# Shock: Most Hospitalized COVID Patients Developed Neurological Disorders

Eighty percent of hospitalized patients developed neurological problems, contributing very significantly to the number of deaths. One cause, "direct neuroinvasion by the virus" states that the virus got directly into the brain.

Neurosurgeon Dr. Russell Blaylock wrote in May 2020 that *"By wearing a mask, the exhaled viruses will not be able to escape and will concentrate in the nasal passages, enter the olfactory nerves and travel into the brain."* He was heavily criticized for this, but mostly by ignorant, non-medical individuals.  TN Editor

## Introduction

As of 8 September 2020, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has led to over 26.5 million confirmed infections and 875,000 deaths from coronavirus disease-2019 (Covid-19) worldwide.1

Like most infections caused by members of the coronavirus family, SARS-CoV-2 manifests itself with upper respiratory tract infections and flu-like symptoms of varying severity.2 However, Covid-19 is unique in its ability to cause a multi-organ disease, with involvement of the central and peripheral nervous system in some individuals.

Indeed, a wide range of neurologic manifestations of SARS-CoV-2 infection have been recognized, and evidence of their severity and persistence is increasing.3–10 However, the frequency of those manifestations and associated risk factors remain unclear. We sought to characterize the incidence of neurologic manifestations, in patients with confirmed Covid-19 and identify factors associated with the development of neurologic manifestations in hospitalized patients with both severe and non-severe respiratory disease. Furthermore, neurologic manifestations, especially encephalopathy, have been associated with worse clinical outcomes in other systemic illnesses including sepsis and may even lead to significant disability.11, 12 Therefore, we sought to identify if encephalopathy was associated with greater morbidity in hospitalized patients with Covid-19.

## Subjects/Materials and Methods

## Patients

We retrospectively analyzed the first consecutive patients admitted with Covid-19 to the Northwestern Medicine Healthcare (NMHC) system between 5 March and 6 April 2020. NMHC consists of one academic medical center (AMC) and nine other hospitals in the Chicago area. Covid-19 diagnosis was confirmed by SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab or broncho-alveolar lavage fluid. All laboratory and radiologic assessments were performed as part of routine clinical care. This study was approved by our institutional review board (STU00212627) with waiver of consent for retrospective analysis.

## Procedures

Demographic, medical comorbidity, pre-hospitalization medication usage, and hospital course data were collected by electronic medical record review. Laboratory data were collected by automated electronic query. Neurologic manifestations were identified by review of clinical notes, diagnostic studies, and physician-documented diagnoses. The identification of neurologic manifestations, the dates of neurologic manifestation onset, and Covid-19 symptom onset dates was facilitated by electronic note templates implemented in the NMHC System as part of the Covid-19 response. In particular, encephalopathy was identified by (a) report of altered mental status or depressed level of consciousness, (b) physician documented diagnosis of encephalopathy or the delirium encephalopathy syndrome, or (c) positive Confusion Assessment Method (CAM) evaluation. The Confusion Assessment Method is a well-validated and widely used clinical and research tool for the identification of the delirium encephalopathy syndrome and has been in routine clinical use at NMHC since 2008.13–15 Neurologic manifestations were included starting on the date of Covid-19 onset, as identified by the patient's clinical provider, through 90 days. In cases where neurologic manifestations were not specifically attributed to a documented diagnosis, the cases were independently adjudicated by two separate neurologists (AB and EML). A third neurologist independently reviewed the chart to serve as a tie-breaker (IJK) in cases of disagreement. In those cases where neurologic manifestations were attributed to a specific neurologic diagnosis (e.g., stroke), the patient was recorded as having that specific diagnosis rather than each component neurologic manifestation. Patients were dichotomized into severe versus non-severe Covid-19 respiratory disease based on the need for mechanical ventilation during hospitalization; this criterion was used to account for the possibility of delayed clinical deterioration after hospital admission.

Functional outcome at hospital discharge was extracted from therapy and rehabilitation medicine physician documentation using the modified Rankin Scale (mRS) categorized as: mRS 0–2, able to look after ones' own affairs without assistance; mRS 3, ambulates unassisted but needs help with ones' own affairs; mRS 4–5, unable to ambulate unassisted and

needs assistance for bodily care; and mRS 6, death. The discharge mRS scores were determined independently by two reviewers and disagreements were reconciled by majority decision after review (EML).

## Statistical analysis

Data were summarized as number of patients (frequency), mean (standard deviation) for normally distributed variables, and median (interquartile range [IQR]) for non-normally distributed variables. Associations were assessed using Fisher's exact test, Spearman's rank correlation test, and Wilcoxon rank-sum test. Binary logistic regression models were developed to identify adjusted predictors of: (1) experiencing any neurologic manifestations, (2) experiencing encephalopathy, and (3) having a favorable discharge functional outcome (mRS 0–2). In each case, we first developed a model using *a priori* variables based on biologic plausibility and review of the recent Covid-19 literature. Then we developed models using the *a priori* variables plus additional variables univariately associated with the model outcome at $P \leq 0.15$ and not highly collinear with a variable already included. To avoid overfitting models to the data, we used a backward variable selection algorithm based on Akaike Information Criteria optimization to develop final *parsimoniously adjusted* models. Details of the *a priori* and *parsimonious* models, including the *a priori* variables for each model, are included in the Table S2. We also developed an *a priori* binary logistic regression model for the association between encephalopathy and 30-day mortality adjusted for age, severe Covid-19 disease, and hospitalization at the AMC; limited numbers of patient deaths prevented inclusion of additional variables for adjustment. Two-sided $P \leq 0.05$ was considered significant and all analyses were performed in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

## Frequency of neurologic manifestations

There were 509 consecutive patients included in the study (age 58.5 ± 16.9 years, 281 (55.2%) males), and 134 (26.3%) had severe Covid-19 requiring mechanical ventilation. Neurologic manifestations were present at Covid-19 onset in 215 patients (42.2%), at hospital admission in 319 patients (62.7%) and at any time during the disease course in 419 patients (82.3%). The most frequent neurologic manifestations were myalgias (228, 44.8%), headaches (192, 37.7%), encephalopathy (162, 31.8%), dizziness (151, 29.7%), dysgeusia (81, 15.9%), and anosmia (58, 11.4%). In addition, reports of generalized fatigue (214 [42.9%] patients) at onset and any time during Covid-19 disease (404 [79.4%] patients) were common. The clinical characteristics of the patients with and without any neurologic manifestations or encephalopathy are summarized in Table 1. Patients presenting with any neurologic manifestations were younger than those without (57.53 [16.31] vs. 62.98 [18.97] years; $P = 0.005$) and had a longer time from COVID onset to hospitalization (7 [4, 10] vs. 5 [2, 9] days; $P = 0.003$). Conversely, patients with encephalopathy were older than those without (65.51 [16.54] vs. 55.22 [16.10] years; $P < 0.001$), had a shorter time from COVID onset to hospitalization (6 [3, 9] vs. 7 [4, 10] days; $P = 0.014$), were more likely to be male, and to have a history of any neurological disorder, cancer, cerebrovascular disease, chronic kidney disease, diabetes, dyslipidemia, heart failure, hypertension and smoking in assessments without multivariate adjustment. There were no differences in use of angiotensin converting enzyme (ACE) inhibitors, angiotensin 2 receptor blocker (ARB), corticosteroids or immunosuppressants prior to admission in patients with and without any neurologic manifestations or encephalopathy (Table S1).

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## Discussion

This study highlights the high frequency and range of neurologic manifestations, which occurred in more than four fifths of Covid-19 patients hospitalized in our hospital network system. These results

expand findings of neurologic manifestations in 36.4% of hospitalized Covid-19 patients in China and 57.4% in Europe16, 17, albeit with increased prevalence in our US cohort. Differences in frequencies may be caused by genetic factors including polymorphism in expression of the viral receptor angiotensin-converting enzyme 2 (ACE 2) in the nervous system, and possibly, SARS-CoV-2 strain variations.18 In addition, our hospital network system was never stressed beyond capacity due to surge preparation and most patients had moderate disease, with only one quarter developing severe respiratory distress requiring mechanical ventilation.19 This may have allowed for more detailed evaluation and identification of neurologic manifestations.

The fact that any neurologic manifestations as a whole were more likely to occur in younger people is surprising, and could potentially be explained by greater clinical emphasis on the risk of respiratory failure than other symptoms in older patients. Alternatively, early neurologic manifestations such as myalgia, headache, or dizziness may have prompted earlier medical care. In contrast, encephalopathy was more frequent in older patients. Risk factors for encephalopathy also included severe Covid-19 disease and history of any neurological disorder or chronic kidney disease. This is consistent with recent literature identifying higher rates of mortality in Covid-19 patients with pre-existing chronic neurological disorders.20

The increased morbidity and mortality associated with encephalopathy, independent of respiratory severity, parallels previous literature in sepsis-associated encephalopathy and delirium-associated mortality11, 21 and emphasizes its relevance in Covid-19. We also found that encephalopathy in Covid-19 was associated with triple the hospital length of stay. Broad recognition and screening for encephalopathy as a contributor to disease severity in Covid-19 may have utility in resource allocation and potential to improve patient outcomes. Furthermore, our findings emphasize the broader need to develop interventions that target encephalopathy as a component of multi-organ system medical illness.

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