Tidsskriftet
DEN NORSKE LEGEFORENING

# How does COVID-19 affect the brain?

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Neurological symptoms may be the first to present in cases of COVID-19, but they more commonly emerge later in the disease course and in severe infections. More and more cases are being reported of diverse neurological manifestations, but to date little is known about the extent of post-infectious neurological sequelae.

Effects on the nervous system are common in severe infections, with symptoms such as headache, dizziness, impaired consciousness, or confusion. Experience to date suggests that neurological manifestations are more common in cases of COVID-19 than in many other viral infections. SARS-CoV-2 appears to have a neurotropic effect similar to that of other coronaviruses (1).

## Neurological symptoms in one in three patients

The symptoms of COVID-19 may be diffuse and atypical, and neurological symptoms can emerge prior to fever, cough and other typical symptoms of infection (2). Impairments in

the sense of taste or smell are so common that new-onset anosmia has been proposed as a screening criterion (3).

In a retrospective study from Wuhan Province in China, neurological manifestations were described in 36.4 % of 214 consecutively hospitalised patients (4). Common central neurological symptoms were dizziness, headaches and impaired consciousness, while the most common peripheral neurological symptoms were impairments in taste, smell or vision, and neuropathic pain. The severity of COVID-19 was evaluated on the basis of respiratory function and the need for ventilatory support (4). Neurological symptoms were recorded in 30.2 % of patients with less severe illness and 45.5 % of those with severe illness (4). Manifestations such as stroke, ataxia, epileptic seizures and impaired consciousness were most common in those with severe illness, and 5.9 % of patients had a stroke (4). The median time from onset of COVID-19 to the onset of stroke symptoms was ten days (4), although in another report stroke was described as the presenting symptom of COVID-19 (5).

## Effects on the nervous system

The entry point for SARS-CoV-2 into the body is usually via angiotensin converting enzyme 2 (ACE2) in alveolar cells of the lungs. However, ACE2 is also expressed in a number of other cells and tissues, including the mucous membranes of the eyes, nose and oral cavity, neurons and glial cells, and endothelial cells, including those of the brain. These are thus potential targets for the virus (6). Transneuronal transmission of the virus via the olfactory nerve to the brain is one of several potential mechanisms by which the virus could act directly on the nervous system (7). SARS-CoV-2 has been detected in the cerebrospinal fluid in cases of encephalitis and meningitis (8). Strong immune responses to the virus in the form of a so-called cytokine storm, in which cytokines cross the blood-brain barrier, are associated with acute necrotising encephalopathy in cases of COVID-19 (9).

During the pandemic, there should be a low threshold for testing for SARS-CoV-2 in cases of new-onset neurological symptoms, including confusional states in the elderly

Nervous tissue can also be damaged indirectly as a result of incidental effects of the immune response, as in cases of Guillain-Barré syndrome (10) or demyelination of the central nervous system (11). Most neurological impairments in cases of COVID-19 are likely to be the result of systemic disease, hypoxia and, in some cases, hypercoagulability, a prominent feature of severe COVID-19 infections (2). SARS-CoV-2 proteins have been shown to interact with human proteins in several ageing-related processes (12). Long-term studies of the disease course will reveal whether COVID-19 leads to neurodegenerative conditions, as was seen with the Spanish influenza.

Increased understanding of neurological manifestations of COVID-19 is required in both the acute and post-infectious phases of the disease course. During the pandemic, there should be a low threshold for testing for SARS-CoV-2 in cases of new-onset neurological symptoms, including confusional states in the elderly. We recommend that these patients are evaluated by a neurologist and receive rehabilitation and follow-up of residual symptoms.

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Published: 23 June 2020. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.20.0444
Received 16.5.2020, accepted 26.5.2020.