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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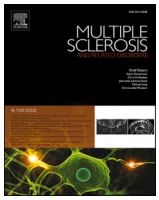

Editorial

Long COVID or post COVID-19 syndrome

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SARS-COV- 2 is now recognized to be responsible not only for a lung condition but a multi-organ syndrome (Ramakrishnan et al., 2021). After the initial acute infection, like many other viral disorders, a multitude of long-lasting symptoms have been described. Although widely discussed in social media the evidence around this new syndrome is scarce. A provisional definition would be persistent symptoms and potential sequelae beyond four weeks from onset, of which the main features are breathlessness, cognitive impairment, fatigue, anxiety and depression (Ramakrishnan et al., 2021). The often mentioned "brain fog" is characterised by difficulties with concentration, memory and executive function (Carfì et al., 2020). Post-viral syndrome is more common in depressed patients but can occur after a number of viral infections, for example EBV, HSV and HTLV (Burrell et al., 2017).

Reports of the prevalence of ongoing symptoms after COVID infection range from 32.6% to 87% of hospitalised patients. (Nalbandian et al., 2021;Bell et al., 2021). In a non-hospitalised cohort, 37% report fatigue and 30% cognitive impairment (Chopra et al., 2021). In Wuhan, China, 76% of infected patients were still troubled with at least one symptom after 6 months after discharge (Huang et al., 2021). A Melbourne study found persistent symptoms in 34% even after 45 weeks (COVID, 2021). These raw data may just reflect local conditions and are unadjusted for standard variables such as age, gender, ethnicity, employment, social deprivation, medications that are sedating, and co-morbidities such as diabetes, obesity and vascular disease.

Neuropsychiatric symptoms that occur during or after infection with SARS-2 are not simply related to emotional stress. This concept is given provisional support by the presence of inflammatory CSF in five cases of childhood Multisystem Inflammatory Syndrome (MIS-C), three of whom presented with neuropsychiatric symptoms one month after acute infection (Ngo et al., 2021), suggesting CNS inflammatory consequences may occur in all age groups. SARS-2 is neurotropic and appears to enter the brain through the olfactory neurons (Meinhardt et al., 2021), spreading to the frontal lobes as shown by impaired executive function and frontal abnormalities on MRI, EEG and PET (Toniolo et al., 2021).

The cause of this post-viral syndrome is not known, though it does resemble chronic fatigue syndrome, now called post viral fatigue syndrome (PVFS). If these symptoms are simply a consequence of critical illness or hypoxia in patients requiring ventilation, it would not explain why it occurs in non-hospitalised patients and why it is not obviously linked to the severity of the initial infection. It has been suggested that a major cause of neuronal damage is indirect: i.e. through immune-related microvascular inflammation and thrombosis. If so, this would explain the absence of viral markers (Farhadian et al., 2021). The degree of proinflammatory markers is correlated with cognitive and behavioural changes. The simple fact that neurofilament light chain (NFL) is elevated in serum implies brain injury in COVID (Ameres et al., 2020), despite the apparent absence of neuronal virus. SARS-RNA, has been found in the frontal lobe of infected individuals and SARS-2 positive polymerase chain reaction (PCR) to this virus has been demonstrated in CSF (Ritchie et al., 2020).

The most supported theory is an autoimmune process with an exaggerated innate immune response and cytokine activation. Most patients with severe COVID-19 exhibit substantially elevated serum levels of pro-inflammatory cytokines including interleukin 6, 1- beta, 2, 8, 17, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, chemokine ligand 2 and 10, and tumour necrosis factor alpha, resulting in the now well- recognised cytokine storm (Ritchie et al., 2011). The presence of oligoclonal IgG bands and activated microglia resemble the process causing fatigue and cognitive impairment in MS (Muccioli et al., 2020).

One study described the expression of human endogenous retrovirus-W envelop protein (HERV-W ENV) being associated with the inflammatory changes in COVID-19[17]. HERVs are elements derived from retroviruses that infected the human ancestral genome millions of years ago and were incorporated into the chromosomal DNA. These integrated genes are epigenetically tightly controlled and can be unleashed or

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transactivated in certain conditions. Expression of this gene is found particularly in CD4 and CD8 cells and less so in B-cells (Balestrieri et al., 2021) and are associated with several proinflammatory cytokines IL-6 and 17, TNF-alpha as well as CCL-2 and CXCL-6. HERV-W-ENV protein has previously been implicated in MS progression, although a clinical trial with a monoclonal antibody against this protein (CHANGE) has failed to achieve its primary outcome (Sawcer et al., 2011). It is uncertain whether blocking this expression with a monoclonal antibody will result in reduced symptoms for Long COVID.

There are currently studies underway to describe the syndrome better, and what can be done to prevent it from occurring. At the moment it is a wide range of symptoms with unclear diagnostic criteria. See: https://clinicaltrials.gov/ct2/show/NCT04564287.

Currently, COVID-19 has infected 221 million individuals worldwide as of 5th of September 2021(https://www.worldometers.info/coronavirus/). Assuming a conservative estimate of 30% survivors who experience persistent symptoms, then over 66,000,000 individuals could be affected by the long-term consequences of COVID-19. With no curative treatment in sight, we need to prevent infection by vaccination. Otherwise, these figures portend an extended public health challenge of gargantuan proportions.

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