Raising the awareness for a possible COVID-19 postinfectious neurocognitive syndrome

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Neurologic and sensory symptoms of COVID-19 are common, including olfactory dysfunction, headache, and dizziness. Other betacoronaviruses show neuroinvasiveness properties, and there is evidence that it may be partially responsible for the acute respiratory failure induced by SARS-CoV-2. Sudden onset anosmia is a prevalent symptom in a large number of paucisymptomatic patients and is probably caused by a dysregulation of the olfactory neuroepithelium. Early signs of anosmia can predict memory impairments even among cognitively healthy individuals. Hence, it is essential to study neurocognition in patients with a history of anosmia and COVID-19.

SARS-CoV-2 | COVID-19 | neuroinvasion | anosmia | postinfection | neurocognition

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Introduction

After the pandemic is over, Coronavirus Disease 19 (COVID-19) will continue as epidemic waves until a vaccine is widely available. One of the possible long-term consequences is a postinfectious neurocognitive syndrome. The first report of acute neurologic symptoms found that 78 out of 214 patients had central nervous symptoms, as headache, dizziness, impaired consciousness, ataxia, and convulsion (1). SARS-CoV-2 RNA was detected in a patient cerebral spinal fluid (2) and similar findings were described during the SARS-CoV-1 epidemic, such as samples of autopsies with viral genome sequences confined to the cytoplasm of neurons (3).

Fig. 1. Possible route of neuroinvasion

Neuroinvasion and Neuropathogenesis

There is evidence that the potential neuroinvasiveness of SARS-CoV-2 is partially responsible for the acute respiratory failure of COVID-19 (4). Neuroinvasion has been documented for other betacoronaviruses, including Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Human Coronavirus (HCoV), Mouse Hepatitis Virus (MHV) and Porcine Hemagglutinating Encephalomyelitis Virus (PHEV) (5–9).

A viral flora in the brain can induce neuro-immunopathology in susceptible individuals or direct neuronal damage (10). For instance, HCoV RNA was found in the brain parenchyma of infected patients (11). Furthermore, SARS-CoV-2 may conceal itself inside neurons from the immune recognition, what means that complete clearance of the virus may not be guaranteed even after recovery from acute infection (4).

Neurologic and sensory symptoms

Neurologic symptoms can present both as central nervous system symptoms, such as headache, dizziness, impaired consciousness, ataxia, and seizures, and as sensory symptoms, such as anosmia/hyposmia and ageusia/dysgeusia (1). Also, the possible dysfunction of the cardiorespiratory center could be another central nervous system symptom (4) since SARS-CoV-2 could have invaded it via a transynaptic route from mechano- and chemoreceptors in the respiratory tract (12, 13).

Sudden onset anosmia with or without dysgeusia is a prevalent sensory symptom in a large number of paucisymptomatic patients (14, 15) and is probably caused by a dysregulation of non-neuronal cells in the olfactory neuroepithelium that co-express SARS-CoV-2 receptor and entry genes (16).

There are no descriptions yet of chronic neurologic symptoms caused by SARS-CoV-2, but researches have already described other CoVs postinfectious neurologic manifestations. A study from Saudi Arabia showed brain lesions after infection with MERS-CoV in three patients (17). In this study, brain MRI revealed widespread bilateral hyperintense lesions on T2-weighted imaging within the white matter and subcortical areas of the frontal, temporal, and parietal lobes, the basal ganglia, and corpus callosum.

Other viral infections, such as Measles and Rubella, can cause a slowly progressive neurological disease that presents several years after the acute viral illness has occurred. Human T cell lymphotropic virus type 1 (HTLV-1) can cause slowly progressive myelopathy in adulthood with no prior history of apparent infection. Human herpes viruses, herpes simplex virus and varicella-zoster virus, are the prototypical viruses that establish lifelong latent infections in human peripheral and CNS sensory ganglia that may episodically reactivate, resulting in acute infection (18).

Neurocognitive symptoms

There is an increased risk of cognitive deficits in viral postinfectious syndromes (19). Although extensively underreported, infection is the most common cause of encephalitis and viruses are the most prevalent etiological agents (20).

Each virus cause specific postinfectious neurocognitive syndromes that will depend on early diagnosis and treatment, age and the cognitive level at the onset, and site and extent of neuronal injury. Japanese Encephalitis (JE), for instance, has an estimated 50,000 cases and 15,000 deaths annually, and about half of the survivors have severe neuropsychiatric sequelae (21). West Nile Fever and JE link to significant long-term neurocognitive deficits, including decreases in psychomotor speed and in verbal and visuospatial learning, which not only persist but also worsen for years after recovery (22). Other viruses may also cause long-term lower scores on tests of fine motor and psychomotor skills as well as on learning and memory (23).

SARS-CoV-2 causes a local dysregulation of the nasal neuroepithelium that may open a path through the cribriform plate to olfactory bulb. From there the virus may reach the entorhinal cortex via the olfactory tract, and later the hippocampus, which, if affected, will impair memory. Accordingly, early signs of anosmia can predict memory impairments even among cognitively healthy individuals (24).

Future perspectives

Scientists should raise the awareness for non-negligible long-term consequences of a possible COVID-19 postinfectious neurocognitive syndrome. It is not yet possible to ascertain that SARS-CoV-2 causes direct neuronal damage since only a few studies assessed neurological symptoms, and no studies assessed neurocognitive symptoms this far. Hence, it is essential to systematically study cognition in patients with a history of anosmia and COVID-19. Along this line, psy-

chiatrists and psychologists when examining these patients should require a neurocognitive assessment. Finally, considering the required physical distancing/isolation, a plan of action to develop a global standardized online neurocognitive assessment is foremost.

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