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## Letter to the Editor

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# How concerned should we be about neurotropism of SARS-Cov-2? A brief clinical consideration of the possible psychiatric implications

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*Dear Editor,*

I have read with great interest the fascinating paper of Ibrahim[1] on the neurological manifestations of COVID-19, and I must admit that I am not impressed at all with such essential and alarming results. Several evidence points out that some of these neurological symptoms may be persistent or even permanent. SARS-CoV-2 discovery in the brain is considerably delayed compared to that within the lungs, consistent with the respiratory system's initial infection before diffusion to the Central Nervous System (CNS).

As a psychiatrist who works in the everyday real-world clinical practice, I am very concerned about the neurotropism of SARS-CoV-2 and the possible repercussions on brain functions and, thus, the potential development of future severe mental illnesses (SMI) even in subjects without previous vulnerability.

The spike protein of SARS-CoV-2 mediates the virus entry in the cells through the angiotensin-converting enzyme 2 (ACE-2) receptors and is activated by a serine two protease transmembrane (TMPRSS2). Both ACE-2 and TMPRSS2 are highly present in the brain in critical regions for psychiatric disorders as the prefrontal cortex and hippocampus. Besides, microglia is a target for the SARS-CoV-2 through the same mechanisms leading to its activation that further damages the brain through a local cytokine storm syndrome reminiscent of mild viral and autoimmune encephalitis. Moreover, the CNS infiltration with CD8-positive T cells has been documented.

Moreover, SARS-CoV-2 is quite different from other coronaviruses, explaining its high infectiousness and that the treatment of patients admitted to the hospital for SARS-CoV-2 infection seems to be different from the treatment of those admitted for SARS-CoV-1 and MERS-CoV infections. Unlike other coronaviruses, SARS-CoV-2 also uses another protein, the neuropilin-1 (NP-1), to enter the cells through a furine cleavage of a site on spike protein.[2] The NP-1 binding potentiates the virus entering and spreading throughout the body, including the brain, whereas NP-1 is highly represented.

The potential of SARS-CoV-2 to infect the CNS and produce psychiatric manifestations is well demonstrated, and psychiatric symptoms are often seen in the clinical picture of COVID-19 patients. Kandemirly et al[3] showed that COVID-19 cases with bilateral frontal involvement had hypoxia as principal pathogenesis, given the underlying respiratory distress, and showed frontotemporal hypoperfusion. The cortical microhemorrhages and breakdown of the blood–brain barrier caused by COVID-19 can accompany hypoxia contributing to CNS damage. Not surprisingly, the psychiatric manifestations as psychosis, mania, delirium may be the results of general hypoxemia. Still, one can argue that these can also be the result of direct brain damage.

Concerning brain damages, recently, Lu et al[4] examined the brain of COVID-19 patients with diffusion tensor imaging and 3D high-resolution T1WI sequences. COVID-19 patients were more likely to show a reduced Mean Diffusivity, Axial Diffusivity, Radial Diffusivity, and an increased Fractional Anisotropy in white matter, thus disrupting the connectome. The detrimental effects of the COVID-19 were present in essential areas as the right cingulate cortex and bilateral hippocampi. One can argue that these lesions may be transient. However, it is possible to hypothesize that the brain microstructure can remain permanently damaged, triggering a kind of "acquired vulnerability": this is the background of the potential development of future psychiatric sequelae. Lu et al wrote that "…the abnormalities in these brain areas might cause long-term burden to COVID-19 patients after recovery, which was thus worth public attention." Interestingly, in younger patients without significant cerebrovascular events there is a link between COVID-19 and new acute neuropsychiatric complications.

Of course, COVID-19 subjects with a previous vulnerability to SMI (ie, those with a familiar positive history for SMI or attenuated symptoms) are at ultra-high risk to develop full-blown psychiatric disorders, and this deserves public attention too. Moreover, subjects with SMI (such

as depression, bipolar disorder, schizophrenia, and Attention-deficit hyperactivity disorder (ADHD)) are more vulnerable to COVID-19 infection, mainly based on ethnic and gender disparities, and have higher mortality and hospitalization rates when the diagnosis of SMI is recent.[5] The inflammation is a common biological factor that may contribute to both several SMI and COVID-19 pathology. Moreover, smoking can promote SARS-CoV-2 cellular entry through the nicotinic acetylcholine receptor (nAChR) signaling, and the nicotine stimulation of the nAChR can increase ACE2 expression. As most subjects with SMI are smokers, they are at high risk of developing severe COVID-19 and, thus, more severe CNS impairment.

All considered, what could we expect from this evidence? Even dreaded, the psychiatric "tsunami" of SMI has not yet arrived even if I have observed an increase in newer cases or re-exempting previous ones. The question in my mind is if this is only a matter of time. The analysis of other coronavirus infection's psychiatric consequences may help us further understand what to expect. SARS-CoV-1 and MERS-CoV infection have been associated with acute and chronic psychiatric manifestations, which point out a probable relationship between coronavirus infections and later psychosis as coronaviruses may proliferate in the limbic structures. In the longer term, the data from SARS-CoV-1 and MERS-CoV showed that the prevalence of depression, anxiety, post-traumatic stress disorder was relatively high.

As psychosocial factors are heavily involved in the development of SMI, the COVID-19 survivors, unlike SARS-CoV-1 and MERS-CoV survivors, will live into an unavoidable period of deep economic crisis, with a scarcity of basic needs in some countries and other countries still in lockdown and enforcing physical isolation. These social hardships will retain high-stress levels after recovery high and increase subjects' risk for long-term psychiatric complications such as anxiety, depression, and psychosis.[5]

Lastly, a newer clinical picture, increasingly referred to as "Long Covid," has been described in subjects with COVID-19 who did not necessitate hospital treatment. These subjects report a wide variety of symptoms, persisting for many months after acute infection, and these include psychiatric symptoms such as anxiety, depression, suicidal ideation, and mood shifts.

In conclusion, the likelihood of late neuropsychiatric manifestations after SARS-CoV-2 infection is probable as the possibility of permanent neurological symptoms. Careful watching of late neuropsychiatric manifestations is essential to plan preventive interventions. "Better safe than sorry!"

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