What Neurologists Can Expect From COVID-19

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Like all healthcare workers dealing with the COVID-19 pandemic, neurologists are having to learn about the disease's various manifestations and complications while simultaneously implementing necessary but highly disruptive new policies at their practices and universities. Medscape recently spoke with central nervous system infection specialist and chair of University of Colorado's neurology department, Dr Kenneth Tyler, about what implications the new coronavirus could have on patients and practice.

How often are coronaviruses characterized by neurologic components?
The good news seems to be that the experience with both severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), and with what we've seen so far with COVID-19—although it's changing every day—is that the neurologic components are obviously not the major focus, which of course are predominantly pulmonary. That said, rare cases of SARS and MERS ended up having significant neurologic complications, so we could see something similar with COVID-19.
With any serious infection that can potentially result in major and multiple organ system dysfunction and failure, or disseminated intravascular coagulation and sepsis, almost by definition those patients are at risk of having what I would call indirect neurologic complications. We've already seen early reports with this infection that there's a subset of patients at risk for vascular events, including both ischemic and hemorrhagic strokes and things of that nature. It's not

surprising to see that the incidence of these is in direct proportion to COVID-19 disease severity, but we need to follow this further.
A paper published on the preprint server medRxiv outlined the initial experience from three of the dedicated coronavirus disease hospitals in Wuhan. By definition, they were looking at patients who were ill enough to be hospitalized. About 60% of that group had milder infection and 40% had more severe infection within the spectrum of hospitalized cases. The neurologic complications that they described were significantly more frequent in the subgroup with more severe disease.

Can you elaborate on the specific neurologic complications that may occur with COVID-19?
Like everything else, we're instructed by past experiences. Although there weren't a lot of data on neurologic aspects of MERS and SARS, there were some papers describing neurologic complications in those patients. In rare cases, complications including ADEM (acute disseminated encephalomyelitis)-like demyelination, encephalitis, and brainstem encephalitis were reported. They also saw some peripheral and non–central nervous system stuff, including things that looked like Guillain-Barré syndrome or what they would sometimes call critical illness polyneuropathy. What everybody's probably wondering about is whether we are going to see direct viral infection and injury of the nervous system.

In the paper I mentioned earlier, of 214 people studied, around 37% had neurologic manifestations, including nearly 50% of those with severe COVID-19 infections. The authors described alterations in mental status in 15% of severe cases and nonspecific symptoms, including headache and dizziness, in nearly 20% of cases. Another common finding was referred to as "skeletal muscle injury" (CPK > 200 IU/mL), seen in approximately 20% of severe cases but unfortunately not really described in terms of whether there were clinical manifestations suggesting myositis or myopathy, or even motor neuron injury. Some recent reports have suggested that loss of sense of smell or taste may also be clues to COVID-19 disease, and neurologists may be the ones who pick up on that during examination or history-taking.
Based on prior experience, those would be the kinds of things that would give us some potential clues.

As new data emerge on the neurologic implications of COVID-19, what do you expect to see?
Things are going to change as more cases and data accumulate. I do think they will continue to show that the neurologic complications are going to be more common in the more severely affected patients. These complications may fall into a spectrum, with altered mental status and perhaps acute cerebrovascular disease—things like that.
What everybody's probably wondering about is whether we are going to see direct viral infection and injury of the nervous system. If you look at all of the neurologic complications reported with MERS and SARS, direct evidence of viral infection in the nervous system was rare. But as I remember, there was one SARS patient who was reported to have a positive reverse transcription

polymerase chain reaction (PCR) for the virus and who died, and did have evidence of virus in the brain.
We know from looking at other nonhuman coronaviruses that they are capable of being neurotropic. I think it will be interesting to see whether a part of the neurologic spectrum of COVID-19 is in fact attributable to direct viral injury, from which the clues would presumably be detection of viral nucleic acid in CSF by RT-PCR; or if a patient dies, that we detect viral antigen, nucleic acid, or particles in the brain. We may also develop tests to measure intrathecal synthesis of antiviral antibodies as another clue to CNS invasion if it occurs.
That's certainly plausible, but I suspect just from what we've been reading that altered mental status and other neurologic symptoms are much more likely to be secondary to the infection.

How could COVID-19 interfere with immunomodulating therapies for conditions like multiple sclerosis (MS)?
It's a good question. One of the things we're always grappling with these different viral infections is, what is the major component or components of the immune system that are responsible for protection against infection and clearance of virus once infection occurs? Obviously the goal is to avoid, whenever feasible, weakening the very parts of the immune system that our patients need to fight off infection. Unfortunately, we are still learning about all of this for COVID-19, so it's unclear what changes to advise at the moment. I would say that therapies such as natalizumab in treatment of MS, or drugs that act to inhibit emigration of T cells into the CNS, are unlikely to increase risk for COVID-19 disease.
Conversely, the thing that's a little bit tricky here is that the really severe cases, and many of the fatal ones, seem to be due to acute respiratory distress syndrome (ARDS). That may be an example where the disease is in part immunopathogenic, meaning that it's actually part of a host of inflammatory response induced by the virus that also causes tissue injury. That could mean proinflammatory cytokines, a cytokine storm, or inflammatory cell infiltrates that can actually be triggered by the infection and that are causing a component of the damage.

In this case, you'd like to knock out a part of the immune system that is doing harm. So, as discussed above, if we learn that the antibody response is critical in protection against COVID-19, we would avoid drugs that blunt host antibody responses. Conversely, if it's the T-cell responses that are critical, we'd avoid drugs that blunted T-cell responses, etc. Unfortunately, we don't yet have enough evidence in this area, and as noted, it may be tricky because the host response may help fight against virus in many cases but contribute to certain forms of severe lung injury in others.
There are also ongoing clinical trials [looking at immunomodulators], both here in the United States and in China, which is a little bit ahead of us in this regard. Among the therapies being considered in different populations of COVID-19 patients are drugs that inhibit proinflammatory cytokines, like IL-6, and sphingosine-phosphate inhibitors, like fingolimod.

As a general first-level reaction, we probably want to be very careful with people who are immunocompromised, who we think are likely at an increased risk for severe infection. Then as we get a little bit smarter about this, we may be able to say that certain types of immunomodulatory drugs are less problematic, in terms of putting or keeping a patient on it, depending on how the timeframe of the epidemic plays out.
And interestingly, some of those therapies may find a repurposing role, if we understand this later component or the subset of patients who seem to move into ARDS.

How has this impacted neurology care at your center and how you see patients?
Of course, we first tried to do everything to make sure that inpatient beds are potentially available if we get an influx of patients. We basically canceled things like elective epilepsy monitoring unit admissions so that those patients won't be in beds.
On the outpatient side, we're already engaged in components of telehealth. We had a very active telestroke service prior to COVID-19 and were already rapidly ramping up virtual visits in neurology through teleneurology. We've been ramping that up like mad so that the doctors can do visits remotely, and we're expanding those to new patient visits. Unfortunately, regular diseases don't go away during a pandemic. If we can find a way to get our patients care without forcing them to potentially expose themselves or healthcare providers to COVID-19, that's a win for everyone.
We have a number of protocols to try to limit doctor and patient interactions, essentially asking whether we can just send one healthcare provider in, unless it's absolutely necessary to have more. And we've also been trying to marshal our forces so that, in the event that providers are exposed or develop symptoms, you have a group of people who are effectively doing everything from home who can fill in if somebody goes down.
Like virtually every center that I'm aware of, we're all emailing back and forth and trying to share best practices. We have regular teleconferences to see what's happening in the inpatient and outpatient services, what the impact is on residents and fellows.
We've also, of course, tried to eliminate as many procedures as possible. We're not surgeons, but neurologists are obviously required to perform everything from nerve blocks and Botox injections to lumbar punctures. We also use a lot of diagnostic studies, like ambulatory EEG and EMG/NCV studies. So we're trying to figure out the subset of procedures that need to continue. That means looking at problems that we hypothetically agree are not organ system–threatening but still might make you unpredictably show up in the emergency room. An example would be the use of Botox for severe migraine. Is it better to try to deal with that in a patient upfront, as opposed to not doing any procedures and risk that they'll have a breakthrough migraine and require care in the emergency room?
There aren't right or wrong answers to this. Everybody is kind of grappling with it, as well as with new information and requirements coming from the state level.

What does this new world mean for medical students? Are they invited into the room anymore?
No. We've essentially almost furloughed all of our medical students, but other volunteer-type opportunities have been created. Things like lectures have gone online on the undergraduate campus as well as at the medical school. All in-person classes are canceled. We've taken the medical students out of the inpatient services.

Do you have any advice for the neurologists out there on how to help address this pandemic?
For those likely to see the neurologic consultations, they need to be aware that this is largely unknown territory. Neurologists should be open-minded if they're asked to see a case of COVID-19 with neurologic complications. They should consider whether neurologic signs and symptoms reflect an indirect effect from organ system dysfunction or systemic illness. They also have to keep up-to-date on any emerging evidence of a more direct process, such as encephalitis or maybe even postinfectious immune-mediated illnesses, including Guillain-Barré syndrome. I think they're going to be on the frontlines of seeing any neurologic complications occurring.
A large swath of patients, such as those with MS, probably see their neurologist more than their primary care physician. Neurologists will need to reinforce the advice that we're getting about vulnerable patients, not only in the immunocompromised but also in those with Parkinson's disease, amyotrophic lateral sclerosis, and myasthenia. These are patients in whom typically manageable things like upper respiratory infections or pneumonia can be much more severe. Because of this, neurologists tend to be really vigilant in counseling their patients on all of the best practices for reducing risk for exposure, such as handwashing and social avoidance.
The data are still limited on whether coronaviruses have a significant neurologic component. There are reports of other coronaviruses entering the brain of patients and experimental animals. Does that mean anything? Right now, we simply don't know.

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