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SPECIAL ISSUE: EFFECTS OF COVID-19 ON THE NERVOUS SYSTEM

ABSTRACT & COMMENTARY

Neurologic Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China

By Alexander E. Merkler, MD

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Dr. Merkler reports he receives grant/research support from the American Heart Association and is a consultant for Medicolegal.

SYNOPSIS: Neurological symptoms and impairments have been found in one-third of hospitalized patients with COVID-19 from countries that have reported these observations so far. This is a rapidly evolving consequence of SARS-CoV-2 infection.

SOURCE: Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with coronarvirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; April 10. doi: 10.1001/jamaneurol.2020/1127. [Online ahead of print].

The world currently is under siege by coronavirus disease 2019 (COVID-19). Since December 2019, COVID-19 has affected more than 4 million people and caused more than 300,000 deaths worldwide. Although the most common manifestations of COVID-19 include fever, cough, and shortness of breath, this study by Mao et al is the first to report the frequency of neurological symptoms in hospitalized patients with COVID-19. In this retrospective, observational study performed at three centers in Wuhan, China, the authors studied the frequency and characteristics of neurological symptoms in hospitalized patients with COVID-19 infection between Jan. 16 and Feb. 19, 2020. For each subject, neurological symptoms were reviewed and confirmed by two trained neurologists, with a third resolving any disagreements.

The authors categorized neurological symptoms of COVID-19 into three categories: central nervous system (dizziness, headache, impaired consciousness, stroke, ataxia, seizures), peripheral nervous system

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(taste or olfactory impairment, vision impairment, and nerve pain), and skeletal muscular injury. Among 214 hospitalized patients, 78 (36.4%) had neurological symptoms; 53 (24.8%) originated from the central nervous system, 19 (8.9%) from the peripheral nervous system, and 23 (10.7%) were skeletal muscular injury. Dizziness (16.8%) and headache (13.1%) were the most common neurological symptoms. Taste and olfactory impairment occurred in 5.6% and 5.1%, respectively. Most neurological symptoms occurred early in the illness (median time one to two days). Neurological symptoms were more common in patients who had severe respiratory disease vs. non-severe respiratory disease (45.5% vs. 30.2%) and in those with lower lymphocyte and platelet counts. Six (2.8%) patients had a stroke. Stroke was the initial presenting complaint in two of the six patients with stroke, and these patients had an absence of typical respiratory manifestations of COVID-19 (fever, cough, diarrhea), although they had typical computed tomography chest findings of COVID-19.

■ COMMENTARY

Neurological symptoms appear to be common in patients with COVID-19, occurring in more than one-third of hospitalized patients. Taste and olfactory loss occurred in 5% of patients, and other reports suggest that impairments in these modalities are common and often seen in milder cases of COVID-19 disease that do not require hospitalization.[1] Stroke occurred in 2.8% of hospitalized patients with COVID-19 and, interestingly, consistent with another report, often was the initial presenting symptom of COVID-19.[2] Stroke mainly occurred in patients with severe COVID-19 infection, which is consistent with another study that found evidence of stroke in 3/13, or 13% of patients with severe COVID-19 infection.[3]

The mechanisms underpinning these neurological symptoms remain unclear. As with other viral infections (such as influenza) inflammation, hypercoagulability, and endothelial injury likely increase the risk of stroke. In addition, many patients hospitalized with severe COVID-19 infection are systemically ill, often requiring mechanical ventilation and developing other risk factors for stroke, such as atrial fibrillation. Loss of olfaction may suggest that the olfactory epithelium could serve as a nose-brain entrance path for the virus, but this remains to be confirmed, and most patients with decreased sense of smell do not develop severe neurological consequences, such as stroke.[4]

Taken together, the neurological symptoms among hospitalized patients with COVID-19 not only are common but may be the sole presenting feature in the disease. The rate of neurological symptoms among people who do not require hospitalization with COVID-19 is uncertain, but clinicians should consider COVID-19 as an etiology of new neurological symptoms, especially in patients with acute onset loss of taste or smell. ■

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ABSTRACT & COMMENTARY

The Effect of Coronaviruses on the Central Nervous System

By Ulrike W. Kaunzner, MD

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Dr. Kaunzner reports no financial relationships relevant to this field of study.

SYNOPSIS: Known coronaviruses (CoV) can enter the central nervous system by different pathophysiologic mechanisms. Neurological presentations linked to the novel SARS-CoV-2 include encephalopathy, encephalitis, cranial neuropathies, Guillain-Barré syndrome and other neuropathies, and ischemic and hemorrhagic strokes.

SOURCES: Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun* 2020; March 30. doi: 10.1016/j.bbi.2020.03.031. [Online ahead of print].

Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immun* 2020; April 10. doi: 10.1016/j.bbi.2020.04.017. [Online ahead of print].

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), a single-stranded ribonucleic acid (RNA) virus, which is the seventh known coronavirus. Typical presentation includes respiratory and systemic symptoms. However, a significant percentage of COVID-19 patients have neurological symptoms, including headache, anosmia, paresthesia, altered mental status (AMS), stroke, and encephalitis. The study by Wu et al discusses different peripheral and central nervous system (CNS) diseases that have been linked to well-studied coronavirus infections in the past. SARS-CoV, which caused SARS in 2003, has been associated with encephalitis, polyneuropathy, and strokes. Middle East respiratory syndrome (MERS), caused by MERS-CoV, also can lead to neurological symptoms, such as stroke, AMS, Guillain-Barré syndrome (GBS), and other neuropathy occurring two to three weeks after the initial respiratory presentation.

The pathophysiologic mechanisms of known coronaviruses affecting the CNS include direct entrance of the virus into the brain, which can occur either via an opening of the blood-brain barrier, or anterograde or retrograde neuronal transport. Angiotensin-converting enzyme 2 (ACE2) receptors on neuronal surfaces and capillary endothelium have been described as targets for different viruses in the past, including coronaviruses, and can be a potential entrance for SARS-CoV-2. Decreased oxygenation from lung infection, causing hypoxic changes in the brain and affecting mitochondria, may lead to anaerobic metabolism and cerebral edema. And activation of the immune system may lead to systemic inflammation affecting the brain or causing direct activation of residential CNS immune and glia cells. The case report by Ye et al describes a patient who presented with typical symptoms of COVID-19, including fever, shortness of breath, and myalgia, and tested positive for SARS-CoV-2. He developed confusion, and cerebrospinal fluid (CSF) analysis was negative for SARS-CoV-2 RNA as well as CSF immunoglobulin M (IgM) and immunoglobulin G (IgG) for SARS-CoV-2. The authors concluded that the patient had COVID-19-related encephalitis and, given the negative polymerase chain reaction (PCR) and serological titers, the presentation might have been related to the immune response. The patient improved with mannitol and supportive measures, returned to his baseline, and eventually was discharged.

■ COMMENTARY

These publications increased awareness of COVID-19-associated CNS disease at an early stage of the COVID-19 pandemic. The review of coronavirus-related pathophysiology is important, since it facilitates the understanding of possible CNS entry routes and disease mechanisms associated with SARS-CoV-2. As the pandemic emerges, new neurological disorders are being observed, such as ataxia, seizures, venous sinus thrombosis, Miller-Fisher syndrome, GBS, and cerebral hemorrhage. Knowledge of CNS involvement of coronaviruses is important.

The case of encephalitis highlights the fact that neither PCR nor serological testing were able to detect SARS-CoV-2 in CSF. The authors commented that bacterial infection and tuberculosis were ruled out, and it would be useful to know that other CSF viral panels were tested as well. The CSF profile does not show a classic pattern of infection, and the authors concluded that an immune/inflammatory response was the most likely etiology.

When this case report was published, only a few cases of encephalitis had been described. However, there now is increasing evidence that SARS-CoV-2 can cause meningitis and encephalitis, and some cases show the presence of viral RNA. These different cases demonstrate that encephalopathy or encephalitis needs to be considered in the presence or absence of SARS-CoV-2 in the CSF. However, whether mechanisms other than direct infection or inflammation contribute to an encephalitis-like picture also needs to be established. Fortunately, only a small number of COVID-19 patients have presented with encephalitis so far. However, many patients have prolonged encephalopathy, and more data are needed. Since viral clearance from the CNS is dependent on T-cells and neuronal apoptosis, as Wu and colleagues discussed, it will be important to see if patients with proven CNS involvement will have long-term sequelae or secondary inflammatory response from their infection.

Overall, establishing the extent of neurological symptoms associated with COVID-19 will be essential to determine if these symptoms are directly related to virus infection or secondary to other immune mechanisms. CSF analysis and autopsy data will show the range of neurotropism of SARS-CoV-2 and inflammatory

response. CNS disease also has been considered an indicator of poor prognosis. Therefore, early recognition and treatment will be important. Documentation of neurological symptoms, close follow-up of respective cohorts, and comprehensive clinical databases will help to assess for the prevalence of neurological diseases in COVID-19 patients. ■

ABSTRACT & COMMENTARY

Guillain-Barré, Miller Fisher Syndrome, and Associated Disorders in Patients with COVID-19

By Alan Z. Segal, MD

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Dr. Segal reports no financial relationships relevant to this field of study.

SYNOPSIS: As the COVID-19 pandemic grows and spreads around the world, investigators in multiple countries are reporting patients with myriad cranial and peripheral nerve disorders that have some, but not all, features of Guillain-Barré syndrome.

SOURCE: Zhao H, Shen D, Zhou H, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: Causality or coincidence? *Lancet Neurol* 2020;19:383-384.

Guillain-Barré syndrome (GBS) is an autoimmune neuropathy, seen following infections, most classically gastroenteritis from *Campylobacter jejuni*. It also has followed outbreaks of other infectious diseases, such as Zika virus, influenza, and, more rarely, the influenza vaccine. With the onset of the COVID-19 pandemic, it was not unexpected that a flurry of GBS would follow. This review highlights the earliest published reports of GBS and associated syndromes, such as Miller Fisher syndrome (MFS), related to SARS-CoV-2 infection.

In the first reported case, on Jan. 23, 2020, a middle-aged woman in Shanghai (who had just returned from Wuhan) was diagnosed with GBS after presenting with acute weakness in both legs and severe fatigue. She had mild initial weakness, which progressed to 3/5 in the legs and 4/5 in the arms, with areflexia and an elevated cerebrospinal fluid (CSF) protein, without cells. Nerve conduction studies revealed a demyelinating neuropathy. A complete blood count showed depressed lymphocyte and platelet counts. Of note, these hematological findings subsequently have been determined to be more prevalent in COVID-19 patients with neurological complications compared to those without. Eight days into GBS illness, this first Chinese patient developed symptoms of a viral upper respiratory tract infection, with subsequent ground glass lung opacities and a positive nasal SARS-CoV-2 swab. She was treated with intravenous immunoglobulin (IVIG) and fully recovered from both COVID and GBS within two to three weeks.

Further reports from the next epicenter of COVID-19 (Northern Italy) detailed a series of five cases of GBS. Lower extremity weakness was the first symptom in four of these patients, with one showing facial diplegia and ataxia. The interval between COVID-19 onset and GBS ranged from five to 10 days. All patients showed an absence of CSF white blood cells, with three of the five showing increased protein. None of the patients had positive CSF polymerase chain reaction (PCR) for SARS-Co-V-2. Electrophysiological studies were notable for low compound muscle action potential (CMAP) amplitude, with prolonged distal latencies and significant muscle fibrillation responses. There was no dysautonomia. The GBS was classified as an axonal variant in three patients and demyelinating in two. Treatments included IVIG, with a subset of patients requiring repeat IVIG and/or plasmapheresis. Magnetic resonance imaging (MRI) showed enhancement of caudal spinal nerve roots in two of the four patients who had a primarily lower extremity presentation, and a unilaterally enhancing facial nerve in the patient with diplegia. The authors could not draw any conclusions regarding GBS-related respiratory failure, but they hypothesized that this would be suggested when overall respiratory deficiencies outweighed pulmonary disease as defined by chest imaging.[1]

Neuro-ophthalmological presentations were the focus of additional reports made by groups in Spain and New York City (including my own institution, New York-Presbyterian, Weill Cornell Medical College). The first Spanish patient was characterized as having a variant of MFS, while the second patient was alternatively diagnosed as "polyneuritis cranialis." Neurological findings in case one included anosmia, ageusia, a right internuclear ophthalmoplegia (INO), a partial right third nerve palsy, ataxia, and areflexia. Testing for anti-

GQ1b antibodies (typically associated with MFS) was negative, but there was a positive titer of anti-GD1b antibodies. The second case also had ageusia, along with bilateral abducens palsies, ataxia, and areflexia. Both patients had cytoalbuminologic dissociation in CSF. The first patient received IVIG, while the second was stable enough to be sent home for observation without treatment. The time lag from COVID-19 symptoms to onset of neurological deficits was three to five days, which is similar to the Italian report.[2]

In contrast to the Spanish patients, the two New York City patients were not diagnosed with MFS or polyneuritis specifically, but rather with multiple cranial neuropathies — a less speculative, conservative characterization. The first patient, who had a history of infantile strabismus, presented with left ptosis, diplopia, and bilateral distal leg paresthesias. Formal cranial nerve examination showed a partial third nerve palsy and bilateral sixth nerve weakness along with ataxia and hyporeflexia. Peripheral lymphocytes were significantly depleted, with an absolute count of 900/ml. The second patient had diplopia with complete right abducens palsy. MRI findings included gadolinium enhancement of the oculomotor nerve in case one and of the optic nerve sheaths in case two. As in previous reports, there was an approximately three- to five-day lag between the onset of viral symptoms (cough, fever, and myalgias) and the first neurological findings.[3]

■ COMMENTARY

The spectrum of CNS disease in COVID-19 includes stroke and encephalitis, often with necrotizing and hemorrhagic components. Given the prominent symptoms of anosmia and dysgeusia, it is thought that the olfactory bulb may serve as a portal of entry for the virus into the nervous system. Although not a consistent finding, sporadic cases with positive SARS-CoV-2 in CSF have been identified.

Taking another perspective, the cases in this review focus on manifestations of COVID primarily affecting the peripheral nervous system. Ascending paralysis with neuropathy has been highly suggestive of GBS, while cranial nerve abnormalities have raised a question of MFS or a less well defined "neuritic" syndrome. Given the limited case numbers described here, more questions are raised than are actually answered.

Do these syndromes reflect the typical post-infectious disorder of GBS, which may lag behind viral infection by many days or even a few weeks? Or does the nearly simultaneous onset of both COVID-19 and the GBS-like syndromes described here suggest that there is more of a "para-infectious" effect? Nerves may be directly infected with the virus or perhaps nerves are bystanders, injured as a consequence of the profound immune reaction and marked inflammatory state in severe COVID cases.

With so few cases, finding a set of clinical features that identify a unique signature of COVID-related neuropathy is difficult. Although typical GBS is demyelinating more often than axonal, it appears that this may be the reverse in COVID. The likelihood of the most protean GBS outcomes, such as autonomic instability or neuromuscular respiratory failure, also remains unclear. In addition, the cases reported here may not be purely peripheral, but rather may have central findings mixed in.

[Nerves may be directly infected with the virus or perhaps nerves are bystanders, injured as a consequence of the profound immune reaction and marked inflammatory state in severe COVID-19 cases.]

The INO in the first Spanish case would be atypical for MFS, and the optic nerve leptomeningeal enhancement in the second New York City patient had no clinical correlate. Although the finding of typical cytoalbuminologic dissociation was common, none of the cases here showed a positive CSF PCR for SARS-CoV-2. Anti-ganglioside antibodies, which are a frequent but not invariable finding in sporadic GBS and imply an autoimmune process, were very rare here. There was only one positive result, but about half of the patients went untested.

Tremendous uncertainty persists regarding the natural history of SARS-CoV-2 and its ongoing pandemic. With the likely accumulation of massive cohorts of COVID patients, larger series of GBS, MFS, and other associated syndromes are sure to follow. ■

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ABSTRACT & COMMENTARY

Two Possible Mechanisms of Disease in COVID-19

By Neal S. Parikh, MD, MS

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Dr. Parikh reports no financial relationships related to this field of study.

SYNOPSIS: COVID-19 infection may be associated with an increased risk of blood clotting and related thrombotic events, but there are insufficient data to support indiscriminately discontinuing medications that play a critical role in the management of chronic cardiovascular disease.

SOURCES: Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020;382:e38.

Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med* 2020; May 1. doi: 10.1056/NEJMoa2007621. [Online ahead of print].

COVID-19 infection has taken the world by storm. The first few months of the pandemic have been met by a powerful demonstration of insightful clinical investigation. Clinicians quickly noticed that patients with COVID-19 infection appear to face an increased risk of cardiovascular events and high rates of mortality, and researchers are striving to understand precisely why this is the case.

Even before clinicians had accrued sufficient COVID-19 patient care experience, investigators were aware of the virus's biology. Early in the pandemic, it was known that COVID-19 gains entry into the human body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. Angiotensin-converting enzyme 1 is the site of action of a commonly used drug class, namely angiotensin-converting enzyme inhibitors (ACE inhibitors). ACE1 and ACE2 are involved in a complex feedback loop. On this basis, it was hypothesized that the use of ACE inhibitors, and the related drug class of angiotensin receptor blockers (ARBs), may increase the expression of ACE2, thereby increasing the entry of COVID-19 into the lungs. This gave rise to the concern that the use of ACE inhibitors and ARBs may increase the severity of COVID-19. At the population level, indiscriminate cessation of these drugs would lead to uncontrolled hypertension, heart failure, and other unintended consequences. Thus, understanding whether these commonly used drugs truly contribute to mortality in COVID-19 demanded investigation.

Mehra and colleagues sought to address this critical question. In a remarkable feat, considering the short period between the first case of COVID-19 and the publication of their manuscript, the authors performed a large, multicenter, observational study using data from 169 hospitals. They tabulated patients' demographics and comorbidities in addition to their medication history. Then, they performed multivariable regression analyses to evaluate whether the use of ACE inhibitors or ARBs was associated with an independently increased risk of in-hospital mortality. Of 8,910 hospitalized patients, 515 (6%) died in the hospital. Patients who died were older and had a higher burden of coexisting conditions, such as heart disease, diabetes, and pulmonary disease.

In their statistical models, older age and heart disease were independently associated with in-hospital mortality, but use of ACE inhibitors and ARBs was not. In fact, ACE inhibitors may have been protective. The authors appropriately noted that they made many statistical comparisons, and their data are retrospective, so it is not justified to conclude that ACE inhibitors are truly protective. However, their data do allay concerns about the safety of these medications in COVID-19.

As clinicians see more cases of COVID-19, they begin to accumulate observations that inform additional hypotheses to explain why this virus dramatically increases the risk of thrombotic events and death. Doctors caring for patients with COVID-19 began to notice a high rate of blood clotting in their patients. To explain this, they investigated whether COVID-19 infection results in antiphospholipid antibody production, which is characteristic of its namesake, sometimes-catastrophic, blood clotting disorder. Provocatively, Zhang and colleagues reported three cases of patients with COVID-19 with positive antibodies. Whether COVID-19 induces a prothrombotic state, and the optimal management of this condition requires further work.

■ COMMENTARY

COVID-19 clinical investigation sets the bar for clinical research. Physicians and investigators have promptly identified and answered critical questions with robust

methods, without neglecting pathophysiology or underestimating the value of empiric clinical observation. Taken together, the data discussed herein demonstrate that COVID-19 is associated with a high rate of in-hospital mortality, but that ACE inhibitors and ARBs likely should not be discontinued, and certainly not in the population at large. Meanwhile, there are emerging data that COVID-19 may, as is the case with other infections, result in a prothrombotic state linked to the generation of antiphospholipid antibodies. If confirmed, future work surely will investigate antithrombotic regimens and perhaps therapies to quell the production of these antibodies. Apart from prevention and mitigation of infection, therapies to prevent complications of COVID-19 are needed urgently. ■

ABSTRACT & COMMENTARY

Expansion and Versatility of Telemedicine During the COVID-19 Pandemic

By Saad A. Mir, MD

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Dr. Mir reports no financial relationships relevant to this field of study.

SYNOPSIS: Telemedicine has rapidly transformed healthcare delivery during the COVID-19 pandemic, but innovative reimbursement models and updated privacy regulations are needed to ensure widespread implementation of high-quality digital care.

SOURCES: Keesara S, Jonas A, Schulman K. Covid-19 and health care's digital revolution. *N Engl J Med* 2020; April 2. doi: 10.1056/NEJMp2005835. [Online ahead of print].

Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med* 2020;382:1679-1681.

COVID-19 has changed healthcare dramatically. Hospitals have converted emergency rooms, operating rooms, and stepdown units into ventilator-capable intensive care beds. Nurses, respiratory therapists, medical students, and physicians have been redeployed within hospital systems to accommodate the surge in ventilated patients. Overwhelmed hospitals graciously have welcomed volunteer care providers who have been granted state-mandated emergency privileges. Aside from brick-and-mortar transformations, hospitals and care providers also have leveraged telemedicine as a vital tool to increase access to care, maintain social distancing among patients and providers, and allow non-COVID patients to maintain essential outpatient management.

In their perspective piece, Keesara et al discuss how telemedicine can reduce the inflexibility of an analog healthcare system during pandemics. However, for telemedicine expansion to be successful, a unified strategy that addresses reimbursement, regulatory relief, and quality of care evaluation must be created. Scarce telemedicine payment structures and the limiting of Medicare reimbursement to rural areas historically have led to poor adoption.

As a response to the pandemic, Congress allowed telemedicine reimbursement for all Medicare patients regardless of geography. However, further reimbursement models need to be created to address novel methods of telemedicine, technical fees to support infrastructure, and innovative care models, such as "hospital-at-home care." With consistent and broad reimbursement structures, regulatory relief would be needed, since 94% of hospital systems cite privacy concerns and penalties as limiting factors in telemedicine implementation.

During the pandemic, the Department of Health and Human Services (HHS) has agreed to waive any penalties for using non-Health Insurance Portability and Accountability Act compliant means of telemedicine. New definitions of security need to be created, since technology advances far faster than the laws created decades ago. One solution would be for HHS to allow the use of commercially available encrypted telemedicine services. Ultimately, studies will be needed to quantify how telemedicine strategies affect quality and cost of care.

In a similar perspective, Hollander and Carr describe a variety of telemedicine initiatives that are being implemented across the United States. These interventions are being used in prehospital, inpatient, and outpatient settings. Patients at home can have paramedic visits with telemedicine physician evaluations to prevent unnecessary visits to hospitals, as has been done successfully by Houston's ETHAN project.

Another model being used at more than 50 hospital systems is a "forward triage" model in which patients at home can be evaluated, treated, and monitored

for COVID-19 symptoms and recovery. Similarly, chat bots are being used to triage patients to testing facilities or escalate them to a care provider. If testing limitations could be addressed, widespread implementation of telemedicine chat bots, forward triage, or paramedic evaluations could reduce the burden on hospital systems significantly. Within hospitals, emergency room telemedicine triage allows providers to cover many areas while maintaining their safety. Disinfected tablets can be given to patients to allow communication with care teams or with family members. For outpatients, many centers have converted routine clinic visits to be done solely via telemedicine. All of these interventions allow providers to expand their availability to multiple care settings, as well as to continue to provide care if they happen to be quarantined.

■ COMMENTARY

Telemedicine is well positioned to alleviate the challenges associated with the current COVID-19 pandemic, while also disrupting traditional paradigms of healthcare moving forward. Many hospitals have expanded existing telemedicine capabilities. At our own institution, New York-Presbyterian Hospital, we have implemented forward triage, increased inpatient telemedicine consults, launched tablet-based communication with inpatients, moved primarily to outpatient telemedicine visits, increased remote patient monitoring to track patients' vitals at home, and are establishing electronic intensive care unit monitoring. For these models to maintain quality care beyond the pandemic, reimbursement structures and government regulation need sweeping modernization to meet the rapid innovations in healthcare. ■

CME QUESTIONS

1. **A 65-year-old man presents with one to two days of anorexia and fatigue followed by acute sudden onset left hemiparesis. He denies cough, fever, or shortness of breath. His vital signs are normal. Which statement is most accurate?**
   a. Stroke can be an initial manifestation of COVID-19, and most patients with stroke will have non-severe respiratory disease.
   b. Stroke can be an initial manifestation of COVID-19, and most patients with stroke will have severe respiratory disease.
   c. Stroke can be an initial manifestation of COVID-19 without any other symptoms.
   d. Stroke occurs as a late manifestation of COVID-19.
2. **At this early time in the pandemic, SARS-CoV-2 infection has been associated with:**
   a. encephalitis.
   b. Guillain-Barré syndrome.
   c. altered mental status and coma.
   d. all of the above
3. **Cases of COVID-19 with cranial and peripheral nervous system findings show which of the following features?**
   a. All of the cases were the demyelinating form of Guillain-Barré syndrome (GBS).
   b. Many cases had positive tests for cerebrospinal fluid (CSF) polymerase chain reaction for SARS-CoV-2 in the CSF.
   c. Depressed lymphocyte and platelet counts are common in COVID-19 patients.
   d. Cases of GBS occurred several weeks after acute SARS-CoV-2 virus infection.
4. **Should angiotensin-converting enzyme inhibitors and angiotensin receptor blockers be discontinued, in light of the COVID-19 pandemic?**
   a. Yes, in all patients, regardless of COVID-19 infection status
   b. Yes, in all patients deemed to be at high risk of COVID-19 infection
   c. Yes, in patients with COVID-19 infection
   d. No, there are observational data that did not demonstrate harm.
5. **What has been identified as the major limiting factor for U.S. healthcare systems to implement telemedicine strategies?**
   a. Poor reimbursement
   b. Fear regarding privacy regulations and data protection
   c. High cost of maintenance
   d. Care provider resistance

[IN FUTURE ISSUES]

Stroke Alert