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Neurological complications in a predominantly African American sample of COVID-19 predict worse outcomes during hospitalization

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ABSTRACT

People with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, COVID-19, can have neurological problems including headache, anosmia, dysgeusia, altered mental status (AMS), ischemic stroke with or without large vessel occlusion, and Guillen-Barre Syndrome. Louisiana was one of the states hit hardest by the pandemic with just over 57,000 laboratory-confirmed cases of COVID-19 by the end of June 2020.

We reviewed the electronic medical records (EMR) of patients hospitalized during the peak of the pandemic, March 1st through March 31st, to document the type and frequency of neurological problems seen in patients with COVID-19 at presentation to the emergency room. Secondary aims were to determine: 1) the frequency of neurological complaints during the hospital stay; 2) whether the presence of any neurological complaint at presentation or any of the individual types of neurological complaints at admission predicted three separate outcomes: death, length of hospital stay, or the need for intubation; and 3) if the presence of any neurological complaint or any of the individual types of neurological complaints developed during hospital stay predicted the previous three outcomes.

A large proportion of our sample (80 %) was African American and had hypertension (79 %). Out of 250 patients, 56 (22 %) patients died, and 72 (29 %) patients required intubation. Thirty-four (14 %) had a neurological chief complaint at presentation; the most common neurological chief complaints in the entire sample were altered mental status (AMS) (8 %), headache (2 %), and syncope (2 %). We used a competing risk model to determine whether neurological symptoms at presentation or during hospital stay were predictors of prolonged hospital stay and death. To establish whether neurological symptoms were associated with higher odds of intubation, we used logistic regression. Age was the only significant demographic predictor of death and hospital stay. The HR (95 %CI) for remaining in the hospital for a ten-year increase in age was 1.2, (1.1, 1.3, $p < 0.0001$), and for death was 1.3, (1.1, 1.5, $p < 0.01$).

There were no demographic characteristics, including age or comorbidities predictive of intubation. Adjusting for age, patients who at presentation had neurological issues as their chief complaint were at significantly increased risk for remaining in the hospital, HR = 1.7, (1.1,2.5, $p = 0.0001$), and dying, HR = 2.1(1.1,3.8, $p = 0.02$), compared to patients without any neurological complaint. Of the individual admission complaints, AMS was associated with a significantly prolonged hospital stay, HR = 1.8, (1.0–3.3, $p = 0.05$). Patients that required dialysis or intubation or had AMS during hospitalization had more extended hospital stays. After adjusting for age, dialysis, and intubation, patients with AMS during hospital stay had a HR of 1.6, (1.1, 2.5, $p = 0.01$) for remaining in the hospital. Patients who had statistically significant higher odds of requiring intubation were those who presented with any neurological chief complaint, OR = 2.8 (1.3,5.8, $p = 0.01$), or with headaches OR = 13.3 (2.1,257.0, $p = 0.008$). Patients with AMS during the hospital stay, as well as those who had seizures, were more likely to need intubation. In the multivariate model, dialysis, OR = 4.9 (2.6,9.4, $p < 0.0001$), and AMS, OR = 8.8 (3.9,21.2, $p < 0.0001$), were the only independent predictors of intubation.

Neurological complaints at presentation and during the hospital stay are associated with a higher risk of death, prolonged hospital stay, and intubation. More work is needed to determine whether the cause of the neurological complaints was direct CNS involvement by the virus or the other systemic complications of the virus.

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which appeared on the radars of epidemiologists at the end of 2019, is the cause of the ongoing world pandemic. The disease caused by SARS-CoV-2 is called coronavirus disease 2019 (COVID-19) and mainly includes respiratory symptoms with the involvement of systematic disease and other organ systems in a small portion of the infected patients [1]. While knowledge about the virus and its athogenesis is still limited, there is growing evidence that COVID-19 is associated with neurologic complications in some patients [2,3].

2. Background

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), which spread in 2003 and mainly caused respiratory disease, is also known to have caused neurologic complications [4]. Tsai et al. hypothesized that some of the neurological problems seen with SARS-CoV may have been the result of direct neurotropic and myotropic effects of the virus [5]. Hung et al. detected virus particles of the SARS-CoV in the central nervous system (CNS) of a patient with SARS-CoV [6], and autopsy studies showed inflammatory findings in the brain [7]. Initial reporting from China demonstrates a genetic similarity between SARS-CoV-2 and SARS-CoV [8], and thus SARS-CoV-2 may also affect the central nervous system.

Coronaviruses, including SARS-CoV-2, use Spike (S) Protein to bind to receptors and gain access to the host cells. One of the primary receptors with which they interact is the Angiotensin-Converting Enzyme-2 (ACE) receptor, found in the vasculature, central nervous system, and many other organs. The viral S proteins need to be primed by host cell serine proteases such as TMPRSS2 in order to enter the host cell [9].

Complaints associated with SARS-CoV-2 include headache, anosmia, and dysgeusia [10]. Altered mental status (AMS), ischemic stroke with or without large vessel occlusion, and Guillen-Barre Syndrome are more severe complications described in the context of COVID-19 [11]. Given the varying nature of the clinical presentations related to COVID-19, it is not surprising that there have been reports of patients having primarily neurological complaints, who later tested positive for SARS-CoV-2. Proposed mechanisms of CNS involvement are the damage of the blood-brain barrier, cytokine-induced neuronal impairment [12], and neuronal transmission of the virus through axonal transport [13].

Louisiana was one of the states hit hardest by the pandemic with just over 57,000 laboratory-confirmed [14] cases of COVID-19 by the end of June 2020. University Medical Center is one of the largest hospitals in New Orleans and serves as a referral center for south Louisiana. Our study retrospectively reviewed medical records that identified neurological complications in laboratory-confirmed cases that required hospitalization at our institution during March 2020.

3. Methods

The Louisiana Health Sciences Center – New Orleans Institutional Review Board and the University Medical Center Clinical Research Review Committee approved the study protocol. The primary aim was to document the type and frequency of neurological problems seen in this one-month sample of patients with COVID-19 at presentation to the emergency room. Secondary aims were to determine: 1) the frequency of neurological complaints during the hospital stay; 2) whether the presence of any neurological complaint at presentation or any of the individual types of neurological complaints at admission predicted three separate outcomes: death, length of hospital stay, or the need for intubation; and 3) if the presence of any neurological complaint or any of the individual types of neurological complaints developed during hospital stay predicted the previous three outcomes.

We reviewed the electronic medical records (EMR) of patients hospitalized during March (March 1st through March 31st) 2020 at the University Medical Center New Orleans (UMCNO), who tested positive for SARS-CoV-2 during the same hospitalization. The EMR team generated a list of 257 patients admitted for COVID-19. We excluded seven patients because of a negative COVID-19 test result or incomplete medical record documentation. Three neurology residents (DC, MS, DB) reviewed the EMR in detail to capture the relevant medical history, clinical course, and laboratory test results and abstracted data into an electronic data collection spreadsheet.

We recorded the presentation or development of the following neurological complaints: headache, syncope, altered mental status, seizure, status epilepticus, and ischemic or hemorrhagic stroke.

4. Statistical analysis

We used "R" (statistics software) and Microsoft Excel to generate summary tables. To analyze hospital length of stay or death, we fitted a competing risks proportional hazards model for time to discharge or death using the *crr*() function in R version 4.0.0. The competing risks model allowed the analysis of hospital stay, taking into account that the censoring of cases due to death was not random. To predict the likelihood of intubation, we used the *glm*() function in R to fit a logistic regression model. For each model, we determined baseline demographic variables predictive of the outcomes and generated adjusted models. For variables with less than five cases per cell, we reported the p-values for Fisher's Exact Test.

5. Results

Table 1 shows the demographic characteristics of our patients. A large proportion (80 %) were African American and had hypertension (79 %). Out of 250 patients, 56 (22 %) patients died, and 72 (29 %) patients required intubation. Thirty-four (14 %) had a neurological chief complaint at presentation. The most common neurological chief complaints, as detailed in Table 2, were altered mental status (AMS), headache, and syncope. Ninety-five patients (38 %) had a neurological complication during hospitalization. Table 3 shows the type and frequency of neurological complications, of which the most common was AMS, occurring in 73(29 %) patients.

6. Baseline predictors

Supplementary Table E1 shows the hospital stay and death hazard ratios and 95 % confidence intervals (HR (95 %CI)) and the intubation odds ratios (OR) for demographics and non-neurologic comorbid clinical characteristics. Age and hypertension were the only demographic/clinical predictors with a significant association with the length of hospital stay, but hypertension was not a significant predictor after adjusting for age. Age was the only significant predictor of death. The HR (95 %CI) for remaining in the hospital for a ten-year increase in age was 1.2, (1.1, 1.3, $p < 0.0001$), and for death was 1.3, (1.1, 1.5, $p < 0.01$). There were no demographic characteristics, including age or comorbidities predictive of intubation.

Adjusting for age, patients who at presentation had neurological issues as their chief complaint were at significantly increased risk for remaining in the hospital, HR = 1.7, (1.1,2.5, $p = 0.0001$), and death, HR = 2.1(1.1,3.8, $p = 0.02$), compared to patients without any neurological complaint. Of the individual admission complaints, AMS was associated with a significantly prolonged hospital stay, HR = 1.8, (1.0–3.3, $p = 0.05$). Other neurological complaints at presentation had too few cases to be able to include them in the competing risk models for death and hospital stay. Patients who had statistically significant higher odds of requiring intubation were those who presented with any neurological chief complaint, OR = 2.8 (1.3,5.8, $p = 0.01$), or with headaches 13.3 (2.1,257.0, $p = 0.008$).

Table 1
Demographic, comorbid medical conditions, and concomitant medications.

	Total Sample N = 250	With Neurological CC N = 34	Without Neurological CC N = 216
	Mean ± SD		
Age	60 ± 15	68 ± 14	59 ± 15*
BMI	34 ± 11	32 ± 10	35 ± 11
–			
	N (%)		
Sex - Male	113 (45 %)	15 (44 %)	98 (45 %)
Race			
Current	199 (80 %)	27 (79 %)	172 (80 %)
Caucasian	15 (6 %)	2 (6 %)	13 (6 %)
Asian	2 (<1 %)	0 (0 %)	2 (1 %)
American Indian or Alaskan	1 (<1 %)	0 (0%)	1 (<1 %)
Missing	33 (13 %)	5 (15 %)	28 (13 %)
Ethnicity - Hispanic	2 (<%)	0 (0 %)	2 (1 %)
Smoking			
Current	19 (8 %)	2 (6 %)	17 (8 %)
Former	72 (29 %)	11 (32 %)	61 (28 %)
Never	15 3(61 %)	18 (53 %)	135 (63 %)
Missing	6 (2 %)	3 (9%)	3 (1%)
Comorbid Medical Conditions			
Asthma	39 (16 %)	5 (15 %)	34 (16 %)
Hypertension	195 (78 %)	25 (71 %)	170 (79 %)
Diabetes	128 (51 %)	15 (44 %)	113 (52 %)
Migraine	3 (1 %)	0 (0 %)	3 (1 %)
Epilepsy	9 (4 %)	1 (3 %)	8 (4 %)
Previous CVA	35 (14 %)	6 (18 %)	29 (13 %)
Concomitant Medications			
ACEI or ARB	107(43 %)	14 (41 %)	93 (43 %)
Immunosuppressors	14 (6 %)	0 (0 %)	14 (6 %)
Beta-Blocker	63 (25 %)	12 (35 %)	51 (24 %)
Anticoagulation Antiplatelet	87 (35 %)	9 (26 %)	78 (36 %)

CC = chief complaint. BMI = body mass index. CVA = cerebrovascular accident. ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin II receptor blocker.

* Statistically significant group difference, $p < 0.002$.

Table 2
Neurological signs reported at presentation.

	N (%)
Neurological Chief Complaint	34 (14 %)
Ageusia	1 (<1%)
Altered Mental Status	19 (8 %)
Headache	6 (2 %)
Lethargy	1 (<1 %)
Seizure	1 (<1 %)
Syncope	6 (2 %)

Table 3
Neurological signs developed during hospitalization.

	N (%)
Neurological Symptom During Hospitalization	95 (38 %)
Ageusia/Anomsia	3 (1 %)
Altered Mental Status	73 (29 %)
Cerebrovascular Accident	1 (<1 %)
Encephalitis	3 (1 %)
Headache	19 (8%)
Seizure	10 (4 %)
Status Epilepticus	1 (<1 %)

7. Neurologic complications during the hospital stay

Supplementary Table E2 shows the HR (95 %CI) for complications during hospital stay associated with prolonged hospital stays. Patients that required dialysis or intubation or had AMS during hospitalization had more extended hospital stays. In the multivariate model (Supplementary Table E2), after adjusting for age, dialysis, and intubation, patients with AMS during hospital stay had a HR of 1.6, (1.1, 2.5, $p = 0.01$) for remaining in the hospital. Supplementary Table E2 also shows the HR (95 %CI) for death. Age, HR = 1.2 (1.0,1.5, $p = 0.05$), and requiring intubation, HR = 9.1 (4.4,19.0, $p < 0.0001$), were the only statistically significant predictors of death in the multivariate model. After adjusting age and intubation, AMS during hospitalization was not a predictor of death.

Regarding intubation, Supplementary Table E2 shows the intubation OR (95 %CI) for complications during the hospital stay. Patients with AMS during the hospital stay, as well as those who had seizures, were more likely to need intubation. In the multivariate model, dialysis, OR = 4.9 (2.6,9.4, $p < 0.0001$), and AMS, OR = 8.8 (3.9,21.2, $p < 0.0001$), were the only independent predictors of intubation.

8. Limitations

This study was a retrospective analysis that only included people who presented to the emergency room, had to be admitted, and tested positive for COVID-19. As such, the patients were already "worse" than other people who tested positive and may have been symptomatic but did not need admission. Thus, results do not extend to outpatients. Our sample had a high proportion of African Americans and a high prevalence of hypertension or diabetes. Race and hypertension were key predictors identified in other studies; the lack of variability in terms of race and hypertension likely explains why these two variables were not significant predictors in our study. The results of our study do not generalize to samples with more diverse racial or ethnic backgrounds or to groups with fewer comorbidities.

Our data came from the first month that UMCNO was managing critically ill patients with COVID-19. However, the results may not generalize to those people treated after that initial month's rapid learning curve that probably resulted in better outcomes overall at UMCNO or future hospital cohorts.

The analysis of neurological symptoms that occurred during the hospital stay was not ideal because these symptoms were time-dependent covariates. However, we did not collect the specific times during hospital stay when the complications of AMS, seizures, or other complications occurred. Thus, it was not determined, for example, if seizures occurred before or after intubation.

AMS is a nonspecific term. Ideally, we try to avoid it and use more specific terms that include the etiologic factors like metabolic encephalopathy or septic encephalopathy. Since this was a retrospective medical record review study and the diagnosis of AMS was determined by a variety of medical providers, it was impossible to be more specific. Additionally, in our IRB submission, we did not include sepsis and metabolic parameters in the data collection. Thus, at this point, we cannot tease apart these crucial contributors to AMS. Future studies with more resources and larger sample sizes should address this limitation of our study.

Our hospital did not perform MRI for patients with COVID-19 in March because of limitations in the decontamination protocols; thus, we could not rule out causes like multiple small strokes.

We did not analyze other important outcomes, such as disability at discharge.

9. Conclusion

We conclude that neurological complaints at presentation or during the hospital stay are not uncommon in patients with COVID-19 who

require hospitalization. AMS was by far the most common complication and was a significant predictor, both at baseline and during the hospital stay, of prolonged hospital stay, death, and intubation. Future studies should try to determine the underlying cause/s of AMS and whether it may have been a result of the SARS-CoV-2 disease process or of another disease process that contributed to the poorer outcomes in these COVID-19 positive patients. The data suggest that neurological complications, such as AMS and seizure, may be associated with worse outcomes in persons hospitalized due to COVID-19, but more studies are needed to determine the nature, incidence, and relevance of these associations.

CRediT authorship contribution statement

David Chachkhiani: Conceptualization, Methodology, Writing - original draft, Supervision, Investigation. **Michael Y. Soliman:** Investigation, Writing - review & editing. **Delphi Barua:** Investigation, Writing - review & editing. **Marine Isakadze:** Writing - review & editing. **Nicole R. Villemarette-Pittman:** Writing - review & editing. **Deidre J. Devier:** Writing - review & editing. **Jesus F. Lovera:** Formal analysis, Methodology, Supervision, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.106173.

References

[1] Na Zhu, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. (2020).
[2] Ling Mao, et al., Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China, JAMA Neurol. 77 (6) (2020) 683–690.
[3] V. Montalvan, et al., Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review, Clin. Neurol. Neurosurg. 194 (2020), 105921.
[4] Yeshun Wu, et al., Nervous system involvement after infection with COVID-19 and other coronaviruses, Brain Behav. Immun. (2020).
[5] L. Tsai, S. Hsieh, Y. Chang, Neurological manifestations in severe acute respiratory syndrome, Acta Neurol. Taiwan. 14 (3) (2005) 113.
[6] Emily C.W. Hung, et al., Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome, Clin. Chem. 49 (12) (2003) 2108.
[7] Kwok-Kwong Lau, et al., Possible central nervous system infection by SARS coronavirus, Emerging Infect. Dis. 10 (2) (2004) 342.
[8] Xiaolu Tang, et al., On the origin and continuing evolution of SARS-CoV-2, Sci. Rev. (2020).
[9] Markus Hoffmann, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, 2020.
[10] Claudio Liguori, et al., Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection, Brain Behav. Immun. (2020).
[11] Avindra Nath, Neurologic Complications of Coronavirus Infections, 2020.
[12] Luca Steardo, Neuroinfection May Contribute to Pathophysiology and Clinical Manifestations of COVID-19, 2020.
[13] Marc Desforges, Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?, 2019.
[14] http://ldh.la.gov/coronavirus/.