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How COVID-19 attacks the brain

Researchers are scrambling to understand just how COVID-19 impacts the brain, and what scientists can do to prevent long-term damage.

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As the COVID-19 pandemic rocketed around the globe, it quickly became clear that COVID-19 was not your average respiratory illness. The disease appears to affect a number of body systems, including the heart and the brain. Early on in the pandemic, there came reports that many people with the disease had lost their sense of smell, a curious symptom suggesting the virus may affect the nervous system. As more people became infected, accounts of strokes

and other neurological complications started coming in.

“There’s documented evidence that patients who are hospitalized with moderate and severe COVID-19 experience a range of neurological, cognitive, psychological, and psychiatric symptoms—and I’ve seen them myself,” says Robert Stevens, MD, FCCM, an intensive care physician at Johns Hopkins Medicine who treats patients with critical neurological illnesses. “Virtually all the COVID-19 patients I’ve treated in the ICU have delirium.”

It’s not yet clear how common neurological side effects are in hospitalized patients, let alone in people with less severe respiratory symptoms who don’t spend time in hospitals. “The picture is still evolving,” Stevens says.

In a review of case reports from 901 COVID-19 patients, Mark Ellul, at the University of Liverpool, and colleagues, reported a range of neurological manifestations, including loss of smell and taste, confusion, encephalitis (inflammation in the brain), and Guillain-Barré syndrome (a disorder in which the immune system attacks the body’s nerves) (*The Lancet Neurology* (https://doi.org/10.1016/S1474-4422(20)30221-0) , published online, 2020). A case report of 58 patients from France described neurologic findings in 67% of patients (Helms, J., et. al, *New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2008597) , Vol. 382, No. 23, 2020).

The prevalence of neurological problems remains an open question, but it’s safe to conclude that “neurological problems are not rare for COVID-19 patients,” says Majid Fotuhi, MD, PhD, medical director of NeuroGrow Brain Fitness and lead author of a comprehensive review of COVID-19’s effects on the nervous system (*Journal of Alzheimer’s Disease* (https://content.iospress.com/articles/journal-of-alzheimers-disease/jad200581) , Vol. 76, No. 1, 2020). “Our best estimate so far is that 30% to 50% of hospitalized patients have neurological issues,” he says.

In that review, he and his colleagues describe the variety of neurological complications in patients with COVID-19.“There’s a wide range of symptoms, including headaches, dizziness, weakness, confusion, eye movement problems, seizures, and paralysis,” he says. “The two most common neurological problems seem to be stroke and delirium.”

In general, people who experience more serious symptoms of COVID-19 tend to have more brain-related complications, Fotuhi says. “Broadly speaking, the sicker they are, the more neurological issues they have.” But there are exceptions to that rule. A study by scientists in England of 43 patients with severe neurological complications from COVID-19 found that while some patients had relatively mild respiratory symptoms, their neurological symptoms were severe (Paterson, R.W., et al., *Brain* (https://doi.org/10.1093/brain/awaa240) , published online, 2020).

Multiple disease process

Now researchers are scrambling to understand just how COVID-19 is damaging the brain. It’s likely that there are several different disease processes at work:

- **Complications from intensive care:** People who have been hospitalized in the ICU, for any reason, are more likely to experience long-term problems with cognition and an increased risk of anxiety and depression. One (pre-COVID-19) study found 20%-40% of ICU patients experienced delirium, with rates climbing to 60%-80% for patients on ventilators (Pandharipande, P.P., et al., *Intensive Care Medicine* (PDF, 1.37MB) (https://link.springer.com/content/pdf/10.1007/s00134-017-4860-7.pdf) , Vol. 43, No. 9, 2017). Such complications are thought to be related both to severe illness and to intensive care treatment. Some portion of people seriously ill with COVID-19 will likely experience delirium and other neurological side effects (/monitor/2020/09/aftermath-covid-19) simply as a result of being in the ICU, Stevens says.
- **Inflammatory or immune response:** In some patients, COVID-19 seems to trigger a runaway immune response that can cause problems throughout the body. In their Brain study of patients with neurological complications, Paterson and colleagues described several types of encephalitis, as well as acute disseminated encephalomyelitis or ADEM (an autoimmune disorder in which the immune system attacks the brain). Patients with encephalitis may experience mild flu-like symptoms, such as headaches, fevers, and fatigue, or may experience more severe symptoms including confusion, seizures, paralysis, problems with speech or hearing, and more.
- **Stroke:** COVID-19 has been found to cause blood clots, both large and small, that can

travel to the brain and cause a stroke. Strokes have occurred in COVID-19 patients of all ages—and in fact, physicians have reported that some adults under 50 have presented to the hospital with a stroke as their first complication from COVID-19, while their respiratory symptoms were mild (Oxley, T.J., et al., *New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2009787?query=featured_home) , Vol. 382, No. e60, 2020).

- **Viral infection of the brain:** There have been a handful of accounts of the virus turning up in cerebrospinal fluid, raising the possibility that SARS-CoV-2, the virus that causes COVID-19, may be able to directly infect brain cells. But the evidence that the virus can make its way into brain cells is still uncertain, both Fotuhi and Stevens agree. “Based on the literature and what we’ve seen so far, if viral infection of the brain occurs, it’s probably pretty rare,” Stevens says. “We think that immune-mediated encephalitis is probably much more common.”

To integrate these concepts and form a preliminary framework for studying COVID-19 in the brain, Fotuhi and colleagues have proposed a three-stage system to classify neurological complications from the disease:

- **Stage 1:** Damage to the nervous system is limited to the epithelial cells in the nose and mouth. The main neurological symptoms include loss of smell and taste. This side effect seems to be quite common. One study found smell reduction in 41.7% of people with COVID-19, while 55.4% experienced taste reduction (Mercante, G., et al., *JAMA Otolaryngology—Head & Neck Surgery* (https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2767510) , published online, 2020).
- **Stage 2:** The virus triggers an inflammatory response that leads to the formation of blood clots, which can cause strokes.
- **Stage 3:** A explosive inflammatory response called a cytokine storm damages the blood-brain barrier. This may allow inflammatory cells and molecules—and, possibly, viral particles—to enter the brain. Patients may develop seizures, confusion, coma, or encephalopathy (brain abnormality that leads to altered mental states or behaviors).

Pandemic neurology: Past, present and future

As researchers continue to gather evidence about COVID-19 and the brain, they're turning to past epidemics for clues. "The 1918 influenza pandemic was associated with a surge in neurological problems, many of which became apparent months or years later," Stevens says. The SARS outbreak in 2003 and MERS outbreak in 2012—both caused by coronaviruses similar to SARS-CoV-2—were also associated with neurological illnesses, including inflammation in the brain. And following each of those outbreaks, Stevens says, "there were reports of people suffering long-lasting neurological injuries."

Neurology experts are concerned that COVID-19 could leave a similar legacy. But many questions remain, Fotuhi says. "The first step is to document what neurological symptoms occur, at what frequency, and what treatments have or have not affected the neuropsychological symptoms."

So far, studies of patients with the disease haven't really drilled down into neuropsychological outcomes, Stevens says. "Trials of antivirals and other therapies being tested to treat COVID-19 are looking at some very coarse outcome measures, like survival or duration of hospitalization. The scientific community needs to include neurological, psychological and psychiatric outcomes as well," he says.

Experts around the world are working to make that happen. Researchers from 70 sites and 15 countries have registered with the Global Consortium to Study Neurological Dysfunction in COVID-19. The collaborative effort, endorsed by the Neurocritical Care Society, is collecting data and evaluating functional and cognitive outcomes to inform treatment strategies (Frontera, J., et al., *Neurocritical Care* (https://link.springer.com/article/10.1007/s12028-020-00995-3) , Vol. 33, No. 1, 2020). But physicians shouldn't wait until all the data are in to start intervening, Stevens suggests. Existing therapies are available to treat autoimmune encephalitis, for example. "But these haven't yet been studied specifically in COVID-19 patients," Stevens says.

The faster such treatments are tested, the better, he adds, since some of the brain damage from COVID-19 may be irreversible. But Fotuhi is hopeful that for some people, interventions may restore brain function. "Targeted brain training may be able to address specific cognitive

symptoms, such as difficulty with executive function or memory," he says. "I think there will be a great need for psychologists to get involved, to help patients recognize their symptoms and seek treatment for them."

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