Cerebrovascular and Neurological Dysfunction

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The recently discovered novel coronavirus, SARS-CoV-2 (COVID-19 virus), has brought the whole world to a standstill with critical challenges, affecting both health and economic sectors worldwide. Although initially, this pandemic was associated with causing severe pulmonary and respiratory disorders, recent case studies reported the association of cerebrovascular-neurological dysfunction in COVID-19 patients, which is also life-threatening. Several SARS-CoV-2 positive case studies have been reported where there are mild or no symptoms of this virus. However, a selection of patients is suffering from large artery ischemic strokes. Although the pathophysiology of the SARS-CoV-2 virus affecting the cerebrovascular system has not been elucidated yet, researchers have identified several pathogenic mechanisms, including a role for the ACE2 receptor. Therefore, it is extremely crucial to identify the risk factors related to the progression and adverse outcome of cerebrovascular-neurological dysfunction in COVID-19 patients. Since many articles have reported the effect of smoking (tobacco and cannabis) and vaping in cerebrovascular and neurological systems, and considering that smokers are more prone to viral and bacterial infection compared to non-smokers, it is high time to explore the probable correlation of smoking in COVID-19 patients. Herein, we have reviewed the possible role of smoking and vaping on cerebrovascular and neurological dysfunction in COVID-19 patients, along with potential pathogenic mechanisms associated with it.

SARS-CoV-2 COVID-19 cerebrovascular neurological smoking CNS blood-brain barrier

1. Neurological and Cerebrovascular Manifestations of COVID-19

SARS-CoV-2, the responsible virus for COVID-19, is 79.5% genetically similar to SARS-CoV and 96% similar to bat coronavirus [1]. The sequence homology of SARS-CoV-2 also showed a 50% similarity to MERS-CoV virus [2]. Although the primary symptoms of COVID-19 include fever, dry cough, and fatigue in most of the patients [3], some COVID-19 patients exhibited sole neurological symptoms including headache, dizziness, languidness, unstable walking, malaise, cerebral hemorrhage, and infarction without showing any of the typical COVID-19 symptoms [4]. Additional studies have also reported a sudden loss of smell or taste in some COVID-19 patients as well [5][6].

A current study comprising 214 patients demonstrated that 36.45% of patients of the total cohort showed neurological symptoms, including acute cerebrovascular disease, impairment of consciousness, and skeletal muscle motor function disability; 18.7% of total admitted patients had these severe neurological manifestations and

required admission to the intensive care unit [4][7]. Other case studies (shown in Table 1) also reported that acute cerebrovascular and neurological symptoms, including headache, dizziness, impaired consciousness, olfactory disorders, have been found in COVID-19 patients. Table 1 summarizes recent case studies related to COVID-19 and neurological dysfunction. However, one of the limitations of the case studies is that the analysis of cerebrospinal fluid (CSF) and electroencephalography (EEG) was not performed to confirm the presence of the virus in the CSF [8].

Table 1. Case studies on neurological and cerebrovascular symptoms in COVID-19 patients.

Study Type	Time	Study Design	Outcome and Symptoms	Reference
Retrospective case series	13 January to 31 March	*N* = 274, admitted patients	Headache (11.31%), Dizziness (7.66%)	[9]
Retrospective case series	16 January 2020 to 29 February 2020	*N* = 221, admitted patients	Acute ischemic stroke (5%), CVST (0.5%), cerebral hemorrhage (0.5%)	[10]
Retrospective case series	16 January 2020 to 19 February 2020	*N* = 214, admitted patients	Nervous system symptoms (36.4%) including CNS symptoms (24.8%): (Headache (13.1%), dizziness (16.8%), impaired consciousness (7.5%), acute cerebrovascular disease (2.8%), ataxia (0.5%), epilepsy (0.5%))	[7]
Retrospective case series	1 January to 28 January, 2020	*N* = 138 admitted patients	Headache (7%), dizziness (9%)	[11]
Retrospective case series	1 January to 20 January, 2020	*N* = 99, admitted patients	Headache (8%), confusion (9%)	[12]
Cross-sectional survey	19 March, 2020	*N* = 59, admitted patients	Headache (3.4%) Taste or olfactory disorder (33.9%), Taste and olfactory disorder (18.6%)	[5]
Retrospective case series	late December 2019- 26 Jan 2020	*N* = 52, admitted patients (critically ill adults)	Headache (6%)	[13]
Prospective case series	By 2 January 2020	*N* = 41, admitted patients	Headache (8%) in 38 patients	[3]

Study Type	Time	Study Design	Outcome and Symptoms	Reference
Case study	23 March to 7 April	*N* = 5	Large-vessel stroke (100%) [14]	[14]

0 and 40 nal blood

Another important finding is the detection of the genome sequence of SARS-CoV-2 in cerebrospinal fluid, which opens up a direction towards the damage of CNS in COVID-19 patients causing viral encephalitis [15]. Moreover, some of the COVID-19 patients were found to suffer from viremia and hypoxia [16], which play a crucial role in developing toxic encephalopathy. The occurrence of headache, disturbance in consciousness, other neurological dysfunction is close to 40% of COVID-19 patients [17], and the concurrent detection of brain tissue edema seems to suggest the existence of a possible link between COVID-19 and infectious, toxic encephalopathy [18]. However, extensive studies need to be conducted to validate this hypothesis further. Additionally, it has been reported that SARS-CoV-2 can initiate a cytokine storm mechanism, which may lead to a range of infectious and non-infectious diseases, including pancreatitis, acute cerebrovascular disease, and multiple organ dysfunction [19][20][21]. Critically-infected patients also showed a high level of D dimer and severe reduction in platelets, which may make the patients more vulnerable to acute cerebrovascular dysfunction [22]. Additionally, it has been speculated that COVID-19 positive patients are vulnerable to other types of pathogenic bacteria, which can damage the integrity of the blood-brain barrier (BBB). Subsequently, this secondary infection may lead to headaches, vomiting, loss of vision, and limb convulsions in COVID-19 patients [15].

Focusing on current case studies and research on COVID-19 patients, it is evident that COVID-19 could be associated with neurological and cerebrovascular dysfunction, which can be life-threatening as well.

2. Pathophysiology of COVID-19 Related Cerebrovascular and Neurological Dysfunction

Although the underlying mechanism behind cerebrovascular and neurological dysfunction in COVID-19 patients has not been elucidated yet, several potential mechanisms could be non-exclusively responsible for the identified comorbidities. One of the critical targets of SARS-CoV-2 is Angiotensin-converting enzyme 2 (ACE2) [4], which is present in different organs including lung, heart, kidney, testis as well neurons and glial cells of the brain [23][24][25][26]. ACE2 plays a pivotal role in the regulation of blood pressure as well as anti-atherosclerosis mechanisms [27]. It has been demonstrated from various studies that different types of CoV and influenza viruses may elevate blood pressure and increase the potential risk of cerebral hemorrhage by binding to ACE2. A recent study has also reported that SARS-CoV-2 enters into the host cell through the interaction of SARS-CoV-2 coat protein SPIKE or (S protein) with ACE2 present on the host cell resulting in the internalization of the virus [28][29][30]. The expression of ACE2 is found to be low in hypertensive patients, which increases the chance of hemorrhagic occurrence. Since SARS-CoV-2 decreases the ACE2 expression [31] it can be speculated that the SARS-CoV-2 infected patients are at high risk of hemorrhagic stroke (see Figure 1).

Additionally, COVID-19 patients suffer from coagulopathy and prothrombin time prolongation, which may contribute to secondary cerebral hemorrhage, although, as of today, no secondary cerebral hemorrhage has been reported in

COVID-19 patients [4]. Moreover, an increased level of D-dimer has been found in COVID-19 patients, which may result in thrombotic vascular events [4][32]. As SARS-CoV-2 has been found in cerebrospinal fluid, it is crucial to evaluate the protective role of the BBB in preventing the virus from getting access to neural tissues [26]. This is of crucial importance since comorbid pathologies (such as those promoted by chronic smoking and vaping [33][34][35][36]) that negatively impact the integrity and function of the BBB may facilitate the virus entry into the CNS.

Another important mechanism behind the cerebrovascular and neurological symptoms in COVID-19 patients could be an immune injury. It has been found that viral infection may damage the nervous system by altering the immune responses [37]. A CoV infection-mediated severe pneumonia could promote systemic inflammatory response syndrome (SIRS). Studies suggested that immune damage could be prevented by early anti-inflammatory intervention and could also decrease the risk of nervous system injury [19][38]. Both SARS and COVID-19 have been found to cause multiple organ failure-mediated fatalities through virus-induced SIRS or SIRS-like immune disorders [20][39].

Cytokines play a pivotal role in regulating immunological and inflammatory function of the body [40]. Additional studies confirmed the release of high level of inflammatory factors, such as interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-15 (IL-15), and tumor necrosis factor-α (TNF-α) from primary glial cells infected with CoV [41]. Recently, Wan et al. reported the correlation of IL-6 with the severity of COVID-19 symptoms [42]. IL-6 may act as a potential biomarker of SARS-CoV-2 as IL-6 level has been found to be increased in COVID-19 patients [40] As CoV infection can infect macrophages, microglia, and astrocytes in the CNS inducing pro-inflammatory conditions [43] and activation of immune cells, it is crucial to find the probable correlation between COVID-19 and neurological damage through immune injury.

Moreover, the proliferation of viruses in the lung tissue may lead to an impaired exchange of alveolar gas, thus triggering hypoxia in CNS. This hypoxia causes anaerobic metabolism in brain cells, which accumulates acid causing cerebral vasodilation, brain cells swelling, interstitial edema, blockage of cerebral blood flow, and headache because of ischemia and congestion [44]. Untreated hypoxia may induce acute cerebrovascular disease encompassing acute ischemic stroke in high-risk COVID-19 patients [15]. As COVID-19 patients often suffer from fatal silent hypoxia, it requires substantial examination and consideration [45]. Additionally, ACE2 also plays a role in controlling inflammatory and atherosclerosis responses of vessels [46]. Thus, COVID-19 may promote atherosclerosis formation, which ultimately may result in brain ischemic stroke by affecting brain microcapillaries.

A neurotrophic virus can also enter the CNS through neuronal pathways such as the olfactory neuron transport system. Studies reported that, in the early stage of infection or nasal vaccination, CoV could reach the brain through the olfactory tract, thus causing inflammation and demyelination [15][47][48]. Therefore, it is evident that CoV viruses can invade the brain by neuronal pathways, and this mechanism should also be investigated in the case of SARS-CoV-2.

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