Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Long-COVID: Cognitive deficits (brain fog) and brain lesions in non−hospitalized patients

The COVID-related pandemic has affected tens of millions of people around the world and resulted in a large number of hospitalizations in either intensive care or in the conventional sector [1]. The initial target of Sars-Cov-2 is the upper and lower respiratory, tract leading to respiratory failure requiring oxygen therapy or mechanical ventilation. Other organs can be involved in COVID such as the heart, the digestive system and blood vessels during direct viral diffusion or through a delayed inflammatory and cytokine storm [2]. Clinical forms can be life-threatening, while in other cases multiple organ lesions are observed following the acute phase in intensive care units or after regular hospitalization. The brain can also be directly or indirectly affected during Sars-Cov-2 infection. A few cases of direct viral cerebral infection have been reported in acute encephalitis. The virus has rarely been detected in the cerebrospinal fluid, a finding suggesting a possible invasion via the olfactory tract (anosmia is common) or by rupture of the blood brain barrier [2]. The few published neuropathological studies of encephalitis cases mainly found ischemic vascular damage, hemorrhagic or inflammatory lesions, sometimes with molecular evidence of viral infections [3,4]. Cerebrospinal fluid anomalies confirming neuronal and astrocytic demise have also been noted, including increased concentrations of neurofilaments and GFAP [5].

In a recent study of 236,379 patients with COVID, the incidence of neurological and psychiatric disorders at 6 months was 33.6% [6]. Many neuropsychiatric conditions have been described after infection with SARS-CoV-2 including chronic malaise, diffuse myalgia, headache, anosmia, cognitive impairment, depression and anxiety [7–9].

If neurological complications are more frequent in hospitalized patients in intensive care units or in regular wards, neurological disorders, particularly cognitive disorders, have also been reported in patients who had mild to moderate forms of COVID infections without hospital admission [10]. A study from the Chicago Neuro-COVID Center included 50 COVID-positive patients and 50 COVID-negative (not tested) patients over a 6-month period and compared long-term neurological and cognitive consequences in both groups. All 100 patients had signs of COVID infection and were seen on average 4.7 months after the onset of infection. No patient was hospitalized. The mean age of the patients was 43.2 years. Signs of depression and anxiety were found in 42% of infected cases. 72% of the patients were females. The most common neurological symptoms were cognitive impairment with brain fog (81%), headaches (68%), paresthesia (60%), ageusia (59%), anosmia (55%), myalgia (55%) dizziness (47%) and pain (43%). Chronic fatigue and impaired daily living activities were reported in 85% of patients. Brain MRIs were found abnormal in 18% of tested patients, mainly revealing white matter changes. COVID-positive patients had more impaired performance on attentional and working memory tests. The main conclusion of this study was that following mild COVID infections, cognitive symptoms were more frequent in young females than in young males.

The brain FDG PET scan can be very useful as a means detecting post-COVID brain damage. A recent study showed that in two hospitalized patients who had a COVID infection, brain FDG PET scans revealed hypometabolic areas of the olfactory gyrus, amygdala, hippocampus, cingulum and pons [11]. We also recently showed that in a patient who had a mild COVID infection (without hospitalization or oxygen supplementation), a marked attentional and executive cognitive impairment was associated on FDG PET with hypometabolic areas of the cingulate cortex [12]. This imaging exam represents an important diagnostic tool for visualizing post-COVID brain damage in subjects with cognitive complaints (brain fog) and confirming that long COVID can be linked to neurological sequalae.

The long-term course of these brain lesions and clinical symptoms in mild forms of COVID is difficult to predict. Some authors have mentioned that an evolution towards neurodegenerative diseases could be seen over a prolonged evolution [2]. It has been reported in previous studies that SARS-CoV-2 can induce hyperphosphorylation of tau protein or activation of the PKR kinase, two proteins that abnormally accumulate in the brains of Alzheimer's patients [12,13]. Long-term neurological and cognitive monitoring of these patients seems to be an important measure in terms of public health and a new approach toward neurodegenerative diseases.

It seems useful to introduce sustained cognitive remediation for these patients; in the event of an associated depression, serotonin reuptake inhibitors, which have an anti-inflammatory effect in the brain, could be proposed [14].

In conclusion, the cognitive disorders associated with long COVID following mild forms of infection could be linked to hypometabolic lesions of the brain, which are probably associated with neuroinflammation. Only long-term follow-up of the patients will be able to conclusively assess the evolution of these lesions and the accompanying clinical signs.

To sum up, neurological complications of COVID may be detected in moderately affected individuals and extensive explorations of these patients should be performed to determine the actual extension of the brain lesions.

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