SARS-CoV-2 Neurological Implications

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Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is an emergent infectious disease that has caused millions of deaths throughout the world. COVID-19 infection's main symptoms are fever, cough, fatigue, and neurological manifestations such as headache, myalgias, anosmia, ageusia, impaired consciousness, seizures, and even neuromuscular junctions' disorders. Due to the neurological symptoms associated to COVID-19, damage in the central nervous system has been suggested as well as the neuroinvasive potential of SARS-CoV-2.

Keywords: COVID-19 ; SARS-CoV-2 ; neurological damage ; central nervous system

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a highly contagious and deadly infectious disease with a broad spectrum of clinical manifestations. COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It was first identified in Wuhan, Hubei, China at the beginning of December 2019 and was declared a global pandemic in March 2020, causing around of 140,000,000 cases and up to 3,000,000 deaths until now [1].

SARS-CoV-2 belongs to the Betacoronavirus genus from the Coronavirinae subfamily within the family of Coronaviridae and Nidovirales order. SARS-CoV-2 shares homology with other coronaviruses responsible for severe acute respiratory syndromes such as SARS-CoV (~79.5% homology), which was first recognized in Guangdon, China in November 2002 and MERS-CoV (~50% homology) identified in 2012 in Jeddah, Saudi Arabia [2]. Coronaviruses are enveloped positive single-stranded RNA viruses with large genomes ranging from 8.4–12 kDa and round virions of 80–120 nm in diameter. The 5´terminal portion contains the open reading frames from viral replication proteins, while the 3´terminal encodes the structural proteins named spike (S), membrane (M), nucleocapsid (N), envelope (E), and haemagglutinin-esterase (HE) proteins. SARS-CoV-2 has a genome of 26–32 kb encoding six non-structural proteins involved in viral replication and four structural proteins [3]. The SARS-CoV-2 structure consists of a lipid bilayer where the glycoprotein type (spike) forms peplomers on the virion surface, giving it a crown-like morphology. The membrane protein spans three times the membrane surface and presents a short N-terminal ectodomain and a cytoplasmic tail, while the E protein travels twice the surface and is constituted by an N- and a C- terminal internal domain, a short ectodomain, a transmembrane domain, and a cytoplasmic tail. Some coronaviruses have a haemagglutinin esterase protein; the role of this has not been fully understood, however, in the SARS-CoV-2 genome, HE is not encoded [4].

The mutation rate of SARS-CoV-2 has been estimated to be between 0.84–1.12 × 10^{-3} substitutions per site per year [2][5]. However, transmission of the SARS-CoV-2 virus and anti-virus treatments used for COVID-19 can favor genetic variability of the virus, contributing to its load, virulence, and the variability of neuropathological findings [6]. For example, the SARS-CoV-2 variant of spike protein D614G has been the most prevalent form in COVID-19 disease and has been linked to a higher viral load in the upper respiratory tract but not to an increase in disease severity [7]. A recent study identified 5775 genome variants, including almost 3000 missense mutations, 1965 synonymous mutations, 484 mutations in non-coding regions, 142 non-coding deletions, 100 in-frame deletions, 66 non-coding insertions, 36 stop-gained changes, 11 frameshift deletions, and two in-frame insertions [2][8]. SARS-CoV-2 is transmitted mainly by respiratory droplets moving from one person to another [9,[9]. The main symptoms of COVID-19 are fever, shortness of breath, cough, fatigue, headache, myalgias, anorexia, and chest pain. Other manifestations could include diarrhea, sore throat, anosmia, ageusia, hemoptysis, sputum production, rhinorrhea, nausea, vomiting, skin rash, impaired consciousness, and seizures. The presence of comorbidities during COVID-19 infection such as hypertension, diabetes, chronic respiratory disease, cardiovascular disease, cancer, or advanced age can negatively impact the prognosis of the disease [10][11][12]. The systemic complications in COVID-19 include adverse respiratory distress syndrome, cardiac injury, acute kidney injury, and liver dysfunction [13]. In addition, damage to the central nervous system (CNS) has been linked to COVID-19 infection; initial neurological characterization of COVID-19 disease in a Wuhan cohort of COVID-19 patients showed a low incidence of neurological complications such as headache, nausea, and vomiting, however, more recent studies have reported that neurological manifestations of SARS-CoV-2 infection can reach more than 35%, evidencing the neuro-invasive potential of SARS-CoV-2. Mild neurological dysfunctions such as anosmia and dysgeusia during COVID-19 are frequent, however, severe neurological disorders such as stroke and encephalopathies have also been reported, although less frequently. On the other hand, post-mortem brain studies have shown association between SARS-CoV-2 infection and pan-encephalitis and meningitis in addition to diffuse edema, gliosis with diffuse activation of microglia, and astrocytes infarctions in cortical and subcortical areas, subarachnoid and punctate hemorrhages, arteriosclerosis, hypoxic-ischemic

injury, and inflammation [14]. Regardless of the lack of studies analyzing SARS-CoV-2 CNS invasion, there is information that suggests the presence of the virus in human brain tissue, such as the detection of SARS-CoV-2 RNA in the cerebrospinal fluid of infected patients [15]. In addition, other human coronaviruses have shown to be able to infect neural cells [16]. Neurological manifestations as well as abnormalities in brain imaging have been reported during infections with SARS-CoV and MERS-CoV. Moreover, particles and genomic sequences of SARS-CoV have been detected in the post-mortem brain tissue of SARS patients as well as in cerebrospinal fluid. Data showed that SARS-CoV is presented in the thalamus, brainstem, hypothalamus, and cortex but not cerebellum in both humans and animals [17]. More recently and using human brain organoids as the experimental model, it has been shown that SARS-CoV-2 can damage the choroid plexus epithelium and impair the normal function of the blood brain barrier [18]. Politi and coworkers report the follow up of brain changes during COVID-19 development in three patients [19], and Bougakov et al. suggest the infection of brain tissue by SARS-CoV-2 by axonal transport through cranial nerves according to the route: nasal cavity olfactory nerve, olfactory bulb, pyriform cortex, and brainstem; the same route that has been demonstrated during HCoV OC43 infection of brain tissue [20][21]. However, the neurotropism of SARS-CoV-2 remains in debate.

Virus, such as SARS-CoV2, infection and replication in pneumocytes causes diffuse alveolar and interstitial inflammatory exudate and alveolar gas exchange disorders [22][23]. Gas exchange disorders are also linked to hypoxia in CNS by increasing anaerobic metabolism and edema. Moreover, SARS-CoV2 infection has been related to a low level of red blood cells (RBC) observed in COVID-19 patients. Several clinical reports have documented abnormal findings in different brain areas associated with blood vessel damage that led to stroke events [24][25]. Hypoxemia reported in COVID-19 patients could be in many cases silent (happy hypoxemia). However, low levels of oxygen lead to damage in several tissues and it has been suggested that this can increase infection by up regulation of furin (via HIF-1α), a host enzyme required for cleaving the S protein of the SARS-CoV2 [26][27]. Hypoxemia has also been related to proinflammatory cytokines [28].

CoV infections are mainly associated with cytokine production, inflammation, and cell death, which are pathophysiological processes also related to redox imbalance or oxidative stress both in animal models and humans [29][30][31][32]. Evidence indicates that the participation of oxidative stress in the pathogenesis of COVID-19 is achieved by enhancing the production of reactive oxygen species (ROS) and causing an imbalance of the host antioxidant system. In addition, the pro-inflammatory state caused by some comorbidities has been suggested as a negative factor for COVID-19 prognosis. Respiratory hypoxia associated with COVID-19 infection could initiate a hypoxic state in the brain and thus trigger oxidative stress. It has been largely documented that hypoxia induces ROS production which are involved in inflammation and immune response. High levels of ROS are the main cause of redox imbalance, macromolecules peroxidation, and the opening of the permeability transition pores of the mitochondria, thus, cellular changes caused by oxidative stress could lead to cell death and contribute to brain tissue damage [33]. Moreover, the oxidative stress triggered by SARS-CoV-2 infections has been compared with the one involved in Parkinson's disease and has demonstrated the activation of nuclear factor kappa B (NF-κB) [34]. It is important to consider that these pro-inflammatory processes are both central and systemic.

Currently, over 150 anti-COVID-19 vaccines are under investigation. In relation to treatment, dexamethasone and remdesivir appear to be promising medical therapies. However, to date a specific treatment for COVID-19 does not exist, and only supportive therapies are available. Until now anti-inflammatory drugs, immunomodulators, anti-vascular endothelial growth factors, modulating drugs, statins, or nutritional supplements have been studied as possible therapeutics agents [35].

2. Pathophysiological Mechanisms of SARS-CoV-2 and Its Neurological Implications

Cell entry of SARS-CoV-2 is mediated mainly by the interaction between the viral trimeric S protein and the cellular angiotensin converting enzyme 2 (ACE2) receptor [36]. The SARS-CoV-2 spike protein determines host tropism by binding to cell receptors through its receptor-binding domain (RBD) and initiates fusion and infection processes. Trimeric S protein has two functional subunits (S1 and S2). S1 binds to ACE2 receptors and induces conformational changes in S2, facilitating infection by membrane fusion. Two heptad (HR-1 and HR2) domains are present in the S2 subunit of the S protein, which play the central role in the fusion membrane during the infection process. The binding of the S protein to ACE2 through the RBD-S1 subunit allows the combination of HR1 and HR2 to form a six-helix bundle core fusion structure (6HB) and enables the proximity of the virus to the cell membrane for fusion [37][38][39].

The ACE2-receptor is a type-I transmembrane receptor with a catalytic extracellular domain, one transmembrane domain, and a cytoplasmic carboxyl domain. The extracellular portion of the ACE-2 receptor is a zinc metallopeptidase catalytic site and the spike binding domain [40]. Similarly to SARS-CoV, SARS-CoV-2 binds to ACE-2 but with higher affinity (10 to 20-fold), being more pathogenic. Viral S-protein priming by cellular transmembrane protease serine 2 (TMPRSS2) exposes its binding S1 domain and fusion S2 domain. The S1 binding to the ACE-2 receptor induces its internalization by upregulation of the ADAM metallopeptidase domain 17 (ADAM 17) activity which cleaves ACE2 from the cell surface. S2 domain exposure starts the viral fusion process to gain entry into cells [38][41] and release the viral genome into the cytoplasm where host ribosomes translate a polypeptide chain (~800 KDa) that is auto-proteolytically cleaved by two

proteases: papain like protease (PLpro) and 3-chyomotrypsin like protease (3CLpro), also called the main protease (Mpro), which are encoded in the viral genome and generate the no-structural proteins required for viral replication [42].

The main ACE-2 function is associated with the cleavage of the renin–angiotensin–aldosterone system (RAAS) peptides and is a regulatory mechanism opposed to the effects of angiotensin II generated by ACE. RAAS is a neurohormonal regulatory system involved in blood pressure and electrolyte homeostasis. Angiotensinogen is produced by the liver and cleaved into angiotensin I (Ang I). ACE catalyzes Ang I conversion to angiotensin II (Ang II), which is the main RAAS metabolite and binds to angiotensin II type 1 receptors. Ang II actions include vasoconstriction, renal sodium reabsorption and potassium excretion, aldosterone synthesis, blood pressure elevation, and inflammatory and pro-fibrotic signaling. ACE-2 cleaves Ang II to Ang (1–7) and exerts vasodilatation, anti-inflammation, and anti-fibrotic effects by Mas receptor system activation. RAAS activation effects depend on the tissue ACE/ACE2 balance, which could be affected by several factors [43][44][45].

ACE and ACE2 expression have been reported in almost all tissues such as vascular endothelia, lungs, brain, intestine, colon, heart, testis, pancreas, eye, thyroid, adipose tissue, gallbladder, and kidneys [46][47]. Interaction between SARS-CoV-2 and the ACE-2 receptor could affect the ACE/ACE2 balance, causing high levels of Ang II and activating Ang II/AT1R signaling. Tissues expressing elevated ACE2 are potential targets for SAR-CoV-2 infection, such as intestine, kidney, testis, gallbladder, and heart [47]. Because of the virus transmission mechanism, the lung is the main target organ for SARS-CoV-2. After entrance of SARS-CoV-2 into pneumocytes vascular permeability and inflammation have been reported, which has been related to ACE-2 downregulation. In addition, studies have demonstrated that Ang II level has a positive correlation with viral load and lung injury. In vitro studies have demonstrated that AT1R activation by Ang II can induce apoptotic death of lung epithelial cells. It has been shown that Ang II induces endothelial damage by cyclooxygenase (COX-2) activation, which in turn generates vasoactive prostaglandins and reactive oxygen species (ROS) [48][49]. The excessive production of ROS can then over activate AngII/AT1R/nicotinamide adenine dinucleotide phosphate (NADPH) oxidase axis and subsequently induce apoptosis by mitochondrial injury [50]. Release of cytochrome C, activation of caspase 3, and p38 mitogen activated protein kinase (MAPK)/Jun N-terminal kinase (JNK) cascade activation have been related to elevated ROS levels. Moreover, the entry of SARS-CoV-2 can cause destruction of lung cells by activating a local immune response mediated by macrophages and monocytes; these cells release cytokines such as interleukin-6 (IL-6), interferon-γ (IFN-γ), monocyte chemoattractant protein-1 (MCP-1) interferon-γ-inducible protein-10 (IP-10), or tumor necrosis factor (TNF) into the blood of patients, thus being indicators of T-cells activation. Other inflammatory pathways activated by Ang II involve the transcriptional nuclear factor NF-kB and the expression of proinflammatory cytokines such as IL-6, IL-1β, and TNFα [51]. In COVID-19 patients, an excessive cytokine release has been documented, which induces an increase in leukocyte recruitment to different body organs leading to multi-organ failure and could result in acute heart injury or acute renal injury. This phenomenon is called cytokine storm syndrome, it also occurs in other viral diseases such as SARS, MERS, and influenza. The result of the ACE2 protection loss is a hyperinflammatory state which can be seen the late phase of COVID-19 [52].

Previous studies on SARS-CoV and MERS-CoV have shown that coronaviruses are able to infect CNS cells in the brainstem, which suggests than infection of this brain region during COVID-19 could compromise respiratory and cardiovascular function [53]. However, the SARS-CoV receptor is different to the MERS-CoV one, which has been reported use Dipeptidyl peptidase 4 (DPP4) to gain access into different tissues, among them the cerebral cortex [54][55]. In relation to the entry of SARS-CoV-2 in CNS, it has been shown that ACE2 expression is highest in the amygdala, pons, and medulla oblongata and then also related to the susceptibility of the subject to respiratory distress [56]. It has been proposed that the SARS-CoV-2 neurovirulence could be related to the degree of expression of the ACE2 receptor in the regions of the CNS [57]

Employing an animal model demonstrated that SARS-CoV accessed brain tissue through the olfactory bulb, data that can be related to anosmia generated during COVID-19 [58]. Moreover, it has been suggested that ACE2 could mediate SARS-CoV-2 neurotropism since it is expressed in neurons, astrocytes, and oligodendrocytes, mainly in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb as well as endothelial cells. In humans, ACE2 has a relatively high expression in the middle temporal gyrus and posterior cingulate cortex but is low in the hippocampus. Its expression has been showed also in the tractus solitarius nucleus, paraventricular nucleus, and rostral ventrolateral medulla, which are regions implicated in cardiovascular regulation [47][59]. Importantly, it has been demonstrated that SARS-CoV-2 can disrupt the brain blood barrier and gain access to brain tissue [18].

Currently, the mechanisms by which SARS-CoV-2 can disturb neurological functions are not known. However, some hypotheses have been proposed. The first one states that the neurological manifestations rise due to direct neurotropic action of the virus causing encephalitis or meningitis; the virus enters the CNS. Virus entry could be from direct blood circulation infecting vascular endothelium, through nasal cells invading the olfactory epithelium along the nerve to the olfactory bulb, or by leukocyte migration across the BBB and neuronal pathways to the Virchow-Robin space surrounding arterioles and venules, and into the lymphatic systems and receptors [46][60]. The other mechanism that has been proposed is the parainfectious disease mechanism, which results in immune-mediated nerve disturbance such as Guillain–Barre syndrome or Miller Fisher syndrome [61]. In addition, it has been shown that the existence of some risk factors predisposes patients with COVID-19 to neurological complications. Among the most common are older age and

the presence of comorbidities, particularly hypertension and smoking since stimulation of the nicotinic acetylcholine (nACh) receptor could increase ACE2 expression in neurons [62]. However, further research is needed in order to clear the mechanism by which SARS-CoV-2 affects brain tissue due to the low expression of ACE2 in human brain [47]

Regardless of the kind of interaction between SARS-CoV-2 and brain tissue, the effects on the CNS are present during COVID-19 disease. Among the most common are smell impairment with normal nasal mucosa and normal imagining of olfactory bulbs; cerebrovascular disease, mainly ischemic events in small and large vessels. Stiff neck, confusion changes in mental status, or seizures have also been reported. Related to peripheral nerves, injury to cranial nerves and muscles has been associated with facial weakness, difficulty breathing, and trouble standing or walking [63]. Cytokine increased production (IL-6, IL-8, IL-10, I, and TNF-α) and microglial activation has been observed in post-mortem brain tissue, and T-cell infiltration has been described in post-mortem brain tissue through mild perivascular infiltration [64], oxidative stress triggered by hypoxia, hypercoagulation and thrombosis [65], gut microbiome dysbiosis [66], unfolded protein response, and accumulation of misfolded proteins such as amyloid-beta/tau/alpha-synuclein [67] and neurological autoimmune response [61], which are the main events that could explain the neurological symptoms during COVID-19.

COVID-19 infection produces mild neurologic manifestations such as headache and loss of smell. Globally, asthenia, myalgia, headache, anosmia, and ageusia are the most common symptoms, followed by encephalopathy, stroke, and seizures [3]. Near to 36% of COVID-19 patients exhibit neurological symptoms, including both central and peripheral signs. The hypercoagulation state observed during COVID-19 disease also affects CNS integrity and damage to the brain vasculature has been observed in 2% of patients [68][69][70][71].

Encephalopathy is considered the most common CNS complication of COVID-19 [72]; about 50% of the hospitalized COVID-19 cases develop it [73]. In addition, age and pre-existent cognitive impairment, several comorbidities, malnutrition, concomitant infections, metabolic disorders, liver, vascular, and kidney dysfunctions, and sepsis are considered risk factors for neurological damage in COVID-19 patients [6]. Anatomopathological findings in the post-mortem brain tissue of COVID-19 patients are the presence of neuroinflammation with encephalitis, hemorrhagic lesions, infarctions, thrombosis, acute cerebral and cerebellar hypoxia-related lesions, reactive gliosis, astrocytosis, and microglia activation, showing a relationship between SARS-CoV-2 and central nervous system sequelae [74]. Table 1 shows the brain damage or neurological manifestations induced by COVID-19 infection reported in clinical cases.

Table 1. Neurological manifestations in patients infected with COVID-19.

Type	Neurological Complications after COVID-19 Infection	Patients' Origin	References
Inflammatory	Encephalitis	Italy	[61][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][
	Meningoencephalitis	Iran	
	Cord myelopathy encephalitis	United States	
	Hypoxic encephalitis	Brazil	
	Autoinmune meningoencephalitis	United Kingdom	
	Acute-disseminated encephalomyelitis	India	
	Autoimmune encephalitis	Egypt	
	Diffuse post hypoxic leukoencephalopathy	Mexico	
		Canada	
	Acute necrotizing encephalopathy	Spain	
	Guillain–Barré Syndrome	South Africa	
	Guillain–Barré Syndrome associated with a cerebral vasculitis-like pattern	Netherlands	
		Belgium	
	Cerebillitis	France	
	Mixed inflammatory cell	Peru	
	Posterior reversible encephalopathy syndrome	Japan	
		Germany	
		Sweden	

Type	Neurological Complications after COVID-19 Infection	Patients' Origin	References
Vascular	Hemorrhage (intracerebral, subarachnoid, and intracranial) Multi-territory hemorrhagic infarctions Microbleeds masquerades Cerebral venous sinus thrombosis Embolic stroke in the right insula and left cerebellum Microinfarcts throughout the cortex Posterior cerebral artery infarct Middle cerebral artery territory infarcts Cuffing of intracerebral blood vessels distant from the infarcts Left cerebral small subdural hematoma with mild brain edema Vasculitis Perfusion abnormalities in brain Large vessel stroke Small subcortical infarcts Brain microvascular occlusive disorder Secondary acute ischemic stroke	United States South Africa Switzerland Germany Mexico India Saudi Arabia Brazil Japan Italy Spain China Turkey	[94][96][105][108][109][110][111][112][113][114][11

Type	Neurological Complications after COVID-19 Infection	Patients' Origin	References
Sensorial	Headache Vertigo Anosmia Ageusia Altered taste Migraine-like features Vision impairment Dizziness	Spain India Egypt China Canada Italy Turkey Germany United States Venezuela Bolivia	[71][96][97][126][127
Behavioral	Confusion Seizure Convulsions Cognitive decay coma Neuropsychiatric disorder Delirium Maniac-like symptoms Depression Altered mental status Psychosis Dementia-like syndrome Dysexecutive syndrome	France China Iran Egypt Saudi Arabia Belgium Spain India United Kingdom	[68][71][95][96][97][124][13

Type	Neurological Complications after COVID-19 Infection	Patients' Origin	References
Peripheral	Peripheral neuropathy Myasthenia gravis Symmetric hypokinetic-rigid syndrome Cranial neuropathy Nerve pain Bell's palsy Balint–Holmes' syndrome Ataxia Anti-diuretic hormone secretion	Belgium Egypt Spain China India Italy	[71][96][97][98
Anatomical lesions	Transtentorial herniation Cytotoxic lesions of the corpus callosum Diffuse corticospinal tract Brain and spine demyelinating lesions Pneumocephalus	United States Italy Saudi Arabia France	[68][124][125][14

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