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LETTER TO THE EDITOR

Increased neuropilin-1 expression by COVID-19: a possible cause of long-term neurological complications and progression of primary brain tumors

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To the Editor,

Nowadays, there is growing evidence of neurological abnormalities with coronavirus disease 2019 (COVID-19) [1–3]. Nevertheless, in COVID-19 cases, the exact mechanisms of the central nervous system (CNS)-related pathological consequences are not entirely understood. Therefore, uncovering underlying mechanisms can open new windows to the prevention and/or treatment of these complications. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the cause of COVID-19) can access the central nervous system (CNS) in three ways: (a) using olfactory bulb neurons (or other nerve endings) to travel from the periphery to the brain, (b) by crossing the blood–brain barrier (BBB) to gain access to the brain, and (c) by neuronal pathways [2].

Recently, the brain-related abnormalities in COVID-19, especially mild cases, exhibited significant damage in the limbic system (atrophied), reduced gray matter thickness in fronto-parietal and temporal regions, and were functionally linked to the primary olfactory cortex. Also, the result of longitudinal MRI revealed the most significant effect observed in the volume of the thalamus, notable cognitive decline events, and the reduction of brain size changes [4].

Here, we hypothesized that SARS-CoV-2 infection could lead to long-term neurological complications and progression in primary brain tumors by upregulating the expression of Neuropilin-1 (NRP-1), especially in those who have contracted SARS-CoV-2 several times.

NRP-1 acts as a viral entry receptor besides angiotensin-converting enzyme 2 (ACE2), Ephrin (Eph) receptor, and CD147 that can contribute to SARS-CoV-2 viral entry to host cells in CNS, as well as stimulating intracellular signaling pathways which may be associated with pathological complications related to CNS and glioblastoma [2, 3, 5–7].

Previous studies have discussed the neurologic impacts of long-COVID, and the implications of this potential neurotropism. It includes how viruses use complete cytokine profiles and cause pain through direct and indirect interactions with nociceptors' plasticity [5].

Recent reports also revealed different nervous system complications observed during the acute and post-infection phases of COVID-19. However, knowledge of the post-acute neurological magnitudes of COVID-19, including memory or cognitive disturbances, insomnia, post-exertional malaise or fatigue, loss of smell or taste, headache, and other sleep disturbances, remained limited. Furthermore, the neurological problems that persisted 3–9 months from their date of infection with SARS-CoV-2 included vertigo, depression, memory, taste or smell disturbances, and cognitive disturbances reported as negatively affecting the neurological health of individuals [1]. In a recent study by Gwenaëlle Douaud et al. [1], the results have shown that COVID-19 can change the brain structure. Their investigation found significant long-term effects in these cases: (a) reduction in gray matter thickness and tissue contrast in the para-hippocampal gyrus and orbitofrontal cortex, (b) changes in tissue damage markers in regions

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functionally connected to the primary olfactory cortex, and (c) total brain size reduction.

Studies conducted previously revealed that the occurrence of neurological symptoms associated with COVID-19, such as acute ischemic stroke (AIS), acute necrotizing encephalitis, encephalopathy, peripheral neuropathy, headaches, seizures, cerebral micro-bleeds, demyelinating diseases, meningitis, Guillain–Barré syndrome, skeletal muscular symptoms, neurodegenerative diseases, as well as multiple cancers like glioblastoma is rapidly increasing [2, 8–10]. According to a study by de Joode et al., overall mortality rates for cancer patients with COVID-19 in some studies are between 32.3 and 35.4% [11], and the pooled case mortality rate among patients with cancer and COVID-19 was 25.6% [12]. Also, it has been reported that patients with primary brain tumors [e.g., glioblastoma, astrocytoma, oligodendroglioma, ependymoma, primary central nervous system lymphoma (PCNSL)] are more prone to experience a severe form of COVID-19 and/or a higher rate of mortality [11].

Infection of the CNS with SARS-CoV-2 could result in neurodegenerative diseases due to entry receptors for the virus in this region. NRP-1 is one of the two homologous neuropilins that plays critical roles in physiological and pathological conditions. An essential function of NRP-1 is to act as a receptor for signaling ligands, such as vascular endothelial growth factor (VEGF) (especially VEGF-A), integrins, semaphorins, transforming growth factor-beta (TGF-β), and plexins. It plays an essential role in many processes, including tumor progression, angiogenesis, viral entry, axonal guidance in the CNS and peripheral nervous system (PNS), and immune function [2]. In a study by Cantuti-Castelvetri et al., SARS-CoV-2 was shown to bind with NRP-1 by S protein and ultimately enter neurons and then increase NRP-1 expression and two crucial factors proteases Furin and Transmembrane serine protease 11A (TMPRSS11A) in SARS-CoV-2-infected cells [13]. Since olfactory epithelial cells express high levels of NRP-1 in COVID-19 patients, and VEGF-A is a ligand for NRP-1 [14], this suggests that one cause of patients' cognitive and neurological impairment may be the vulnerability of these brain regions to SARS-CoV-2. In addition, increased expression of NRP-1 may promote viral entry, stimulate intracellular signaling pathways in CNS cells, and contribute to the development and progression of neurodegenerative diseases and primary brain tumors in susceptible individuals.

A part of NRPs involved in binding vascular endothelial growth factor A (VEGF-A) is their extracellular b1b2 domain. This receptor plays a major role in angiogenesis as co-receptors for VEGFR-1 and -2 [15]. As VEGF-A binds to NRP-1, it increases the interaction between NRP-1 and GIPC1 (a scaffold protein) and facilitates the assembly of the GAIP/RGS19-interacting protein (GIPC1) + Syx signaling molecular complex, resulting in RhoA GTP binding. RhoA is activated and this activated form leads to the tumor suppressor p27 protein degradation. Therefore, this leads to the proliferation of tumor cells [16]. In addition, angiogenesis, proliferation, and migration mediated by NRP-1/GIPC1 are likely to be regulated by PI3K/Akt/NF-κB pathway activation [15].

In conclusion, we hypothesized that upregulated expression of NRP-1 by COVID-19 may be a significant cause of long-term CNS-related pathological complications and possibly lead to progression of primary brain tumors, especially in cases infected by SARS-CoV-2 several times. Therefore, we suggest that pharmacological targeting of NRP-1 in such susceptible patients could be beneficial and a promising therapeutic approach to combat long-term neurological complications and reduce the risk of primary brain tumors' progression.

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Declarations

Conflict of interest There is no conflict of interest.

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