

Review article

Neurological consequences of SARS-COV-2 infection: A review

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Abstract

As the current understanding of COVID-19 continues to emerge, the compilation of literature on the neurological impact of this novel virus might facilitate inform clinical management and highlight potential non-investigative approaches. Besides, perceiving the potential mechanisms of neurologic injury can guide efforts to better understand these conditions. Therefore, in this review, we include the scope of pre-terminal observation and a series of preliminary cases describing the likelihood and potential neurological manifestations related to SARS-CoV-2 infection. Reported manifestations of the nervous system vary from anosmia and ageusia to hemorrhage and infarction and numerous other serious complications. While the number of studies on COVID-19 related cases continues to grow, previous experimental virus-related work suggests possible ways in which the novel coronavirus will have an effect on the nervous system and cause neurological issues. In depth awareness of the necessary neurotropism of CoVs might contribute to the early detection of signs and symptoms of infection and injury to the nervous system caused by the virus and pave way to new prognostic testing and targeted medical interventions.

Keywords: SARS-CoV-2; Nervous system; Neurological complications; Neuroinvasion

Introduction

Coronaviruses (CoVs), are large enveloped non-segmented group of viruses containing positive-sense RNA, which are often seen causing respiratory complications in animals and humans. The novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus-2: SARS-CoV-2) appeared and began to be discovered for the first time in December, 2019 in China and led to a national outbreak of pneumonia in China¹, and now it seems to be spreading rapidly around the world and has already passed the necessary epidemiological criteria for it to be declared a pandemic, and has resulted in more than 243,572,402 confirmed cases and more than 4,948,434 deaths across 218 countries and geographical regions as of October 26, 2021². The RNA virus SARS-CoV-2 belongs to the family of

β -coronavirus, and has a length of 29,881 bp with 9860 coding amino acids³. The virus envelope contains a lipid bilayer consisting of structural proteins i.e., spike protein (S), an envelope protein (E), membrane protein (M), and a nucleocapsid protein (N)⁴. The interaction between protein particularly the spike protein and the host cell receptor has been identified as an important requirement for virulence and infection⁵. In terms of its functioning, according to Mousavizadeh et al., SARS-CoV-2 appears to bind to ACE2 (Angiotensin-Converting Enzyme 2) receptors that are present on the cells which permit SARS-CoV-2 to gain entry thereby infecting of cells⁶. Apart from the very evident respiratory difficulties faced by SARS-CoV-2 infected patients, neurological complications are also found to be present in an increased number in SARS-CoV-2 cases. The various potential neurological symptoms and

syndromes caused by SARS-CoV-2 infection includes mild to moderate headache, fatigue, dizziness, anosmia, ageusia, anorexia, myalgias and severe cases of meningoencephalitis, hemorrhage, altered consciousness, Guillain-Barré syndrome, syncope, seizure, stroke⁷. The novel SARS-CoV-2 belongs to the same beta coronavirus (β CoV) family of MERS-CoV (Middle East respiratory syndrome-related coronavirus) and SARS-CoV and share a high sequence similarity with SARS-CoV which was confirmed as a result of genomic analysis. Evidence suggests that SARS-CoV-2 shares similar pathogenesis with pneumonia triggered by SARS-CoV or MERS-CoV⁸. As a result of next-generation sequencing conducted on the emergence of the pandemic, it showed that SARS-CoV-2 was found to be significantly identical to the two colonies found by bats such as SARS-like coronaviruses - bat-SL-CoVZC45 (with 87.9% sequence identity) and bat-SL-CoVZXC21 (with 87.2% sequence identity) and much reserved from SARS-CoV (with 79% sequence identity) and MERS-CoV (with 50% sequence identity). Furthermore, based on the results of a recent study, SARS-CoV-2 invasion into human host cells was shown to have a stronger affinity with ACE2 molecules, which are present in the human cell surface, and this seems to be the same mechanism followed by other CoVs^{9, 10}. ACE2 exhibits a diffuse distribution in various organs including neural cells and brain cells even though it is mainly respiratory system being its primary target. However, mild to moderate neurological symptoms including headache, anosmia, ageusia, confusion, fainting, and encephalopathy are more frequently been reported in patients with SARS-CoV-2 infection¹¹. The neurological complications as a result of SARS-COV-2 infection were first reported in China in the form of headache¹².

When looked into the range of symptoms shown by the current pandemic caused by SARS-CoV-2, it is seen to emerge from mild to severe with fever, cough, and shortness of breath being the most common symptoms of the disease¹³. Although various lines of evidence support the involvement of the human nervous system in SARS-CoV, MERS-CoV, and SARS-CoV-2 infections, it is still difficult to determine how different neurological factors relate to the overall pathophysiology; that is, whether they lead directly or indirectly as a result of a viral infection, or appear in other ways, such as multiple organ failure, hypoxia, or sepsis. A possible hypothesis may be that since the loss of sense of smell (anosmia) and the loss of sense of taste (ageusia) are the first SARS-COV-2 infection symptoms, this provides some evidence of infection in the olfactory nerve and brain. The lack of smell is often considered the first visible sign of Central Nervous System (CNS) damage and is also the first sign of diseases such as Parkinson's¹⁴ and Alzheimer's¹⁵, thus suggesting that germs can reach the brain and cause dysfunction as a consequence of the virus traveling through the olfactory nerve by penetrating itself into the Cerebrospinal fluid (CSF) and entering the spinal cord continuing to infect nerve endings and/or attach to existing ACE2 receptors and ultimately affect the CNS (Fig. 1). The brainstem respiratory centre can be considered as one of the main targets of SARS-CoV-2 leading to various respiratory illnesses and dysfunction in patients¹. While many studies have focused on the respiratory manifestations of SARS-COV-2, the neurological manifestations of the recent SARS-CoV-2 outbreak are increasingly a major cause for concern.

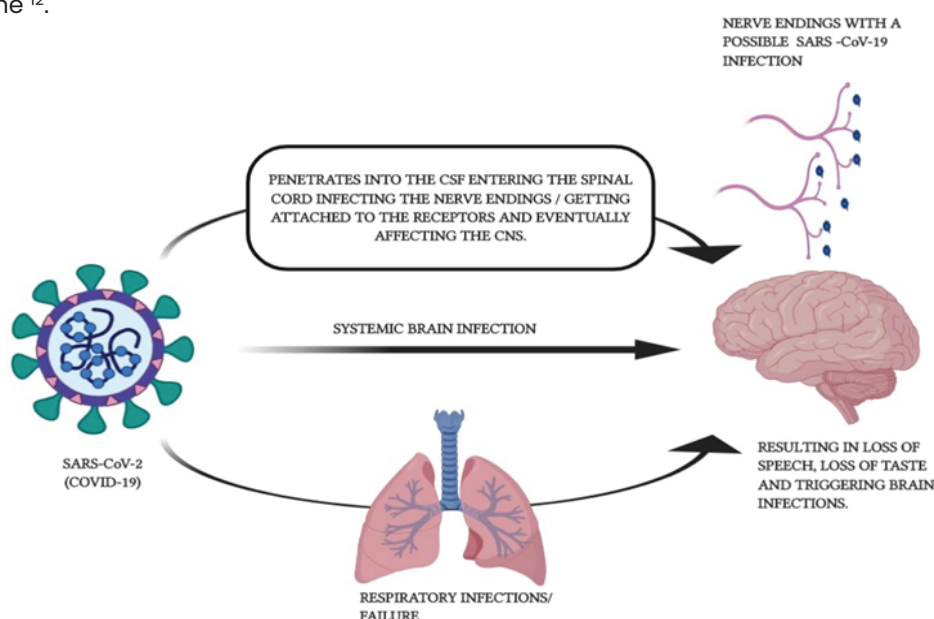


Fig.1.:SARS-COV-2 entry into CNS. The entry of human Coronavirus in CNS through olfactory bulb upon nasal infection which could cause inflammation and infection (created with biorender.com).

These viruses have been shown to have the capability to invade the CNS which was confirmed by examining the CSF samples collected from patients affected with SARS-CoV and MERS-CoV. Besides that, the SARS-CoV virus antigen were found mainly in bulb olfactory, piriform, basal ganglia, midbrain and other regions of infected patients suspecting that direct inoculation of the olfactory bulb through the cribriform plate may be one mechanism for the intrusion of the virus into the CNS⁷. Concerning the before mentioned similarities existing between SARS-CoV-2 and other beta coronaviruses, it is not an unexpected fact that patients with SARS-COV-2 show neurological symptoms and complications. Many patients with the novel coronavirus have reported a wide range of neurological symptoms ranging from mild and indirect symptoms such as anosmia, hyposmia, headache, nausea, vomiting, fatigue, myalgia, and irregular mobility to more serious symptoms such as meningitis, encephalitis, cerebral hemorrhage. and other neurological problems. In addition to the olfactory pathway, it has been shown that SARS-CoV-2 could invade the CNS either via hematogenic, retrograde, or through anterograde neuronal transport¹.

Understanding neuroinvasion mechanisms of the virus can help researchers identify disease-related outcomes in the best way possible by prioritizing the best diagnostic criteria and working to improve the management and treatment of the disease. In this review article, we summarize the potential SARS-CoV-2 infiltration leading to the symptoms of SARS-COV-2 infection in the CNS and the Peripheral Nervous System (PNS) which further illuminates viral neuropathology and other viral effects. nervous and nervous disorders.

The Possible Entrance Mechanisms Of Sars-Cov-2 Into The Nervous System And Its Neuropathology

Even though there exist several proposed ways SARS-CoV-2 is integrated into the nervous system, the exact mechanism of its neural infiltration has not yet been elucidated. The virus can directly attack nerve tissue based on its exposure to CSF and brain tissue. SARS-CoV-2 can also spread through the bloodstream to conquer various organs. Patients with SARS-CoV-2 syndrome are exposed to the presence of the virus in the CSF, the virus happens to gain access into the CNS via the olfactory pathway by infecting the olfactory receptor neurons (ORNs) or non-neural cells with the help of both ACE2 receptor and spike protein protease

TMPRSS2 (Trans Membrane Protease, Serine 2), which are also required for SARS-CoV-2 infiltration^{16,17}. It is seen that the ACE2 and TMPRSS2 receptors involved in the transmission route are strongly expressed in the olfactory mucosa of humans and mice, and their expression increases with age in the mouse model¹⁸.

Various studies and reports have shown that the mechanism of infection is based on ACE2, which functions as a functional receptor for SARS-CoV-2. Viral spike proteins interact with ACE 2 receptors expressed in brain neurons and glial cells, making the brain susceptible to nerve infiltration. After binding to the ACE 2 receptor, TMPRSS2 causes proteolytic cleavage and priming of the spike protein, allowing the virus to invade the host cell and causing a variety of neurological complications¹⁹. Li et al., stated that the pathways associated with viral entry into the brain may be primarily related to specific transduction pathways and the presence of receptors in viral cells. The vascular pathway to the brain is theoretically fast, but only if the disease has progressed to some extent and the blood-brain barrier (BBB) has become inactive. In addition, the delineating neuronal pathways in peripheral neural pathways is slow. However, the olfactory epithelium is characterized by the presence of sensory neurons. SARS-CoV-2 can enter sensory neurons and replicate quickly. In addition, previous research suggests that CoVs may first attack the peripheral nerve terminals and then enter the brain by means of transmission of a nerve impulse across a synapse. Because the olfactory nerve is physically close to the center, the sensory pathway may prove to be one of the major mechanisms by which the virus invades the brain during the early onset of infection²⁰.

These viruses also infect BBB endothelial cells and invade nervous tissue by breaking the blood cerebrospinal fluid barrier or by using leukocytes as a vector for distribution in the CNS²¹. The role of brain professional phagocytes, especially microglia act as BBB's first line of defense to contain the virus and prevent access to nervous tissue, but this phenomenon needs further investigation in patients diagnosed with SARS-COV-2 as to find out what exactly happens and how the virus crosses the BBB. On collecting clinical findings, inflammation of the blood vessels as a major cause of acquired syndrome known as SARS-CoV-2-related coagulopathy which is a multifactorial condition with the involvement of veins, arteries, and the microcirculatory system, and others and distinct from other viral illnesses and was recently suggested that particles of of

SARS-CoV-2 virus also infect endothelial cells²². ACE2 protein has been observed in human brain vessels, a finding recently attributed to expression in pericytes and smooth muscle cells in the vascular wall, but not in the endothelium lining cerebral vessels²³. The expression pattern of ACE-2 on cells in almost all organs suggests that the SARS-CoV-2, once present in the circulation, can spread easily through the body²⁴. Pericyte deficiency leads to increased endothelial proliferation and release of von Willebrand factor and intravascular platelets, followed by fibrin synthesis, suggesting that pericytes act by reducing the thrombus-promoting response of the endothelium. This may provide important clues to SARS-COV-2 disease, as pericytes are protected behind the endothelial barrier and become infected only when this boundary is disrupted by SARS-COV-2 risk factors²⁵. Therefore, further studies focusing on mechanisms under the influence of SARS-CoV-2 in the brain and associated cells may provide promising future research methods aimed at improved understanding of SARS-CoV-2 neurotropism.

The neuroinvasive component of SARS-CoV-2 can cause neurological damage in a variety of neuropathological pathways. Because of the similar structure and mode of infection between SARS-CoV-2 and other members of the coronavirus family, the same neuropathology approach can be speculated. As the mechanism of action of the SARS-CoV-2 nervous system remains to be determined. Several theories have been submitted including ACE2 receptor expression, olfactory pathway neuronal pathway, direct invasion, blood circulatory pathway, hypoxia injury, immune injury/cytokine storm syndromes, among various other²⁶. Reportedly, one of the most common neuropathological processes of SARS-CoV-2 is caused by hyperinflammatory disease. The excess immune system leads to the massive release of inflammatory cytokines such as Interleukin 2 (IL2), Interleukin 6 (IL6), Interleukin 7 (IL7), Interleukin 10 (IL 10), Tumor Necrosis Factor- α (TNF- α), and Granulocyte colony-stimulating factor (G-CSF or GCSF) and chemokines (CXCL10, and CCL2)²⁷. These factors have conceivably altered the BBB's influx which increases the beginning of neuroinflammatory cascades. An important feature of SARS-CoV-2 is the maladaptive immune response characterized by increased innate immunity and subsequent immunosuppression²³. Rahman et al.,²⁰²⁰ suggest that SARS-CoV-2 virus could easily spread to the medullary cardiorespiratory centre in the brainstem via chemoreceptors and mechanoreceptors of the lung, as observed in several other respiratory viruses. Suggests. This increases the

likelihood of a neurological mechanism of respiratory failure in some SARS-COV-2-infected patients. ACE2 receptors are found in the alveolar epithelium of the lungs, but the mechanism by which the virus migrates from the lungs to the nervous system remains unclear. The detection of SARS-CoV-2 by CSF or brain biopsy further reveals this potential pathway. In addition to the inflammatory effects of the brain, neurological symptoms can also be caused by hypoxia-related damage²⁸.

Further, destruction of cells in the sensory nerve epithelium can cause inflammatory changes that impair the function of the olfactory receptor neurons, causing subsequent damage to the olfactory receptor neurons, and / or impairing subsequent neurogenesis. Such changes can cause temporary or long-term sensory dysfunction. This has led to the suggestion that SARS-CoV-2 can penetrate intracranially and have downstream effects on the olfactory and non-olfactory areas of the brain, which can have serious effects on olfactory function²⁹. Moreover, studies with human samples are not enough to prove that this approach is the current leading belief. A better picture on the mechanism and the onset of these manifestations are been studied using animal models³⁰; 26. Concerning the existing evidence of neurotropism of SARS and MERS and other β CoVs^{31,26}, and based on current evidence of the presence of viral receptors in myelin and olfactory cells neural epithelium, SARS-CoV-2's neurotrophic attack on the sensory pathway appears plausible. This seems to clarify most of the neurological symptoms in SARS-COV-2. There are opportunities for multiple pathways followed by SARS-CoV-2 to gain access to the brain, or multiple pathways may be involved in the pathogenesis of neurological symptoms³². Several potentially interacting mechanisms have been suggested for neurological symptoms including hypoxia, severe cytokine storms during and post-infection autoimmune reactions, hypercoagulation, endotheliopathy, multiple organ failure (eg, liver failure leading to metabolic disorders), and possibly direct nerve infiltration³³. Currently, although specific pieces of evidence on specific SARS-CoV-2 neuropathogenic compounds are very limited. Future research conducted and tested in an in-situ / in-vivo environment will be needed to get a clearer view of the virus-host interaction and may provide a better understanding of its mechanism of action.

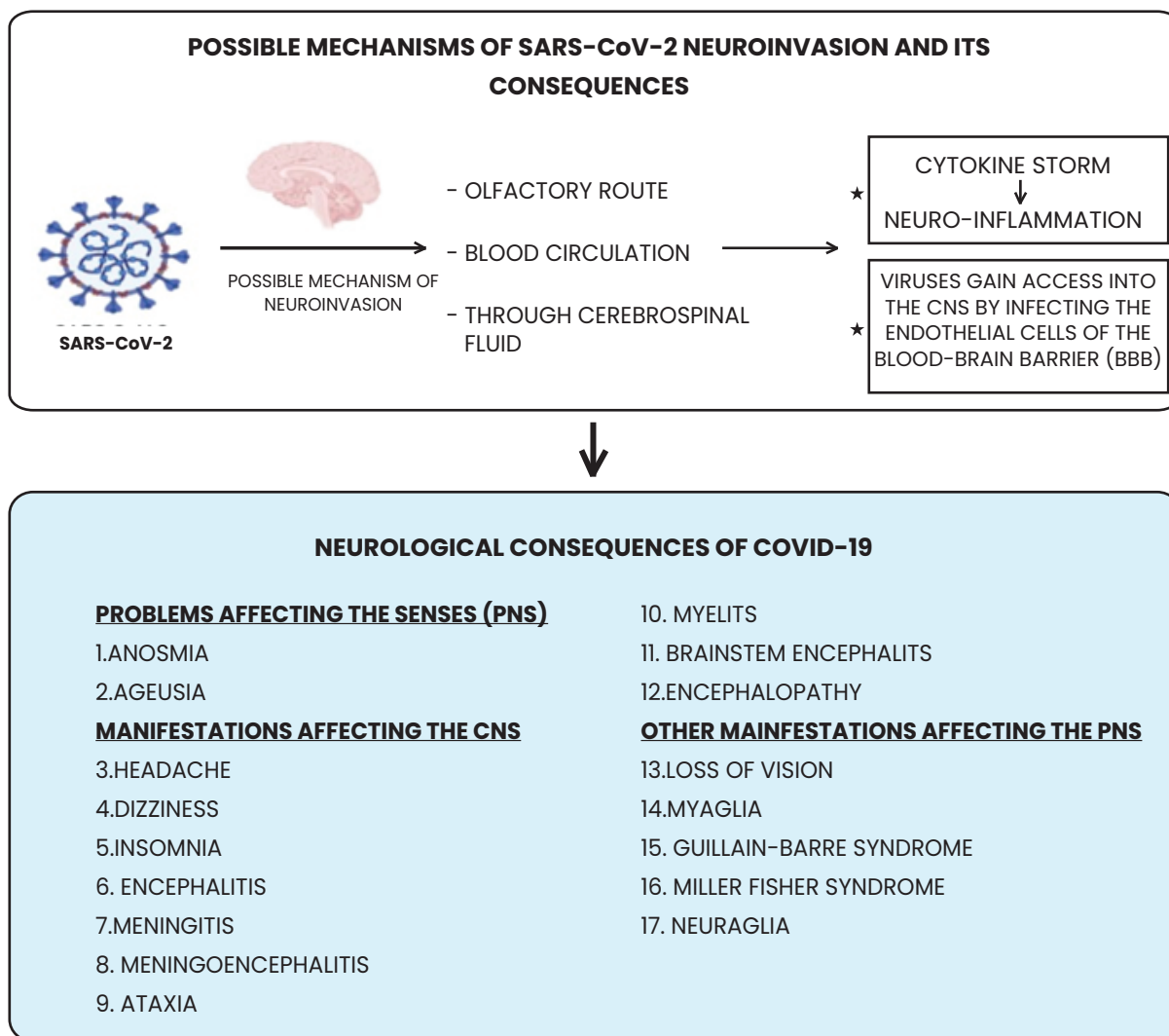


Fig.2. - Possible mechanisms of neuroinvasion by SARS-CoV-2 and its resulting neurological manifestations (Created with biorender.com).

Neurological Manifestations Of Patients With Sars-Cov-2 Infection

SARS-CoV-2 is known to bind to ACE2. ACE2 is upregulated in the human cerebrovascular system in cases of hypertension and dementia. Endothelial cells of the brain exhibit a marked pro-inflammatory response when exposed to various SARS-CoV-2 peplomer subunits. BBB function is adversely affected by the SARS-CoV-2 spike protein subunit. Mechanistically, barrier disruption can be explained by the induction of members of the matrix metalloproteinase (MMP) protein family. An analysis conducted by Buzhdygan et al., provides evidence that the SARS-CoV -2 spike protein directly affects the barrier function of BBB, allowing deeper insight into the neuropathology

associated with SARS-COV-2. It has also been found that SARS-CoV-2 can induce microclot formation in blood vessels of peripheral tissues and blood vessels of CNS³⁴. Given the previous evidence of possible SARS-CoV invasion into the central nervous system and the fact that SARS-CoV-2 has genetic similarities to it, the neurological complications that may result from SARS-CoV2 infection should be taken into consideration. The mode of infection for both viruses is found to be via ACE 2 receptors to gain access inside the cells. Till date, there have been various neurological complications reported in patients all around the world. Some being mild, some moderate and some being very severe. Summary of various studies on neurological manifestations in coronavirus disease 2019 (COVID-19) patients are enlisted in Table-1.

STUDY	DIAGNOSIS	GENERAL FINDINGS	NEUROLOGICAL ANALYSIS AND FINDINGS	CONCLUSION	REFERENCE
<p>A Prospective, case series study was conducted in 62 post mortem brain MRI obtained early (<24h) after death.</p>	<p>SARS-CoV-2 was detected on nasopharyngeal swab specimen, chest computerized tomographic (CT) scan suggestive of COVID-19, absence of known focal brain lesion, and MRI compatibility</p>	<p>Subcortical micro- and macro-bleeds (2 decedents), cortico-subcortical edematous changes evocative of posterior reversible encephalopathy syndrome (PRES, one decedent), and nonspecific deep white matter changes (one decedent) were observed. Asymmetric olfactory bulbs were found in 4 other decedents without downstream olfactory tract abnormalities.</p>	<p>Signs of acute brain injury and MRI signal abnormalities along the olfactory tract and brainstem were observed.</p>	<p>Postmortem brain MRI demonstrates hemorrhagic and PRES-related lesions in non-survivors of COVID-19 that might be triggered by the virus-induced endothelial disturbances. SARS-CoV-2-related olfactory impairment seems to be limited to olfactory bulbs</p>	<p>35</p>
<p>A pilot investigation of the pathophysiological processes underlying the brain involvement by the SARS-CoV-2 infection using brain Magnetic Resonance Spectroscopic Imaging (MRSI) was performed in three consecutive COVID-19 patients</p>	<p>One patient among suffered with necrotizing leukoencephalopathy, one after a recent cardiac arrest without leukoencephalopathy, and one without frank encephalopathy or recent severe hypoxic episode.</p>		<p>N-acetyl-aspartate reduction, choline elevation, and glutamate/glutamine elevation was found in the COVID necrotizing leukoencephalopathy patient and, to a lesser degree, the COVID post-cardiac arrest patient, follow a similar pattern as seen with the delayed post-hypoxic leukoencephalopathy patient. Lactate elevation was most pronounced in the patient with COVID necrotizing leukoencephalopathy.</p>		<p>36</p>

<p>A case-series study on 10 consecutive COVID-19 patients who reported anosmia.</p>		<p>Each patient prospectively underwent a validated olfactory test (Sniffin Sticks test) and a brain MRI</p>	<p>Hypersignal intensity lesions of the central olfactory system were found in 3 subjects on 3D T2 FLAIR and 2D T2. Further High-Resolution images with a lesion involving the olfactory bulbs and/or the orbitofrontal cortex. These 3 subjects showed a severe and persistent loss of smell on the olfactory test. Mucosal hyperplasia of the upper nasal cavities was found in two other subjects with significant smell disorders.</p>	<p>Anomalies of the central olfactory system could be responsible for anosmia in patients with COVID-19 infection</p>	<p>37</p>
<p>A nationwide, multicentric, retrospective study was conducted during the French COVID-19 epidemic in March-April 2020. The study included 222 COVID-19 patients with neurological manifestations from 46 centers throughout the country.</p>	<p>The median age was 65 years (IQR 53-72), and 136 patients (61.3%) were male. COVID-19 was severe or critical in almost half of the patients (102, 45.2%). The most common neurological diseases were COVID-19 associated encephalopathy (67/222, 30.2%), acute ischemic cerebrovascular syndrome (57/222, 25.7%), encephalitis (21/222, 9.5%), and Guillain-Barre Syndrome (15/222, 6.8%).</p>	<p>Cerebrospinal fluid was analyzed in 97 patients (43.7%), with pleocytosis in 18 patients (18.6%). A SARS-CoV-2 PCR was performed in 75 patients and was positive only in 2 encephalitis patients. Among patients with encephalitis, ten out of 21 (47.6%) Less common neurological manifestations included isolated seizure (8/222, 3.6%), critical illness neuropathy (8/222, 3.6%), transient alteration of consciousness (5/222, 2.3%), intracranial hemorrhage (5/222, 2.3%), acute benign lymphocytic meningitis (3/222, 1.4%), cranial neuropathy (3/222, 1.4%), single acute demyelinating</p>	<p>Neurological manifestations associated with COVID-19 mainly included CAE, AICS, encephalitis, and GBS. Clinical spectrum and outcomes were broad and heterogeneous, suggesting different underlying pathogenic processes</p>	<p>38</p>	

<p>An evidence-based prospective study including 78 ISOA (initial sudden olfactory anosmia) patients was conducted.</p>	<p>46 patients performed psychophysical olfactory evaluation using sniffing tests. Based on the duration of the ISOA, two groups of patients were compared: patients with anosmia duration ≤12 days (group 1) and those with duration >12 days (group 2).</p>	<p>Antigens included proteins well-established in clinical routine, but also a variety of specific undetermined epitopes on brain sections. This included vessel endothelium, astrocytic proteins, and neuropil of</p>	<p>Most patients showed signs of CSF inflammation and increased levels of neurofilament light chain. All patients had anti-neuronal autoantibodies in serum or CSF when assessing a large panel of autoantibodies</p>	<p>The high frequency of autoantibodies targeting the brain in the absence of other explanations suggests a causal relationship to clinical symptoms, in particular to hyperexcitability (myoclonus, seizures). While several underlying autoantigens still await identification</p>	<p>40</p>
<p>lesion (2/222, 0.9%), Tapia syndrome (2/222, 0.9%), cerebral venous thrombosis (1/222, 0.5%), sudden paraparesis (1/222, 0.5%), generalized myoclonus and cerebellar ataxia (1/222, 0.5%), bilateral fibular palsy (1/222, 0.5%) and isolated neurological symptoms (headache, anosmia, dizziness, sensitive or auditive symptoms, hiccups, 15/222, 6.8%).</p>	<p>Among group 1, 42 patients (87.5%) had a positive viral load regarding RT-PCR while 6 patients (12.5%) were negative. In group 2, 7 patients (23%) had a positive viral load and 23 patients (77%) were negative. Among the 46 patients having performed a psychophysical olfactory evaluation, we observed anosmia in 52% (N=24), hyposmia in 24% (N=11), and normosmia in 24% (N=11) of patients</p>	<p>Our results support that a high proportion of ISOA patients are Covid+. Our study supports the need to add anosmia to the list of symptoms used in screening tools for possible COVID-19 infection.</p>	<p>39</p>		
<p>A study was conducted to determine whether anti-neuronal or anti-glial autoantibodies are present in 11 consecutive severely ill COVID-19 patients presenting with unexplained neurological symptoms.</p>	<p>The patients showed symptoms that included myoclonus, cranial nerve involvement, oculomotor disturbance, delirium, dystonia, and epileptic seizures.</p>	<p>Antigens included proteins well-established in clinical routine, but also a variety of specific undetermined epitopes on brain sections. This included vessel endothelium, astrocytic proteins, and neuropil of</p>	<p>Most patients showed signs of CSF inflammation and increased levels of neurofilament light chain. All patients had anti-neuronal autoantibodies in serum or CSF when assessing a large panel of autoantibodies</p>	<p>The high frequency of autoantibodies targeting the brain in the absence of other explanations suggests a causal relationship to clinical symptoms, in particular to hyperexcitability (myoclonus, seizures). While several underlying autoantigens still await identification</p>	<p>40</p>

		<p>basal ganglia, hippocampus, or olfactory bulb.</p>	<p>against intracellular and surface antigens relevant for central nervous system diseases using cell-based assays and indirect immunofluorescence on murine brain sections.</p>	<p>in future studies, the presence of autoantibodies may explain some aspects of multi-organ disease in COVID-19 and can guide immunotherapy in selected cases.</p>	
<p>Detailed mapping of viral RNA in 61 tissues and organs of 11 deceased patients with the diagnosis COVID-19.</p>		<p>The autopsies were performed within the (very) early postmortem interval (mean: 5.6 hours) to avoid bias due to viral RNA and tissue degradation. Viral loads, blood levels of cytokines, prothrombotic factors as well as macro- and micro-morphology were correlated.</p>	<p>Very high (> 104 copies/ml) viral loads were detected in the lungs of most patients and then correlated to severe tissue damage. Intact viral particles could be verified in the lung tissue by transmission electron microscopy. Viral loads in the lymph nodes were associated with a loss of follicular architecture. Viral RNA was detected throughout further extra-pulmonary tissues and organs without visible tissue damage. Inflammatory cytokines as well as the prothrombotic factors were elevated in all patients.</p>	<p>The dissemination of SARS-CoV-2-RNA throughout the body supports the hypothesis of a maladaptive host response with viremia and multi-organ dysfunction.</p>	<p>41</p>
<p>Retrospective case series with 106 patients from Huoshenshan Hospital in Wuhan, China, showing neurological disease was conducted</p>	<p>Participants: From 4 February to 14 April 2020, 106 patients with neurological diseases were enrolled from all patients in the hospital with confirmed COVID-19 and divided into a severe group and a nonsevere group according to their COVID-19 diagnosis</p>		<p>The mean (standard deviation, SD) age of patients was 72.7 (11.8) years, and 64 patients were male (60.4%). Among patients with co-morbid neurological diseases, 81 had a previous cerebral infarction (76.4%), 20 had dementia (18.9%), 10 had acute cerebral infarction</p>	<p>Patients with COVID-19 with co-morbid neurological diseases had an advanced age, a high rate of severe illness, and a high mortality rate. Among the neurological symptoms, altered mental status was more common in patients with severe COVID-19 with co-morbid neurological diseases.</p>	<p>42</p>

<p>A study was conducted on 25 Covid-19 patients showing neurological manifestation post-COVID19 infection.</p>	<p>The most common indication for brain MRI was an altered mental state (n = 18), mainly confusion (n = 10). Hypertension was the most common comorbidity (n = 10). In all, 17 patients presented at least one possible precipitating factor for PRES, mainly hypertension, renal failure, and septic shock.</p>		<p>(9.4%), 5 had sequelae of cerebral haemorrhage (4.7%), 4 had intracranial mass lesions (3.8%), 3 had epilepsy (2.8%), 2 had Parkinsons disease (1.9%), and 1 had myelopathy (0.9%). Fever (n = 62, 58.5%) was the most common symptom. The most common neurological symptoms were myalgia (n = 26, 24.5%), followed by extremity paralysis (n = 20, 18.9%), impaired consciousness (n = 17, 16%), and positive focal neurological signs (n = 42, 39.6%). Eight patients (7.5%) died.</p>	
<p>The first case of meningitis is associated with SARS-Cov-2 Meningitis/encephalitis associated with SARS-Cov-2.</p>	<p>Hyperintensity along the wall of the inferior horn of the right lateral ventricle, hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal Atrophy</p>		<p>Cerebrospinal fluid from 12 patients was normal (n=8) or showed mildly elevated proteinorachia (n=4) but no meningitis or pleocytosis. Covid-19 PCR findings for cerebrospinal fluid were negative for all tested patients.</p>	<p>43</p>
			<p>Specific SARS- CoV-2 RNA was detected in CSF, The CSF cell count was 12/mL-10 mononuclear and 2 polymorphonuclear cells without red blood cells</p>	<p>44</p>

<p>A case study on a 72-year-old man of non-traumatic intracranial hemorrhage on olfactory gyrus in a patient who is tested to be positive on SARS-COV-2.</p>		<p>Laboratory studies showed mild leukocytosis with transiently elevated bands. SAR-CoV2-RNA was positive in a nasopharyngeal swab. C-Reactive Protein was elevated to 164 mg/L (0-8 mg/L) and procalcitonin was 0.22 ng/ml (0.00 - 0.10 ng/ml). A comprehensive metabolic panel, coagulation studies, lactate dehydrogenase, lipid panel, hemoglobin A1c, blood alcohol level, urinalysis, blood culture, and chest x-ray were normal.</p>	<p>Neurological exam showed a post-ictal state, drowsy, but he was following commands consistently, inattentive, without right-left confusion, intact cranial nerves with mild left-sided hemiparesis.</p>	<p>Once cerebral vascular endothelium is affected by the virus through ACE-2, the function of the microvasculature could be altered, possibly leading to hemorrhage. Altered mental status in addition to anosmia and ageusia, and detection of the virus in cerebrospinal fluid, is consistent with the neurotropic and neuroinvasive nature of the virus. Animal studies with previous coronaviruses (e.g. SARS-CoV, MERS-CoV) indicated that infiltration of the virus starts from the olfactory nerves</p>	<p>45</p>
<p>A study reporting a 39-year-old female with parainfectious encephalitis patient with clinical, laboratory, and imaging findings during the evolution and convalescence phase of coronavirus infection.</p>		<p>The patient was presented to the emergency department (ED) with fever, myalgias, anorexia, drowsiness, and dry cough. Fever and myalgias had been present for nine days; she did not experience any improvement with rest and anti-inflammatory drugs (NSAIDs). The patient showed a fluctuating level of consciousness. During the investigation for a decreased level of consciousness, BMRI revealed T2- fluid-attenuated inversion recovery (FLAIR) high signal intensities in bilateral thalami, medial temporal and pons</p>	<p>As for the patient, neurological symptoms not correlating with respiratory and metabolic conditions should be an alarm for the possibility of CNS involvement. Similar to many other viral agents, SARS-CoV 2 seems capable of causing encephalitis</p>		<p>46</p>

<p>Clinical data from 214 patients with COVID-19 demonstrated neurological symptoms</p>		<p>Neurological symptoms included headache, impaired consciousness, ataxia, acute cerebrovascular disease, seizures, hyposmia, hypogeusia, and neuralgias.</p>	<p>The data suggest that patients with more severe systemic presentations were more likely to have neurologic symptoms, such as acute cerebrovascular diseases (5.7 % vs. 0.8 %), impaired consciousness (14.8 % vs. 2.4 %), and skeletal muscle injury (19.3 % vs. 4.8 %), in comparison with those with milder forms of the infection</p>	<p>Clinical data from 214 patients with COVID-19 demonstrated neurological symptoms in 36.4 % of patients.</p>	<p>47</p>
<p>In an observational study of 41 patients with COVID-19, the headache was found in 8% of patients, and myalgia was found</p>		<p>In most of these cases, headaches appeared to be a non-specific symptom, without features suggestive of meningeal irritation. The occurrence of isolated headaches in the absence of other neurological-type symptoms suggests the mechanism was more likely due to the systemic illness rather than a primary invasion of the CNS by the virus.</p>	<p>In an observational study of 41 patients with COVID-19, the headache was found in 8% of patients, and myalgia was found in 12 %</p>		<p>3</p>

Table 1: - Summary of various studies on neurological manifestations in SARS-CoV-2 infected Patient

Another potential neurological problem is Multiple Sclerosis (MS). Given the strong link between SARS-CoV and the high risk of developing multiple sclerosis 57, this condition may also pose a threat to the current COVID-19. Although the risk of death/illness in MS patients with COVID-19 treated with Disease-Modifying Therapies (DMTs), is probably very low. Besides, the administration of immunosuppressants in these patients could lead to limited lung capacity to increase the risk of COVID-19 pneumonia 58, thereby increasing the DMT for COVID-infected MS patients. Besides, a major complication of COVID-19 infection may arise from an overdose of the virus 59. It is thought that moderate immunosuppression treatment taken by MS patients may increase the risk of severe COVID-19 complications 60. In this line, many more trials are being done and more is yet to be studied to test the effectiveness of these antibodies in the immune response to the virus 61, 62. Autopsy studies in which coronavirus-like molecules and molecules such as murine neurotropic coronaviruses have been detected in brain tissues obtained from MS patients which is an indication of a CNS infection. Besides, HCoV RNA and coronavirus antigens have been found in the brain 63 and cerebrospinal fluid of MS and other neurological patients 64, 21. Most importantly, a recent study in Germany showed that SARS-CoV-2 RNA can be found in brain biopsies in 36.4% (8/22) of COVID-19 fatal cases 65, demonstrating the potential for viral infections in the human brain. To date, there is no experimental evidence for SARS-CoV-2 infection in the CNS.

In addition to severe neurological conditions, there have been many reported cases of neuropsychiatric and psychiatric disorders associated with COVID-19, although such presentation may replicate the broader social and economic effects of this pandemic on mental health. Depression, anxiety, and traumatic symptoms have been associated with CoV outbreaks, but it is still unclear whether the risks are due to the virus itself or the host-viral response. Studies of health care workers during the SARS-CoV-1 pandemic, the MERS-CoV outbreak, and the current SARS-CoV-2 epidemic suggest that the frequency and severity of psychiatric symptoms are associated with proximity to CoV-infected patients 66, 67. Neuropsychiatric effects that appear as a sequence of brain injury or disease can be exacerbated by direct effects of CNS infection or indirectly through physical or therapeutic response. A systematic review and meta-analysis conducted by Rogers et al., on the neuropsychiatric demonstration of SARS and MERS CoV, revealed

that during acute illness, common psychological symptoms such as insomnia 41.9%, anxiety (35.7%), impaired memory (34.1%), feelings of depression (32.6%) and followed by confusion (27.9%) were reported 68. A retrospective study of 13,783 records from patient management revealed that it was linked to an increase in the incidence of the first episode of schizophrenia with a change in age at onset.

69. With similar findings from the outbreak of SARS-CoV and MERS, not all patients diagnosed with SARS-CoV-2 infection have regained 100% of their original emotional and neurocognitive function. A follow-up study of neuropsychiatric sequelae 31-50 months after severe SARS-CoV infection found evidence of post-traumatic stress disorder (39%), depression (36.4%), severe psychiatric disorders (15.6%), and anxiety disorders (15.6 %) 67. Though there are only a limited number of SARS-CoV-2 studies on its neurotrophic effects, available evidence strongly suggests a diminished effect on CNS, and also the presence of a novel coronavirus in the brain can also be seen in psychiatric conditions. SARS-CoV-2 has been reported to be able to cross the blood-brain barrier and reach the brain via the olfactory bulb. The virus has been shown to interact with the ACE2 receptor, but the exact mechanism underlying its adverse effects on CNS is unknown.

Conclusion

COVID-19 is expected to affect a very high proportion of the world's population, setting it apart from other viruses in terms of mortality and infection rates. However, the neurological and neuropsychiatric burden of this pandemic can be significant. Although the number of patients with vascular symptoms is small compared to respiratory problems, reports indicate that SARS-CoV-2 has organotropism beyond the respiratory tract, including the brain, and it is thought that organotropism contributes to the course of COVID-19 disease and, possibly strengthens the existing conditions. Careful clinical, diagnostic, and pathological studies are needed to explain neurological symptoms and burden. The neurological symptoms of the early stages of COVID-19 infection are often unspecified, increasing the risk of developing the disease or making a late diagnosis. Due to the adverse effects of COVID-19 at the CNS, PNS and neuropsychiatric levels, more research is needed to determine the long-term effects of SARS-CoV-2 on the active nervous system, and light on the specific mechanism of its neural infiltration. Also, to detect the neuroinvasive characteristic of SARS-CoV-2, in vitro and in vivo studies should also be performed to demon-

strate the neuroinfiltration properties of SARS-CoV-2. Studies conducted mainly using animal models and brain tissue can provide a better understanding of the modus operandi of the virus and the various mechanistic pathways that can be followed for the infection that can cause neuroinflammation and neurodegeneration.

Authors' Contribution

All authors contributed equally to the drafting and editing of the final manuscript.

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