COVID-19 related strokes, other neurological impact under study

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Dr. Elizabeth Rutkowski. Credit: Phil Jones, Senior Photographer, Augusta University

Traditional stroke treatments like clot-dissolving tPA and surgical

removal of big clots in the brain are good choices as well when the stroke results from SARS-CoV-2 infection, investigators report.

Excessive blood clotting and stroke—even in young, previously healthy people—are among the myriad of effects the virus is having on people across the globe. Another effect is keeping people away from hospitals even when they experience signs of stroke, like sudden and particularly one-sided weakness in the face, arm or leg, say stroke specialists at the Medical College of Georgia and Augusta University Health System.

"What we know about COVID-19 and stroke is people need to be treated urgently and they tend to do really well with tPA and mechanical thrombectomy (clot removal) if they come in within a short time window," says Dr. David Hess, stroke specialist and MCG dean, who encourages those with signs of stroke for any reason to get to the hospital as soon as possible.

Hess and Dr. Elizabeth Rutkowski, a neurologist whose expertise includes brain infections as well as stroke, are authors of a review paper in the journal *Translational Stroke Research* highlighting both established and emerging treatment options that may help improve stroke outcomes or reduce stroke risk in these unprecedented times when the extremely infectious SARS-CoV-2 has been added to the traditional risk factors for stroke like high blood pressure and diabetes.

They also have begun a five-year study to assess the overall neurological impact of SARS-CoV-2 infection long term in more than 500 Georgians.

Because signs of the virus' impact neurologically include not only stroke, but the loss of sense of smell, called anosmia; a reduced sense of taste, called hypogeusia; and brain involvement called encephalopathy that may impact consciousness and cause confusion and headaches, as well as seizures.

In fact, loss of smell can be an early or even lone indicator of SARS-CoV-2 infection. Whether it's a lasting loss is one of the many things the investigators want to learn. "The hypothesis may be that the people who have anosmia may be more at risk for developing cognitive and other neurological problems," Hess says.

The brain is a pretty direct target for the virus, which the Centers for Disease Control and Prevention says is mostly spread by human-to-human contact. When an infected individual coughs or sneezes in close proximity, a bystander's nasal passageway provides a pretty direct route for the virus to first make its way through the olfactory bulb in the front of the brain, which picks up and processes odors detected by cells in the nasal cavity, then to spread throughout the brain. The mouth affords a different route that can take the virus directly to the brain stem, and the neurologists say it's likely the virus could take both routes in one person.

The direct access to the brain enables a sort of double attack, with a direct hit by the virus to an organ, like the lungs, and to the organ's control centers in the brain. There are reports, Rutkowski notes, of patients seeming to do better but then they just stop breathing. While she and Hess agree that it's most often the lung failure that causes death with COVID-19, they suspect it's both this direct lung invasion and infection of breathing centers in the brain responsible.

While investigators are working in real time to determine what treatments are best for the still emerging array of problems caused by COVID-19, the MCG neurologists say the limited data out there on stroke indicate the standard therapies should work in this scenario as well.

"We think the pathogenesis behind the clots that form during this infection are a little different, but those clots people are describing with COVID-19 are very fresh and tPA seems to be really effective for

those," says Rutkowski. "You see this in people with sepsis and with other viruses," Hess says of the clotting that can result in stroke and as well as damage to other organs. The neurologists suspect it is this propensity to clot coupled with the virus' attachment to ACE2 receptors, found throughout the body and considered protective, that leaves patients vulnerable to stroke.

Many viruses, including influenza and shingles, as well as other overwhelming infections such as sepsis, which is often driven by bacteria, result in excessive inflammation which can lead to increased coagulation that causes blood clots, including producing microscopic clots in the tiny air sacs of the lung, that can contribute to adult respiratory distress syndrome—a major cause of severe illness and death in COVID-19—as well as the dysfunction and failure of other organs.

Patients' blood will have telltale high levels of D-dimer, a protein fragment produced when a clot is degraded, and their blood clots much faster than usual.

The now familiar spiky virus latches onto the angiotensin converting enzyme 2, or ACE2, an enzyme found on cells—in the lungs, heart, kidneys, intestines and brain as well as the nasal mucosa—which explains its pervasive impact in the body. ACE2 is a part of the renin angiotensin system, which helps regulate blood pressure and is essentially a balance for angiotensin II, a powerful blood vessel constrictor and inflammation promoter. "It probably depletes ACE2 so you get this imbalance, you get too much angiotensin II, which is generally very bad," Hess says.

Rutkowski notes physicians at Mount Sinai Health System in New York, who have treated hundreds of patients, reporting how dialysis catheters are getting plugged with clots and how clots have even formed on the tip of a catheter during an interventional procedure to remove a clot from

the brain.

Confusion is a common problem the neurologists also are seeing in patients with COVID-19, but it's hard to know in some patients whether that results from the fact that they are so sick and their oxygen levels are low or it's a direct result of brain infection, Rutkowski says. In others there are clear cases of a brain infection and of virus present in the spinal fluid. As part of their study, which is just getting started, the neurologists will be looking at what happens to cognition and the sense of smell in survivors over time, Rutkowski says, noting that in some pandemics, a viral or bacterial infection actually sets off a neurodegenerative condition that worsens with time. In the wake of the Spanish Flu Pandemic of 1918, for example, physicians were seeing immediate problems like delirium and encephalitis lethargica, which causes troubles like excessive sleepiness and movement problems, and—sometimes years later—a form of Parkinson's. "We could have the same thing happening here," Hess says of the current pandemic.

Their new study now underway at MCG and AU Health System likely will be expanded in coming months to MCG campuses statewide, starting with Albany which has one of the highest per capita COVID-19 death rates in the country.

With ongoing concern about COVID-19, those interested in the study can participate remotely or in person. Those enrolled in person will be examined by an MCG neurologist at AU Health System and those enrolled remotely will undergo a telehealth neurological evaluation. Both remote and onsite evaluations will include cognitive testing and a scent identification test where study participants will be asked to identify different smells like chocolate, bubble gum and root beer, queries that will provide more objective measure of changes in the smell sense, Rutkowski says.

They also are taking a more comprehensive look on what type of neurological effects the virus has, and if there are risk factors like preexisting medical problems or gender— males seem preferentially impacted by COVID-19—that make people more susceptible to those effects, Rutkowski says.

Participants will provide details like medications they are taking, demographics and any COVID-19 related symptoms. Those opting for remote participation will receive similar remote examinations annually for five years. Those who opt for onsite participation will be asked to provide blood samples within a month of diagnosis or soon after a follow-up test shows they are disease free, then again at three and 12 months, then yearly. Blood will be examined for markers of inflammation like cytokines and chemokines and genetic factors like changes in the ACE2 gene that may predispose to neurological problems. Blood also will be examined for the presence and levels off antibodies against the virus and antibodies against sugars coating the virus, both signs of an attack by the immune system.

Blood samples will be studied and stored at the MCG Center for Biotechnology and Genomic Medicine where Dr. Jin-Xiong She, center director, also will be looking at variants in the ACE2 receptor that may make some more vulnerable to neurological problems, as well as antibodies people are making to the natural sugar coating on the virus. She says the antibodies may provide a disease history and help determine whether the severity of symptoms is associated with certain antibodies.

Other collaborators include Dr. John Morgan, director of the Parkinson's Foundation Center of Excellence and Movement and Memory Disorder Programs in the MCG Department of Neurology, who is conducting cognitive testing; and Dr. Lynnette McCluskey, neurobiologist in the MCG Department of Neuroscience and Regenerative Medicine, who is coordinating smell and taste testing.

Information collected during the study will be shared with the participants' primary care physician if desired. The investigators hope to add brain imaging to the examination if funding becomes available, Hess says.

In terms of addressing the disease's impact today, the blood thinner, low molecular weight heparin, used to prevent clots and treat deep vein thrombosis and pulmonary embolism and whose effect is considered to last longer and be more predictable than standard heparin, may be useful in reducing excessive clotting and potentially avoiding a stroke as well as other clot-related organ damage, they say. Rutkowski and Hess note that some physicians are already using it prophylactically and that it's essentially impossible in the midst of a pandemic to do standard clinical trials to more objectively measure if patients benefit from different therapies.

A more targeted therapy for these patients may be human recombinant soluble ACE2, which has been shown to help restore healthier ACE2 levels and interfere with SARS-CoV-2's ability to attach to cells, reducing the overall viral load, which decreases disease severity. The clinical grade ACE2 has already undergone early human studies for adult respiratory distress syndrome, the often deadly consequence of this virus, and other significant infections. An interventional study is now enrolling hospitalized adults in Austria, Denmark and Germany.

A clinical trial also is underway in patients with COVID-19 or suspected of having it who have bilateral viral pneumonia, infusing them with the blood vessel dilator angiotensin (1-7), which is significantly depleted in COVID-19 to hopefully improve lung function. Drugs that block the receptor for blood vessel constricting angiotensin II may work from another direction to help restore a healthier balance, the investigators say.