Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of the Neurological Sciences 415 (2020) 116969

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

Pranusha Pinna[1,*], Parneet Grewal[1], Julianne P. Hall, Tachira Tavarez, Rima M. Dafer, Rajeev Garg, Nicholas D. Osteraas, Danielle R. Pellack, Anjali Asthana, Kelsey Fegan, Vikram Patel, James J. Conners, Sayona John, Ivan Da Silva

Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

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 [2,3]. 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

2.1.1. Study design and patient population

This was a retrospective observational case series conducted at a

* Corresponding author at: pranusha_pinna@rush.edu, Department of Neurological Sciences, Rush University Medical Center, 1725 W. Harrison St., Professional Building, Suite 1118, Chicago, IL 60612, USA.

E-mail address: pranusha_pinna@rush.edu (P. Pinna).

[1] Dr. Pinna and Dr. Grewal contributed equally in the paper as first authors

https://doi.org/10.1016/j.jns.2020.116969
Received 28 May 2020; Accepted 29 May 2020
Available online 03 June 2020
0022-510X/ Published by Elsevier B.V.

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 $\pm$ 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 extraocular 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.

Table 1
Clinical characteristics of patient population.

	Total	Neuro first	COVID first	*p* Value[+]
	($n = 50$)	$n = 26$ (%)	$n = 24$ (%)	
Sex				
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
Illicit 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).

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 ($p = .047$, $p = .0.049$). (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 2
Observed neurologic manifestations.

Neurologic manifestation	Total	Neuro first	COVID first	*p* Value[+]
	n = 50 (%)	*n* = 26 (%)	*n* = 24 (%)	
CNS				
Altered mental status	30 (60)	12 (46)	18 (76)	**0.047**
Seizures	13 (26)	5 (19)	8 (33)	0.338
Headache	12 (24)	8 (31)	4 (17)	0.326
Short-term memory loss	12 (24)	8 (31)	4 (17)	0.326
Acute ischemic stroke	10 (20)	5 (19)	5 (21)	0.788
Hypoxic ischemic brain injury	7 (14)	1 (4)	6 (25)	**0.045**
ICH	4 (8)	4 (15)	0	–
SAH	4 (8)	2 (8)	2 (8)	0.897
PRES	2 (4)	0	2 (8)	–
TIA	1 (2)	1 (4)	0	–
PNS				
Dysautonomia	6 (12)	3 (11)	3 (12)	0.654
Muscle injury	6 (12)	3 (11)	3 (12)	0.654
Hypogeusia/Dysgeusia	5 (10)	5 (19)	0	–
Hyposmia	3 (6)	3 (11)	0	–
Extraocular muscle abnormalities	5 (10)	2 (8)	3 (12)	0.323
Facial Palsy	3(6)	1 (4)	2 (8)	0.602
Parasthesias	1 (2)	1 (4)	0	–
Ataxia	1 (2)	0	1 (4)	–

Median admission vital signs for our total cohort along with both the groups.
+ *p* values compare "COVID First" and "Neuro First" Groups.
Abbreviations: CNS (central nervous system), PRES (posterior reversible encephalopathy syndrome), Acute ischemic stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage), TIA (transient ischemic attack), PNS (peripheral nervous system.

Table 3
Vital signs on admission

Vital sign	Total	Neuro First	COVID First	*p* Value*
	n = 50	*n* = 26	*n* = 24	
Temperature (F)	99.7	98.8	100.2	0.102
Heart rate/ Minute	94.6	89	92.9	0.174
Mean arterial pressure (mm Hg)	93	96	85	0.088
Respiratory rate/ per minute	22.8	18	23.5	**0.003**
Pulse oxygen saturation (%)	92	96	92.5	**0.022**

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

4. Discussion

Our tertiary care center cares for patients from the greater Chicago, Illinois. This area is traditionally known to be underserved in regard to healthcare with lower socioeconomic status of patients. Several neurological manifestations were observed in COVID-19 patients affecting both CNS and PNS. Majority of the patients in our cohort were elderly African American and Latino individuals, which highlights the racial/ethnic disparities seen with this viral infection [8]. The common neurological features included altered mental status, cerebrovascular events, seizures, short term memory impairment, and muscle injury. To determine the disease course and outcome, we divided our cohort into the "Neuro first" and COVID first" groups. Despite no difference in baseline demographics and comorbidities, "COVID first" group was sicker, had abnormal vital signs on admission, had elevated inflammatory and coagulopathy markers and were more likely to require intubation and ICU care. The "COVID first" group had more cases of altered mental status, hypoxic ischemic injury, and seizures compared to the "Neuro first" group. This could reflect the severity of the systemic disease seen in these patients.

In a retrospective analysis in the Asian population by Mao, et al., the prevalence of neurological manifestations in COVID-19 was 36.4%, which is significantly higher than our cohort [6]. Apart from racial differences, our patient population was similar to their severely affected population in terms to age (58.2 ± 15.0 vs 59.6 ± 14.3) and sex (50.0% vs 58% males). Our patients had a higher percentage of pre-existing comorbidities including hypertension (60% vs 36.4%) and DM 2 (60% vs 17.0%), both of which have been reported to be associated with worse outcomes [6]. Unlike the population described by Mao, et al., our cohort had higher percentages of altered mental status (60% vs 14.8%), followed by headache (24% vs 13%). Cerebrovascular complications were more common in our patient population (20% vs 2.8%) [11]. This difference might have been due to selective sampling of our patient population.

A study from Strasbourg, France reported several neurological symptoms and signs in COVID-19 patients, including agitation (69%), corticospinal tract signs (67%) and dysexecutive syndrome (36%) [7]. These findings were nonspecific to the underlying mechanism of disease in contrast to our findings.

Some reported conditions that we did not observe in our cohort were hemorrhagic necrotizing encephalitis, Guillain Barre syndrome, Miller Fisher syndrome and polyneuritis cranialis [12–14].

The mechanisms of neurologic manifestations in COVID-19 are likely diverse. Angiotensin converting enzyme (ACE2) which is a target site of SARS-CoV-2 is expressed by glial cells and neurons rendering the brain a potential target of the virus [15]. It has been speculated that nervous system manifestations can occur due to spread of the virus via peripheral nerves, hematogenous route, direct endothelial damage, or as a result of a hypercoagulable state [16,17,6].

5. Limitations

Our study has several limitations, with its retrospective approach and patient selection bias, as only those evaluated by the neurology service were included in this analysis. Not all COVID-19 patients admitted during the same timeframe underwent a full neurological evaluation. Additionally, long term follow-up and outcome data were unavailable, thus delayed neurological symptoms were not captured. We plan to perform further targeted data review of all COVID-19 patients to focus on delayed neurological symptoms and long-term outcomes.

6. Conclusion

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.

Author disclosures

Dr. P. Pinna does not report any disclosures relevant to the manuscript.

Dr. P. Grewal does not report any disclosures relevant to the manuscript.

Dr. J. Hall does not report any disclosures relevant to the manuscript.

Dr. R. Dafer does not report any disclosures relevant to the manuscript.

Dr. Pellack does not report any disclosures relevant to the manuscript.

Dr. T. Tavarez does not report any disclosures relevant to the manuscript.

Dr. R. Garg does not report any disclosures relevant to the manuscript.

Dr. N. Osteraas does not report any disclosures relevant to the manuscript.

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
	Maximum	10.72	18.01	**0.0415**
Neutrophil count (normal: 1.5–8 K/u) (median)	Admission	4.07	4.79	0.150
	Maximum	9.69	12.74	0.129
Lymphocyte count (normal: 0.72–5.20 K/uL) (median)	Admission	1.18	0.91	0.346
	Lowest	0.66	0.56	0.103
CK	Admission	168	224	0.662
(normal: 10–205 U/L) (median)	Maximum	578	1430	**0.047**
Creatinine	Admission	1.33	1.37	0.797
(normal: 0.75–1.20 mg/dL) (median)	Maximum	1.72	4.7	**0.061**
D-Dimer	Admission	1.04	4.07	0.416
(normal: 0.0–0.60 mg/L FEU) (median)	Maximum	7.27	12.82	**0.043**
Platelet count	Admission	213	181	0.547
(normal: 150–399 K/uL) (median)	Lowest	168	114	**0.001**
LDH	Admission	407	448	0.390
(normal: 110–240 U/L) (median)	Maximum	494	869	**0.011**
AST	Admission	31.5	45	0.256
(normal: 3–44 U/L) (median)	Maximum	50.5	121.5	**0.009**
ALT	Admission	32	32.5	0.371
(normal: 0–40 U/L) (median)	Maximum	103	157	**0.048**
Bilirubin	Admission	0.6	0.6	0.977
(normal: 0 to 0.4 mg/dL) (median)	Maximum	0.9	2.0	**0.003**
CRP	Admission	73.2	98.7	0.632
(normal: 0.3 to 10 mg/L) (median)	Maximum	232	332	**0.032**
Maximum Ferritin		1254	2056	0.126
(normal: 12–410 ng/mL) (median)				

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.

A. Asthana does not report any disclosures relevant to the manuscript.

K. Fegan does not report any disclosures relevant to the manuscript.

V. Patel does not report any disclosures relevant to the manuscript.

Dr. S. John does not report any disclosures relevant to the manuscript.

Dr. J. Conners does not report any disclosures relevant to the manuscript.

Dr. I. Da Silva does not report any disclosures relevant to the manuscript.

Declaration of interests

None.

Sources of funding

None.

Acknowledgments

None.

References

[1] N. Zhu, D. Zhang, W. Wang, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727–733.
[2] World Health Organization Coronavirus Disease (COVID-19), Situation Report- 117, Accessed May 16, 2020 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200516-covid-19-sitrep-117.pdf?sfvrsn=8f562cc_2.
[3] A.J. Rodriguez-Morales, J.A. Cardona-Ospina, E. Gutiérrez-Ocampo, et al., Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis, Travel Med. Infect. Dis. (2020) 101623.
[4] N. Chen, M. Zhou, X. Dong, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513.
[5] Z. Wu, McGoogan JM, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, JAMA (2020) 1–4.
[6] L. Mao, H. Jin, M. Wang, et al., Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China, JAMA Neurol. (2020) 1–5.
[7] J. Helms, S. Kremer, H. Merdji, et al., Neurologic features in severe SARS-CoV-2 infection, N. Engl. J. Med. (2020) 1–7.
[8] C.W. Yancy, COVID-19 and African Americans, JAMA (2020) 1–3.
[9] Novel Coronavirus pneumonia diagnosis and treatment plan (Provisional 7th Edition), Accessed April 30, 2020 https://www.chinalawtranslate.com/en/coronavirus-treatment-plan-7/.
[10] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform. 42 (2009) 377–381.
[11] L.Q. Li, T. Huang, Y.Q. Wang, et al., COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis, J. Med. Virol. (2020) 1–6.
[12] N. Poyiadji, G. Shahin, D. Noujaim, M. Stone, S. Patel, B. Griffith, COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI features, Radiology (2020) 201187.
[13] A. Virani, E. Rabold, T. Hanson, et al., Guillain-Barré Syndrome associated with SARS-CoV-2 infection, IDCases (2020) e00771.
[14] C. Gutiérrez-Ortiz, A. Méndez, S. Rodrigo-Rey, et al., Miller Fisher Syndrome and polyneuritis cranialis in COVID-19, Neurology (2020) 1–2.
[15] A.M. Baig, A. Khaleeq, U. Ali, H. Syeda, Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms, ACS Chem. Neurosci. 11 (2020) 995–998.
[16] A.M. Baig, Neurological manifestations in COVID-19 caused by SARS-CoV-2, CNS Neurosci. Ther. 26 (2020) 499–501.
[17] K. Bohmwald, Gálvez NMS, M. Ríos, A.M. Kalergis, Neurologic alterations due to Respiratory Virus Infections, Front. Cell. Neurosci. 12 (2018) 386.