hospitalized with Coronavirus disease 2019 (COVID-19) from a large academic medical center in Chicago, Illinois.

Methods: We retrospectively reviewed data records of 50 patients with COVID-19 who were evaluated by the neurology services from March 1, 2020 - April 30, 2020. Patients were categorized into 2 groups based on timing of developing neurological manifestations: the “Neuro first” group had neurological manifestations upon initial assessment, and the “COVID first” group developed neurological symptoms greater than 24 h after hospitalization. The demographics, comorbidities, disease severity and neurological symptoms and diagnoses of both groups were analyzed. Statistical analysis was performed to compare the two groups.

Results: A total of 50 patients (48% African American and 24% Latino) were included in the analysis. Most common neurological manifestations observed were encephalopathy (n = 30), cerebrovascular disease (n = 20), cognitive impairment (n = 13), seizures (n = 13), hypoxic brain injury (n = 7), dysgeusia (n = 5), and extraocular movement abnormalities (n = 5). The “COVID-19 first” group had more evidence of physiologic disturbances on arrival with a more severe/critical disease course (83.3% vs 53.8%, p 0.025).

Conclusion: Neurologic manifestations of COVID-19 are highly variable and can occur prior to the diagnosis of or as a complication of the viral infection. Despite similar baseline comorbidities and demographics, the COVID-19 patients who developed neurologic symptoms later in hospitalization had more severe disease courses. Differently from previous studies, we noted a high percentage of African American and Latino individuals in both groups.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan city, China and has since spread to 215 countries. As of the date to this manuscript submission, over 4.8 million cases have been confirmed worldwide with numbers continuing to rise [1,2]. The most commonly reported symptoms of COVID-19 include fever, cough, dyspnea, myalgia, fatigue, sputum production, sore throat, diarrhea, and headache, with a majority of the population having a mild or uncomplicated course [3,4]. Less than 5% of the infected patients developed serious complications including respiratory failure, septic shock, and/or multi organ involvement [4,5]. Cases of neurologic involvement in patients with COVID-19 have been reported from cohorts in Wuhan, China and Strasbourg, France [6,7]. However, there has yet to be a sizable case series of patients with COVID-19 with neurologic manifestations to be reported from a diverse patient population in the United States.

In light of the growing number of cases, familiarizing physicians with various neurological features which may be observed in these patients is extremely important. Several reports suggested that African Americans and Latinos are likely to have more severe disease course, as well as individuals with lower socioeconomic status [8]. In this manuscript, we present findings from our tertiary care center which is a major hub to the metropolitan city of Chicago, Illinois and its suburbs, and which regularly cares for an underserved and diverse patient population with lower socio-economic status.

2. Methods

2.1. Study design and patient population

This was a retrospective observational case series conducted at a...
large tertiary care academic center located on the west side of Chicago, Illinois. The study was approved by the local institutional review board (IRB). We reviewed the medical records of all patients admitted between March 1, 2020 and April 30, 2020 with COVID-19 confirmed with real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) assay from nasopharyngeal swab. A total of 650 patients were hospitalized with COVID-19 during this time frame. Patients that were admitted to an inpatient neurology unit or had a formal neurology consultation for concern of neurologic illness were included in this case series.

2.1.2. Data collection
Demographics including age, gender, race and ethnicity, and pre-existing co-morbidities were extracted from the electronic medical record (EMR) system. Admission vital signs were obtained either from emergency department records or from transfer summaries of outside hospitals. Laboratory tests including complete blood cell count (CBC) with differential, liver and renal function assessment, C-reactive protein (CRP), ferritin level, creatinine kinase (CK), D-Dimer, and lactate dehydrogenase (LDH) were reviewed. COVID-19 severity was defined as mild, regular, or severe/critical based on the 7th edition of “Novel Coronavirus Pneumonia Diagnosis and Treatment Plan”. Patients were grouped into four categories: mild (minor clinical symptoms and absent lung inflammation on chest X-ray), regular (fever and respiratory tract symptoms, with visible lung inflammation on imaging), severe (shortness of breath, RR > 30 breaths/min or sPO2 < 93% at rest) and critical (mechanical ventilation, shock, or combined failure of other organs requiring ICU monitoring) [9].

Charts were reviewed for neurologic symptoms or signs affecting the central or peripheral nervous systems. Patients were then categorized into two groups: “Neuro first” with neurological manifestations upon initial assessment, and “COVID first” who developed neurological symptoms greater than 24 h after hospitalization for COVID-19. Study data were managed using REDCap, an electronic data capture tool hosted at our institution [10].

2.1.3. Statistical analysis
Statistical testing was used to detect in-between group differences and association of individual variables to the pre-selected clinical groups. The cohort groups were compared using Student’s t-test for parametric continuous variables, Mann-Whitney U test for non-parametric continuous variables, and Fisher’s exact test for dichotomous variables. All analyses were performed using commercially available SPSS (v. 21, Chicago IL, USA) statistical software. Significance was set at $p < .05$ for statistical comparisons.

3. Results
A total of 50 patients with confirmed COVID-19 were included in this analysis. There were 650 patients hospitalized with COVID-19 at the time of data collection, with an estimated prevalence of neurological manifestations at 7.7%. Demographics, pre-existing comorbidities, and COVID-19 severity are presented in Table 1. There were 58% men ($n = 29$) in the cohort with mean age of 59.6 ± 14.3 years. The vast majority of the patients were African Americans at 48% ($n = 24$) of patients and Latinos at 24% ($n = 12$). Overall, hypertension (60%), diabetes mellitus type 2 (DM) (60%), and obesity (42%) were common with similar prevalence in both groups. The “COVID first” group had more severe/critical cases compared to the “Neuro first group” (83.3% vs 53.8%, $p = .025$), and was more likely to require intubation and mechanical ventilation (83.3% vs 50%, $p = 0.029$).

A multitude of neurological manifestations were observed in the cohort of 50 patients. Of note, some patients had more than one neurologic manifestation. The most commonly observed symptom was altered mental status (60% or $n = 30$). Cerebrovascular events occurred in 40% ($n = 20$) of patients, divided as ischemic stroke in 20% ($n = 10$), intracerebral hemorrhage (ICH) in 8% ($n = 4$), non-aneurysmal subarachnoid hemorrhage (SAH) in 8% ($n = 4$), and transient ischemic attack in 4% ($n = 2$). New onset seizures or breakthrough seizures were also common, occurring in 26% of patients ($n = 13$), followed by headache and cognitive abnormalities at 24% each ($n = 12$), in particular short-term memory impairment. The headache characteristics and seizure pattern were not defined. Hypoxic ischemic brain injury occurred in 14% ($n = 7$) of patients. Two patients (4%) had posterior reversible encephalopathy syndrome (PRES). Peripheral nervous system (PNS) symptoms were frequent, in particular signs of probable dysautonomia which occurred in 12% ($n = 6$) of patients, followed by muscle injury with elevated CK levels in 12% ($n = 6$), dysgeusia in 10% ($n = 5$), and hyposmia in 6% ($n = 3$). Isolated unilateral peripheral facial palsy was observed in 6% ($n = 3$), and extracranial muscle movement abnormalities in 10% ($n = 5$). Dysautonomia was defined as rapid fluctuations in vital signs. Only one patient reported paresthesia, and one patient had coordination impairment and gait ataxia with no clear CNS pathology.

PRES was only reported in the “COVID first” group. This group had a high percentage of altered mental status, seizures, and hypoxic anoxic brain injury. The “neuro first” group most commonly had cognitive abnormalities, altered mental status, and headache. Please refer to Table 2 for further details. The prevalence of altered mental status and hypoxic anoxic brain injury was higher in the “COVID first” group ($p = .047$, $p = .0049$). (See Tables 3 and 4.)

The “COVID first” group had higher respiratory rate and lower oxygen saturation at presentation (23.5 vs 18, $p = 0.003$ and 92.5 vs 96, $p = 0.022$). Laboratory values from the hospitalization are shown in Table 4. Inflammatory and coagulation markers including d-dimer, ferritin, LDH, CRP, along with other laboratory findings were compared between the two groups. The “COVID-first” group had significantly higher maximum white blood cell counts (18.01 vs 10.72 K/U, $p = 0.0415$), d-dimer (12.82 vs 7.27 ng/L, $p = 0.043$), CRP (332 vs 232 mg/L, $p = .032$), LDH (869 vs 494 U/L, $p = .011$) and CK (1430 vs 578 U/L, $p = .047$) levels.

### Table 1
Clinical characteristics of patient population.

| Sex                  | (Total) | Neuro first | COVID first | p Value* |
|----------------------|---------|-------------|-------------|----------|
| Percentage male      | 58      | 61.5        | 58.3        | 0.773    |
| Age (mean)           | 59.6    | 62          | 57          | 0.223    |
| Race/Ethnicity (in percentage) |          |             |             |          |
| African American     | 48      | 53.8        | 41.6        | –        |
| Hispanic             | 24      | 30.76       | 16.6        | 0.059    |
| Comorbidities (in percentage) |          |             |             |          |
| Hypertension         | 60      | 65.3        | 50          | 0.265    |
| Hyperlipidemia       | 44      | 46.2        | 41.6        | 0.782    |
| DM Type 2            | 60      | 65.3        | 54.16       | 0.563    |
| CAD                  | 20      | 19.23       | 20.83       | 0.582    |
| Chronic kidney disease | 22    | 23          | 20.8        | 0.560    |
| Obesity (BMI > 30)   | 42      | 38.4        | 45.83       | 0.775    |
| Tobacco abuse        | 20      | 23          | 16.6        | 0.727    |
| Illict drug abuse     | 2       | 3.8         | 0           | –        |
| COVID-19 classification|          |             |             |          |
| Percent severe/critical | 68%  | 53.8%       | 83.3%       | 0.025    |
| Intubation (percent intubated) | 66% | 50%        | 83.3%       | 0.029    |

*Demographics, comorbidities and disease severity of our total patient population along with both the groups. + p values compare “COVID First” and “Neuro First” Groups. Abbreviations: DM (diabetes mellitus), CAD (coronary artery disease) and BMI (body mass index).
Neurological manifestations are common in the setting of COVID-19 and can present variably in the disease course. The burden of COVID-19 and its neurological manifestations on the healthcare system is expected to increase profoundly. Thus, urgent recognition and familiarity with these neurological conditions is imperative in treating these patients urgently.

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Table 4
Table with laboratory values for patient population.

| Variable                        | Neuro first | COVID first | p Value, |
|---------------------------------|-------------|-------------|----------|
| White blood cell count (normal: 4–11 K/u) (median) | Admission 5.94 | 6.29 | 0.371 |
| Neutrophil count (normal: 1.5–8 K/u) (median) | Maximum 10.72 | 18.01 | 0.0415 |
| Lymphocyte count (normal: 0.72–5.20 K/u/L) (median) | Admission 1.18 | 0.91 | 0.346 |
| Creatinine (normal: 0.75–1.20 mg/dL) (median) | Maximum 1.72 | 4.7 | 0.061 |
| D-Dimer (normal: 0.0–0.60 mg/L FEU) (median) | Admission 1.04 | 4.07 | 0.416 |
| Neutrophil count (normal: 1.5–8 K/u) (median) | Admission 7.27 | 12.82 | 0.043 |
| Platelet count (normal: 150–399 K/u/L) (median) | Admission 213 | 181 | 0.547 |
| LDH (normal: 0–40 U/L) (median) | Admission 407 | 448 | 0.390 |
| AST (normal: 3–44 U/L) (median) | Admission 31.5 | 45 | 0.256 |
| ALT (normal: 0–40 U/L) (median) | Admission 32 | 32.5 | 0.371 |
| Bilirubin (normal: 0 to 0.4 mg/dL) (median) | Admission 0.6 | 0.6 | 0.977 |
| CRP (normal: 0.3 to 10 mg/L) (median) | Admission 73.2 | 98.7 | 0.632 |
| Maximum Ferritin (normal: 12–410 ng/mL) (median) | Maximum 494 | 869 | 0.011 |

Laboratory values including admission, lowest, and maximum values as specified for patient population. Abbreviations: ALT (Alanine transaminase), AST (Aspartate transaminase), CRP (C-reactive protein), LDH (lactate dehydrogenase), CK (Creatinine kinase).

* p values compare COVID First Group and Neuro First Group only.

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Declaration of interests

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