Disputes & Debates: Editors’ Choice

Steven Galetta, MD, FAAN, Section Editor

Editor’s Note: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Dr. Frontera et al. examined the prevalence and associated mortality of well-defined neurologic diagnoses in a prospective, multicenter, observational study of 4,491 consecutive hospitalized adults in the New York City (NYC) metropolitan area with laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Neurologic disorders were diagnosed in 13.5% of these patients with coronavirus disease-2019 (COVID-19) and were associated with higher in-hospital mortality and lower likelihood of discharge home. In response, Dr. Kumar et al. contrast the most common neurologic clinical diagnoses in this study (toxic/metabolic encephalopathy, stroke, seizure, and hypoxic/ischemic brain injury) with the most common imaging diagnoses in another study by Dr. Kremer et al. of patients with COVID-19 who underwent brain MRI (ischemic strokes, leptomeningeal enhancement, and encephalitis). They note that the study by Dr. Frontera et al. reported raised protein in the CSF in several of the patients, suggestive of intrathecal inflammation as may be seen with meningitis/encephalitis, although white cell counts were low. They wonder whether the low frequency of brain MRI in the study may have led to underdetection of meningitis/encephalitis. In another response, Dr. Liotta et al. note that they reported similar rates of stroke, seizure, Guillain-Barre Syndrome, encephalitis, and meningitis in their recent Chicago-based study but had higher rates of encephalopathy. They note that in their own study, they adjudicated all charts, not just those for patients receiving neurologic consultations, and used protocolized delirium assessments to identify encephalopathy. They contend that Dr. Frontera et al. may have missed several cases of encephalopathy with their methodology and suggest that excluding headache as a neurologic symptom may have limited the scope of SARS-CoV-2 neuropathogenesis. They also note the lower in-hospital mortality in their cohort, potentially related to the absence of an overwhelming case surge in Chicago compared with NYC, and emphasize the importance of public health measures against COVID-19 to help sustain health care infrastructure. Responding to these comments, the authors question whether patients in the imaging study by Dr. Kremer et al. actually met accepted diagnostic criteria for encephalitis, noting that CSF SARS-CoV-2 RT-PCR (reverse transcription PCR) was negative in 20 patients and positing that some of the imaging findings could have represented postinfectious encephalitis. They also caution that many of the reported MRI findings are nonspecific and can be seen with nonencephalitic conditions, in particular hypoxic/ischemic injury, given the high frequency of acute respiratory distress syndrome and supplemental oxygen requirement among these patients. They also note that the elevated CSF protein in their own study is a nonspecific finding and highlight the need to follow rigorous standards when ascribing meningitis/encephalitis to SARS-CoV-2 infection. Regarding their lower rates of encephalopathy compared with the Chicago study, the authors argue that they coded toxic-metabolic encephalopathy only in patients off sedation or after a sedation washout, whereas the Chicago study may have included patients with sedation-related delirium, which may have different outcomes than other etiologies of encephalopathy. However, they acknowledge that they may have underestimated the overall prevalence of neurologic injury in the most critically ill patients who could not be assessed off sedation, or who were unable to express other neurologic symptoms. Notwithstanding the older age of their cohort, they agree that the critical surge and strain on health care resources in NYC likely affected mortality and echo the importance of public health measures to stem such surges. This exchange demonstrates important differences that can arise in incidence or frequency estimates of different neurologic manifestations in COVID-19 based on the methodology that is followed.

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Neurology® 2021;96:548. doi:10.1212/WNL.0000000000011604

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Reader Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

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Neurology® 2021;96;549. doi:10.1212/WNL.0000000000011614

We read with interest the article by Frontera et al.1 studying neurologic disorders in hospitalized COVID-19 patients in New York City. The overall prevalence of neurologic disorders among hospitalized COVID-19 patients was 13.5%. The most common neurologic symptoms were toxic/metabolic encephalopathy (309/606, 51%), stroke (84/606, 14%), seizure (74/606, 12%), and hypoxic/ischemic brain injury (65/606, 11%). In a recent study by Kremer et al.,2 correlated neurologic and neuroimaging findings of COVID-19 patients concluded that among 64 patients with neurologic symptoms who underwent brain MRI, ischemic strokes (27%) were the most common finding, followed by leptomeningeal enhancement (17%) and encephalitis (13%). Even in present study, the CSF findings (table 2) show raised protein [median 61, IQR (42–106) mg/dL], favoring intrathecal inflammation and possibility of meningitis and/or encephalitis. Although there were few cells in the CSF [2 (1–4)], in COVID-19 patients, atypical inflammatory response without CSF pleocytosis is not uncommon.3 Another possible explanation of not picking up any encephalitis or meningitis in the present study is the lesser number of brain MRI (15%) being performed. We are unable to understand the difference between stroke and hypoxic/ischemic brain injury because they were categorized separately in the current study!


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Author Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

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Neurology® 2021;96;549–550. doi:10.1212/WNL.0000000000011609

We appreciate the comments by Kumar et al. on our article.1 The referenced Kremer study2 was a retrospective case series and included patients with positive MRI findings only. It is unclear whether the patients with the diagnosis of “encephalitis” met diagnostic or causal criteria outlined by the International Encephalitis Consortium3 and others.4 Indeed, CSF SARS-CoV-2 RT-PCR was negative in 20 patients. In 2 of 3 with CSF pleocytosis (>5 cell/mm³), imaging was performed >2 weeks from symptom onset, possibly representing postinfectious autoimmune encephalitis and not infectious encephalitis. Many of the MRI findings described are nonspecific and can be seen in hypoxic/ischemic brain injury, metabolic encephalopathy, or postseizure. Notably, 100% of “encephalitis” patients required oxygen and 75% had ARDS, suggesting that a proportion of the MRI changes may represent hypoxic/ischemic injury (defined as a global insult due to hypoxemia, hypotension, or cardiac arrest). Although we detected elevated CSF protein in some patients,1 this is nonspecific and can be found in stroke, hemorrhage (or traumatic tap), hypoxic/ischemic injury, diabetes, uremia, tumor, neuropathy, and many other conditions. Because the implications of SARS-CoV-2 neurotropism are far reaching, we believe that it is critical to follow the most rigorous standards and criteria when ascribing encephalitis/meningitis/myelitis to SARS-CoV-2 infection.


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Reader Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Eric M. Liotta (Chicago), Ayush Batra (Chicago), and Igor J. Koralnik (Chicago)

Frontera et al. should be commended on the breadth of their report on neurologic diagnoses in COVID-19. Although stroke, seizure, GBS, encephalitis, and meningitis rates are similar to our recent study, and others, their rates of encephalopathy were markedly lower (6.9% vs 31.8%). This likely reflects their methodology of adjudicating diagnoses only from chart review of patients with neurologic consultation. Our study similarly included patients with confirmed SARS-CoV-2 RT PCR and ascribed diagnoses by neurologist adjudication. We recognized that delirium—an entity within the encephalopathy spectrum—is the purview of multiple specialties. As such, encephalopathy would not reliably result in neurologic consultation; we adjudicated all charts and leveraged protocolized delirium assessments. The methodology of Frontera et al. likely failed to identify many encephalopathic patients, limiting their estimation of neurologic morbidity. Nevertheless, encephalopathy remained the most frequent neurologic diagnosis. In addition, prematurely excluding headache as a “neurologic symptom” limits the scope and understanding of SARS-CoV-2 neuropathogenesis. As we determine optimal management and decipher the long-term consequences of COVID-19 and encephalopathy, study methodologies should consider that not all neurologic complications result in in-hospital neurologic consultation. Consistently, neurologic manifestations of COVID-19 are common and encephalopathy impacts morbidity. Interestingly, despite similar ventilation rates (26.3% vs 22.0%), our cohort’s hospital mortality was considerably lower (8.4% vs 21.4%). Although New York experienced a critical strain on hospital infrastructure early in the pandemic, our Chicago area hospital system never experienced the same overwhelming case surge. Taken together, Frontera et al. and our study may reflect the magnitude of public health benefit that could be realized by avoiding case volumes that overwhelm health care infrastructure. This should further emphasize the benefit of universal masking, social distancing, and building redundancy into health care infrastructure.

We appreciate these comments on our article.\(^1\) We coded toxic-metabolic encephalopathy only in patients off sedation or after an adequate sedation washout, in contrast to the Chicago study,\(^2\) which included patients who may have been receiving sedation or had a positive Confusion Assessment Method (CAM). Although sedation-related delirium has been associated with worse outcomes, the implications for long-term neurologic recovery differ based on the underlying etiologies of encephalopathy, which can best be ascertained when eliminating the confounding effect of sedative medications. Because a proportion of patients were too hypoxic for assessment off sedation, we recognize that we may be underestimating the overall prevalence of neurologic injury in the most critically ill patients. Similarly, hospitalized patients are often unable to express neurologic symptoms because of the severity of illness; hence, findings such as headache, anosmia, or dysgeusia are typically underrepresented and their prevalence is better studied in the outpatient setting. Although our cohort was somewhat older than the Chicago group—median age 65 vs 58 years—we agree that the critical surge and strain on resources in NYC likely impacted mortality rates, which were similarly high in other area hospitals during this time frame.\(^3,4\) Preventative efforts to stem such surges in hospitalizations—including masking and social distancing—are essential.

Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19

Neurology 2021;96:551
DOI 10.1212/WNL.0000000000011607

This information is current as of March 15, 2021

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