How COVID can lodge itself in our brains

In early 2020, COVID appeared to be mostly respiratory, with blame for the shattering of delicate lung tissues initially placed on the violent “cytokine storms” unleashed from overactive immune responses. At first, autopsy series focused on the inflammation and antibodies, not finding evidence of the virus itself. But that view has changed.

As the fourth year of the pandemic dawns, a study published in Nature from Daniel Chertow, MD, MPH, head of the Emerging Pathogens Section at the NIH Clinical Center and colleagues, finds the virus in many body parts – particularly, the brain. The discovery may explain cases of long COVID.

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Indirect attack on the brain

At first, researchers thought the role of the virus on the brain was indirect.

In July 2022, Avindra Nath, MD, clinical director of the National Institute of Neurological Disorders and Stroke and colleagues reported in the journal Brain changes in the brains of nine people who died quickly from COVID. Autopsies revealed antibodies glommed onto viral antigens on the tile-like endothelial cells that form the blood-brain barrier. As capillaries disintegrated, the risk of stroke skyrocketed amid catastrophic destruction.

The COVID-infected brain is a mess.

“Activation of the endothelial cells brings platelets that stick to the blood vessel walls, causing clots and leakage. At the same time the tight junctions between the endothelial cells get disrupted, causing them to leak. Once leakage occurs, immune cells such as macrophages may come to repair the damage, setting up inflammation. This, in turn, causes damage to neurons,” Nath explained.

The team’s analysis of more than 300 genes with altered activity in the attacked lining cells in the brains indicated oxidative stress, DNA damage, and abnormal metabolism. These effects might explain neurological symptoms such as headache, fatigue, loss of taste and smell, sleep problems, and the infamous “brain fog.”

But Nath’s team didn’t find viruses – just mangled brain vasculature. “It is quite possible that this same immune response persists in long COVID patients, resulting in neuronal injury. There could be a small indolent immune response that is continuing, which means that immune-modulating therapies might help these patients,” he said.

Other studies confirmed the immune-mediated brain damage in COVID. But not detecting the virus doesn't mean it wasn't there. Now, researchers have found direct evidence that SARS-CoV-2 indeed takes up residence beyond the respiratory tract.

Into the brain and beyond

In the study recently reported in *Nature*, the researchers autopsied 44 patients who died with COVID, sampling the central nervous system (brain and spinal cord) in 11 of them, up to seven months after symptoms began.

The team improved upon earlier efforts to identify virus: dissecting fresh brains before fixing and flash-freezing them, to preserve viral RNA, and teaming PCR and immunohistochemistry to amplify and quantify the virus in a variety of body parts.

The patients were ethnically diverse, 30 percent female, median age 62.5 years, and all unvaccinated. Nearly two-thirds of them had three or more underlying conditions that elevated risk of severe symptoms and complications. On average the patients had been hospitalized on the sixth day and died by 18 days.

So where does the virus go? A lot of places, it turns out, even seven months after infection begins.

The investigation found SARS-CoV-2 RNA in 84 anatomical locations and body fluids. The researchers displayed the findings in a heat map, revealing patterns at a glance. Red shades were applied to body parts harboring abundant virus, and hues of blue for relatively virus-free areas.

As expected, parts of the respiratory tract – salivary glands, trachea, bronchi, and lungs – lit up red. But a second sweep of red echoed the nervous system. Locations included the optic nerve, cerebral cortex, thalamus, hypothalamus, the dura mater (a membrane surrounding the brain), and the spinal cord. The promiscuous virus also ended up in the heart, lymph nodes, thyroid, spleen, esophagus, skin, adrenal glands, and the ovary and testis.

major respiratory organs

Image not found or type unknown

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Past investigations attributed finding virus outside the respiratory system to contamination through blood, but that apparently didn’t happen here, the researchers wrote. Blood plasma from most of the people autopsied *didn’t* have virus. Plus, the dissection part of the protocol lessened the chance of blood contamination.

The researchers tracked the viral gene for the spike protein as well as the gene that encodes the nucleocapsid protein. These proteins aggregate, forming a protective shell around the viral genetic material, RNA.

The conclusion is chilling:

> *… SARS-CoV-2 is capable of infecting and replicating within … many … tissues, including brain.*

Another compelling finding from the autopsies is that slight genetic differences among the viral RNAs indicate a separate seeding in body parts, rather than, or in addition to, spread from initially infected lungs.

The researchers propose a scenario: viruses first go to the respiratory tract. That makes sense; we breathe them in. Then they spread. It's a little like outdoor concert-goers entering and surveying the vast lawn and then choosing their spots and settling in.

In short, SARS-CoV-2 seems to be able to go anywhere in a human body. And there may be a good reason for that.

Did the virus come from us?

Viruses enter the cells of their hosts through proteins that form portals of sorts, called receptors, that jut from and are part of cell surfaces. HIV and West Nile virus enter through CCR5 receptors, which dot white blood cells. Influenza viruses bind a type of sugar called sialic acid. Herpes simplex virus uses 3 different doorways.

Some coronaviruses, including SARS-CoV-2, enter human cells through a receptor called ACE2. That stands for angiotensin-converting enzyme 2. Prior to the pandemic, ACE2 receptors were best known as the targets of blood pressure medications called ACE2 inhibitors.

The coronavirus binds human cells by its spikes. How does the precise lock-and-key-like fit happen?

According to the "escaped gene" hypothesis, viruses originated as pieces of the host (our) genome that at some point in evolutionary time exited the cells, encasing themselves in protective proteins and fats from the cell membrane as they budded off. Such an origin explains the dependence of the virus on the host, as well as its ability to rapidly fill a cell. And if those particular receptors dot many types of cells, the virus can go pretty much anywhere. And so a virus may arise as a by-product of biochemistry and evolution.

On a more practical level, the ability of SARS-CoV-2 to worm its way into many of our cell types may explain the odd constellation of manifestations that are now emerging as we enter this once unimaginable fourth year of COVID – from the initial brain fog and fatigue, to the many symptoms of long COVID that affect all organ systems.

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