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Neurology

How covid-19 affects the brain

The coronavirus can cause neurological symptoms. Research is starting to reveal how they occur and if they are treatable, reports **Michael Marshall**

FROM the first weeks of the covid-19 pandemic, it has been clear that the condition often causes neurological symptoms – ranging from headaches and brain fog to strokes and paralysis. We are now getting a clearer picture of covid-19's neurological symptoms and how the SARS-CoV-2 coronavirus indirectly affects the brain, pointing the way to potential treatments and raising

“Neurological complications are also something that can affect people with mild covid-19 symptoms”

questions about the effects that other viral infections may have on our brain.

Covid-19 infections are commonly associated with neurological symptoms. Some studies have estimated that about 1 in 3 people with the infection will subsequently be diagnosed with a neurological or psychiatric condition. Common symptoms include loss of sense of smell, weakness and fatigue, headache, mood conditions like depression and cognitive difficulties such as memory loss. A small percentage of cases experience major neurological events like strokes and seizures. While neurological conditions are most likely to arise soon after infection, people who have had covid-19 remain at an elevated risk of developing one for up to two years afterwards.

The consequences can be serious. In a study published last year, Anna Cervantes-Arslanian at Boston University Chobanian & Avedisian School of Medicine in Massachusetts and her colleagues compiled data on 16,225 people hospitalised with covid-19. They found that 12.9 per cent of those studied developed serious neurological symptoms.



A person's sense of smell is tested near La Plata, Argentina, in May 2020

The most common was encephalopathy, an umbrella term that refers to general brain dysfunction, which can lead to altered mental states or delirium. All the symptoms analysed – which also included strokes, seizures and meningitis – were associated with worse outcomes: people who had them were more likely to need intensive care, to die during the study period and to have long-term symptoms if they survived.

Reduced blood flow

“This has been borne out in many studies,” says Cervantes-Arslanian. “For people that are more seriously impacted in terms of neurologic conditions, their likelihood of surviving is lower and their likelihood of disability is very high.”

In another 2022 study, Adam Hampshire at Imperial College London and his colleagues gave

cognitive assessments to 46 people who survived after being hospitalised for severe covid-19. They found the participants were slower and gave less accurate answers in the assessment than people who hadn't been hospitalised with covid-19, and especially struggled with complex tasks like spatial planning and reasoning by analogy.

But it isn't just hospitalised patients who are affected. “Neurological complications are also something that impacts people that have mild covid,” says Cervantes-Arslanian. People with the lingering symptoms dubbed long covid often complain of neurological issues such as brain fog. “I think a lot of the neurological symptoms are the most concerning [for people with long covid], because they provide a lot of disability,” she says.

There is no single explanation for the neurological impacts of

12.9%
of those with severe covid-19 get serious neurological symptoms

covid-19, but multiple mechanisms have been identified that may be involved.

One pathway could be the effect that SARS-CoV-2 can have on blood vessels and blood flow, causing indirect harm to the brain. In a study published last year, researchers including Laura Benjamin at University College London reviewed 83 studies of neurological symptoms associated with covid-19 and found that 26 per cent of cases included cerebrovascular events, such as strokes, in which part of the brain's blood supply is cut off. These events were associated with worse outcomes.

Inflammation

Another key factor is disruption to the immune system, which can affect the brain. Ed Needham at the University of Cambridge and his colleagues recently studied 175 people hospitalised with covid-19. Those with more severe illness – meaning they needed to be given oxygen or ventilation – showed higher levels in their blood of two proteins associated with brain injury. They also had higher levels of immune system molecules called cytokines, which promote inflammation, and of autoantibodies, which target their own body tissues rather than the virus.

“This is all, by its nature, observational,” emphasises Needham. “It’s definitely association rather than causation.” But the implication is clear: rather than the virus directly harming the brain, the immune system’s response to the virus could be doing damage by causing the brain to become inflamed. “We know from a myriad of other studies that systemic inflammation triggers

neuroinflammation, and neuroinflammation is often detrimental and causes brain injury,” says Needham.

These findings reflect a broader shift in immunological thinking. It had been thought that the brain was almost entirely cut off from the rest of the body behind the blood-brain barrier, so immune overactivation in the rest of the body wouldn’t affect it. “The idea that you can have rampant systemic inflammation and your brain sits nicely cocooned away and it’s not affected by it at all, I think is wrong and has been put to bed,” says Needham.

There has also been a shift in thinking on the question of whether SARS-CoV-2 can enter the brain. Despite some early reports, many researchers had been sceptical because autopsies showed little or no evidence of the virus in the brain. However, it now seems clear that the virus does get in, at least in some cases.

One of the strongest data sets comes from a team led by Daniel Chertow at the National Institutes of Health in Bethesda, Maryland,

Blood samples being analysed at a long covid clinic in Australia



LISA MAREE WILLIAMS/GETTY IMAGES

which was published in December 2022. The researchers autopsied 44 people who died of covid-19, including 11 where they took multiple samples from the brain. They found SARS-CoV-2 in many tissues, including the brain, albeit often in low quantities.

“Systemic inflammation triggers neuroinflammation and that can cause brain injury”

Furthermore, they were able to grow the virus from the brain samples, showing that it was biologically active. “It is there and it is capable of replicating,” says Chertow.

However, the viruses in these people’s brains weren’t associated with damage. “What we did not see is pathology that was attributable to viral infection,” says Chertow. Nor did they find evidence of inflammation in the brain.

This aligns with other studies suggesting that SARS-CoV-2 infection in the brain may not cause significant harm. “Is it neuroinvasive? Yes, we’ve seen evidence of the virus in the brain,” says Benjamin. But is the virus strongly attracted to brain cells

and causing damage? “Not convincingly,” she says.

Chertow’s study highlights two uncertainties. The first is the extent to which viruses of any kind can persist in our bodies at low levels, long after the initial infection and when the acute illness has ended. Virologists generally believe that our bodies eliminate many viruses within a few weeks, says Chertow. But “clearly, there are opportunities” for them to linger on, he says.

The second uncertainty is whether a small number of virus particles can cause meaningful harm in the short or long term, or if there is a threshold below which they don’t matter. “I don’t think we know that,” says Chertow.

Given this complex picture, it is perhaps no surprise that the best treatment for preventing neurological symptoms from covid-19 appears to be a mix of drugs. In a study published last year, researchers led by Ian Galea at the University of Southampton, UK, assessed neurological outcomes in patients given the anti-inflammatory drug dexamethasone, the antiviral drug remdesivir or both. The two individual medications helped, but combining them reduced neurological complications the most.

The immediate challenge is to find ways to rapidly determine the cause of neurological symptoms in each person, so that the most appropriate treatments can be given.

But to develop better treatments, we will first need a more detailed understanding of the two key questions covid-19 is raising about viral infections in general: how does being seriously ill harm our brains, and what do viruses do when they manage to get into them? ■