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## COVID-19: Neurologists in Italy to Colleagues in US: Look for Poorly-Defined Neurologic Conditions in Patients with the Coronavirus

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By Jamie Talan

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They don't stop coming—patients in Italy with respiratory problems that make it so hard to catch a breath that they brave the streets in this city in the Lombardia region to get to the emergency room at University of Brescia. This is no time for patients with chronic diseases in Italy, who are often told to stay home.

Many of the beds are filled with patients testing positive for COVID-19 or they have the symptoms that make testing seem senseless. They are fighting the disease, and many are losing it. With more than 80,000 positive cases in Italy as of late March, and approximately 8,000 deaths, neurologists on the front lines of this pandemic are noticing a set of worrisome symptoms that may be a sign that the virus doesn't discriminate to the lungs or the heart but is leading to a number of neurological disorders that no one was suspecting.

### A Neuro-COVID-19 Unit

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Alessandro Pezzini, MD, associate professor of neurology at the University of Brescia, and his colleagues have already opened a neuro-COVID-19 unit to separate patients from others who have acute neurologic events without signs of the coronavirus. There, on the 18-bed unit, patients are being treated for stroke, delirium, epileptic seizures, and non-specific neurologic syndromes that look very much like encephalitis, said Dr. Pezzini. And they are fighting the COVID-19 virus.

While it is not clear whether these neurologic syndromes are a direct cause of the virus entering their central nervous system (CNS), or an indirect response to the viral storm in their bodies, neurologists in Brescia are reaching out to colleagues throughout Italy to warn them to look out for acute neurologic complaints in their sick patients.

"There is a change in the neurologic patients we are treating," said Dr. Pezzini. "There is a dramatic increase in the number of vascular events, ischemic strokes, and thrombosis, which is likely due to the virus affecting coagulating mechanisms."

He said that he believes that they are seeing an increase in the number of acute strokes at the hospital. In some cases, they can't identify another cause for the stroke other than the virus.

Dr. Pezzini's message to his colleagues in the United States: "Deal with respiratory problems and cerebrovascular events and consider the possibility that there will also be patients with poorly-defined neurological conditions. I simply don't even know how to define these patients yet."

"There needs to be more investigation into this link between the virus and neurological symptoms, he said, noting that the additional CNS burden leads to worse outcomes in these patients.

"We decided to establish this unit because of the high number of acute neurology patients testing positive for COVID-19," said Dr. Pezzini, a stroke specialist. "We have been following the same guidelines for patients with acute neurological disease. Stroke patients who are not too compromised by respiratory insufficiency are being treated with tissue plasminogen activator and/or mechanical thrombectomy."

The neurologists at the hospital and throughout the hard-hit region of northern Italy have had to learn how to don protective masks, gloves, and special jackets. Five of Dr. Pezzini's colleagues in neurology have come down with the virus and have been taken out of the daily mix of tending to patients. They are in their homes, getting better, he said. They are now collaborating with other centers to begin an active study on COVID-19 and its relationship to CNS diseases. While the neurologist consults with others across the country, the most important piece of advice to the public is this: "Lock the doors and stay inside."

Alessandro Padovani, MD, professor of neurology and director of the Institute of Neurology at the University of Brescia, agrees. He and seven other neurologists wrote and sent a statement from the Italian Society of Neurology to their colleagues throughout the country.

"The recent onset of the pandemic caused by COVID-19 has rekindled attention to the possible neurovirulence of this virus and the possible involvement of the CNS and peripheral nervous system. Neuro-invasion usually occurs by hematogenous route or by retrograde axonal transport through some cranial nerves, such as the olfactory nerve, the trigeminal nerve, the glossopharyngeal nerve and the vagus, or peripheral nerves,"

#### **Additional CNS Complications**

In the last week, reports have been emerging from China, South Korea, and Italy suggesting that COVID-19 carriers can experience a loss of smell, and that could be a marker for identifying those infected with the virus who may or may not have any other symptoms. But now, it seems that neurologic symptoms are emerging in this pandemic.

"Psychiatric and neurological complications had been reported during the SARS epidemic in 2003," the neurologists wrote to their society members in Italy. "Apart from mood alterations in the depressive sense, anxiety disorder and suicidal ideas, cases of organic hallucinosis (visual and auditory hallucinations), behavioral disturbances, delusions of persecution, temporal-spatial disorientation, hypomanic disorder have been reported. In some cases these manifestations have been classified as secondary to steroid therapy. Other reports have reported isolated cases of fatal encephalomyelitis from coronavirus OC43 due to poor lung involvement and generalized crises in patients with SARS-CoV infection and CSF positivity.

"There are some recent data suggesting that COVID-19 virus also reaches the central nervous system. Neurological symptoms in patients with COVID-19 infection fall into three categories: neurological expressions of the symptoms of the underlying disease (headache, dizziness, disturbances of the state of consciousness, ataxia, epileptic manifestations and stroke;) symptoms of neuro-peripheral origin (hypo-ageusia, hyposmia, neuralgia;) symptoms of skeletal muscle damage, often associated with liver and kidney damage."

Chinese scientists in Wuhan, led by Bo Hu, MD, PhD, reported data from 214 patients at three COVID-19-designated care hospitals of the Union Hospital, part of the Tongji Medical College at Huazhong University of Science and Technology. They reported that 78 of the 214 patients had neurologic manifestations. The more severe patients were likely to have neurologic symptoms, such as acute cerebrovascular diseases; impaired consciousness. and skeletal muscle injury.

The paper (<https://www.medrxiv.org/content/10.1101/2020.02.22.20026500v1>), which was uploaded to a preprint server called MedRxiv on February 25, is now under review in a major US journal.

David Wang, DO, a neurovascular specialist at the Barrow Neurological Institute/Saint Joseph Hospital Medical Center Phoenix, was a collaborator on the study, which outlined the possible neuro-invasive potential of the virus.

Dr. Padovani said that he and his colleagues in northern Italy are not surprised. They are seeing the same conditions in their COVID-19 patients. "Many of the patients on the neuro-COVID-19 unit initially presented with stroke, delirium, or encephalitis, and then developed respiratory distress," he said. "We just don't know who will even be alive tomorrow. It is devastating. Our patients are receiving oxygen but we don't have ventilators in our unit as they are limited and they are going to patients with the best chance of survival."

He said that it is not clear now how widespread the neurologic symptoms might be as only the very sick make it to the hospital. "Many are dying at home," he added, "and neurologic symptoms get overlooked."

Dr. Padovani speaks to colleagues around the region via video conferencing sites every day. "COVID-19 exhausts most of our energies. This is a very bad time for us, and we don't see a light at the end of the tunnel."

#### **No Outpatient Clinics in Milan**

Alberto Priori, MD, PhD, professor of neurology and director of the department of clinical neurology at the University of Milan, San Paolo University Hospital, is working in one of the first-line hospitals in Milan treating COVID-19 patients. The neurology beds and stroke unit have closed to the standard neurology cases and are dedicated to COVID-19 patients. There are no outpatient neurology clinics. All area neurologists are part of COVID-19 teams that include one internal medicine specialist, one pulmonologist, one infection disease specialist, and one neurologist.

He said that in his experience "most cases of the severe systemic and respiratory impairment obscures the detection of subtle neurologic changes. In addition, in this emergency phase doctors pay more attention to vital functions than anything else."

He added that they have sent out an online survey to be used for screening of neurologic symptoms in patients with COVID-19. They have collected a hundred surveys so far.

"I can anticipate that more than three-quarters of our colleagues have seen neurological disturbances," Dr. Priori said. "I think in some patients we can speculate that the virus can spread or even enter from the central nervous system."

"From our experience, I would say that headache, confusion, taste and smell abnormalities, muscle ache, and severe weakness are the most common (neurological) manifestations," he continued. "They can also be caused by a systemic infection, of course. My personal hypothesis is that there might be some neurological dysfunction contributing to the severity of respiratory impairment due to lung pathological changes."

Now, he added, "we are in a war environment."

Dr. Priori warns his US colleagues: "Be prepared. Be ready. All neurologists should be trained for the basic aspects of mechanical ventilation to help other colleagues. The virus is extremely infectious, and everyone should be trained to use protections. It is not enough to have the devices for individual protection but all must know their use.

"You should always think of what it is like in an operating room. We have had too many deaths among colleagues in all specialties. The other important thing is that all medical staff should be isolated at home even if asymptomatic. I am staying away from my family to avoid possible infection."

Kenneth L. Tyler, MD, FAAN, the Louise Baum endowed chair and chair of neurology at the University of Colorado School of Medicine, said he is not surprised that a subset of COVID-19 patients are exhibiting neurologic symptoms.

"To date most of the neurological symptoms have been in patients with more severe COVID-19 disease and are likely the result of secondary effects of major organ system failure and/or DIC and sepsis. These can include acute cerebrovascular events and encephalopathy among others. It remains to be seen whether we will see direct effects of SARS-CoV2 invasion of the CNS such as encephalitis, as these happened in rare patients with SARS and MERS.

"We may also see post-viral immune-mediated complications like acute disseminated encephalomyelitis and Guillain-Barré syndrome, as again these occurred in patients with SARS and MERS "Right now, this is the Wild West. Keep your eyes open. We may find things that we hadn't expected, and then we have to sort it out."

Meanwhile, neurologists (and all medical specialists) need to figure out how to take care of their own patients during this pandemic. Giancarlo Logroscino MD, PhD, professor of neurology and director of the Center for Neurodegenerative Diseases and the Aging Brain at the University of Bari in Tricase has been on the front lines of this effort with his own patients.

Dr. Logroscino, who is in the southeastern region, said that the area has not seen the same devastation as his northern colleagues but still, he said, "the situation is serious and very difficult. In a very short time, this is changing the way we practice neurology. We have had to shift to a new system to support our neurology patients at home."

Last week, Dr. Logroscino and his staff implemented a telemedicine approach and called 30 patients with amyotrophic lateral sclerosis for a teleconsult. They were asked if they could do it on video, and those who agreed met face-to-face with a health professional to talk about their condition and see if they had to formulate new treatment plans. Next week, they will make contact with frontotemporal patients and their caregivers. They are working with a company to create an app that would make it easier for video conferencing. "We need to think in different ways how we are going to manage our patients," he added. "For many, our talk with them broke their isolation."

Link Up for More Information:

AAN COVID-19 Neurology Resource Center (<https://www.aan.com/tools-and-resources/covid-19-neurology-resource-center/>)

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