EDITORIAL

The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection

Neurologists Move to the Frontlines

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The global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has emerged as an unprecedented worldwide crisis in the early months of 2020, overwhelming health systems and challenging societies as we seek to contain its spread. In the tremendous flood of viral pneumonia cases and resultant life-threatening respiratory complications, the extent of potential neurologic manifestations of coronavirus disease 2019 (COVID-19) has remained unclear. In this issue of *JAMA Neurology*, a retrospective consecutive case series[1] of 214 patients from Wuhan, China, with either moderate or severe COVID-19 reports an early view of the incidence and types of neurologic complications and sets the stage for future longitudinal work in the area.

Related article

Prevalence of Neurologic Disease in SARS (SARS-CoV-1)

Severe acute respiratory syndrome (SARS) first appeared in China in late 2002, spreading to other areas in Asia in early 2003.[2] By April 2003, a new coronavirus, SARS-CoV (now SARS-CoV-1), was identified as the causative agent.[2] The typical clinical syndrome was a respiratory illness with severe lung injury and viral pneumonia, and there was a very high mortality in patients older than 65 years (approximately 50%).[2] Aggressive public health efforts, taking into the account the incubation period of 2 to 10 days and the relative lack of easy transmissibility, led to limitation of the original outbreak and successful containment of the virus.[2] We now know that SARS is similar in many ways clinically to COVID-19, which is caused by a very related coronavirus (SARS-CoV-2). However, the key apparent differences are dramatically increased infectivity and perhaps somewhat reduced lethality, elements that have been major drivers of the global pandemic.[3]

Although the SARS epidemic was limited to about 8000 patients worldwide, there were some limited reports of neurologic complications of SARS that appeared in patients 2 to 3 weeks into the course of the illness, mainly consisting of either an axonal peripheral neuropathy or a myopathy with elevated creatinine kinase.[4] At the time, it was unclear whether some of these manifestations might be owing to critical illness-related effects,[5] but pathology subsequently showed that patients with SARS had widespread vasculitis seen in many organs, including striated muscle,[6] suggesting that the clinical features in these neuromuscular patients might be more than just nonspecific complications of severe illness. Interestingly, there was a single report of a patient with SARS with olfactory neuropathy with onset 3 weeks into the illness.[7]

In addition to these peripheral syndromes, 5 of 206 patients with SARS in Singapore developed large-vessel strokes. Four of these patients had their strokes in the setting of critical illness owing to SARS, and 3 were associated with significant episodes of hypotension.

Prevalence and Timing of COVID-19 Neurologic Symptoms in Disease Course

In light of the sparse history of neurologic manifestations of SARS-CoV-1–associated disease, the report by Mao et al[1] is important. In these 214 patients, they report 36.4% had some nervous system–related clinical finding.[1] These neurologic manifestations ranged from fairly specific symptoms (eg, loss of sense of smell or taste, myopathy, and stroke) to more nonspecific symptoms (eg, headache, depressed level of consciousness, dizziness, or seizure).[1] Whether these more nonspecific symptoms are manifestations of the disease itself or consistent with a systemic inflammatory response in patients who were quite ill will need to be defined in future studies. Importantly, the authors found that patients in their series with some of the more common specific symptoms, including smell or taste impairment and myopathy, tended to have these symptoms early in their clinical course; this appears to be quite distinct from SARS, where manifestations appeared quite late in established disease. A report[8] of viral infiltration of the brainstem in a very limited number of pathologic specimens also raises the possibility that some of the crucial pathophysiology behind respiratory failure may be owing to central nervous system pathology, further expanding the view of which clinical manifestations of the current pandemic are truly neurologic in nature.

Most Stroke and Depressed Level of Consciousness Occurs Later and in More Severe Disease

Mao et al[1] also found that neurologic symptoms were more common in patients with more severe disease (30.2% in nonsevere patients and 45.5% in severe patients). As has commonly been the case, they defined the severity based on respiratory features, defining mild as not requiring respiratory intervention, moderate as requiring some respiratory support, and severe as requiring mechanical ventilation. The more dramatic neurologic symptoms, such as stroke, ataxia, seizure, and depressed level of consciousness, all were more common in severely affected patients, accounting for the increased incidence in these patients.[1] However, these associations should be considered in light of our understanding that

patients with severe complications from SARS-COV-2 are more likely to have medical comorbidities, especially vascular risk factors such as hypertension.[9] The occurrence of cerebrovascular events in critically ill patients with underlying high blood pressure and cardiovascular disease is therefore potentially unrelated to a direct effect of the infection itself or an inappropriate host response.

Continued Surveillance for Other Acute or Postinfectious Conditions and Challenges

The finding that many patients presented early with neurologic symptoms, such as anosmia, ageusia, and myopathy, along with less severe respiratory symptoms suggests that neurologists may be confronted by patients presenting with new-onset neurologic symptoms and should be potentially concerned that these could be owing to COVID-19. Reports have emphasized anosmia as a common early feature of COVID-19 illness, as in many upper respiratory tract infections,[10] although with COVID 19, many patients have loss of sense of smell without congestion.

The aforementioned previous studies that demonstrated axonal neuropathy in a small number of patients with SARS raise questions of whether this will likewise be the case in COVID-19. Unfortunately, the series by Mao et al[1] was unable to shed clear light on these questions because the authors were unable to pursue detailed electromyography/nerve conduction studies or lumbar puncture in their patients owing to concerns about the pandemic and highly infectious nature of COVID-19. The authors did report nerve pain in 4 of the severely affected patients, and myopathy was also more common in severe patients. Given the likely shared vasculitic pathology of SARS and COVID-19, it seems probable that further studies will reveal neuropathy as another rare finding in COVID-19.

Coronavirus disease 2019 has now reached pandemic status and is common all over the world; thus, with so many affected patients, we can expect as neurologists to be confronted with these patients commonly in coming months and years. It is clear that this small series does not reflect the entire spectrum of neurologic disease in COVID-19 disease, and much is left to be learned with thorough neurologic testing in large data sets of patients with COVID-19. As the means for reliably assessing infection and prior exposure become available, less common neurologic complications should be anticipated; however, this glimpse into neurologic manifestations opens a window into neurologists' role and places them on the front lines of the pandemic.

ARTICLE INFORMATION

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