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Review

# Coronavirus 2019 disease, COVID-19: neurological manifestations and complications

## Enfermedad por coronavirus 2019, COVID-19: manifestaciones neurológicas y complicaciones

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**ABSTRACT**

In December 2019, a new coronavirus SARS-CoV-2 erupted in Wuhan, China, which caused a rapidly spreading pneumonia outbreak globally. In February 2020, the World Health Organization named this clinical manifestation as Coronavirus Disease 2019, Covid-19. As of June 21, 2020, the global number of those infected with COVID-19 is 8'708.008, with 461,715 deceased, it is well known that the respiratory system is the most affected structure by the virus, some systematic reviews, numerous experimental studies, and case reports have shown the potential neurotropism of SARS-CoV2, which involves neurological complications affecting the central and peripheral nervous system. During the coronavirus outbreaks between 2002-2003 and 2012 (SARS-CoV-1 and MERS-CoV), cases with neurological complications. Traditionally, coronaviruses affect the animal kingdom, specifically the mammalian species. Compromising the respiratory system and, in some cases, the nervous system. Mutations in the viral genome are considered to have allowed the virus to transcend to the human species over time. This transition happened due to intermediate hosts, generally mammals from East Asia and the Middle East. In some countries, due to their local customs, like the food supply or the current use of these intermediate hosts for mobility purposes, it has put human beings at risk. Leading the human species to suffer respiratory and gastrointestinal outbreaks throughout the years without neglecting neurological compromise. This review aims to analyze the neurological consequences secondary to SARS-CoV-2 infection, the neuroinvasive characteristics of the virus,

***RESUMEN***

*En diciembre de 2019, un nuevo coronavirus SARS-CoV-2 irrumpió en Wuhan, China, lo que provocó un brote de neumonía de rápida propagación a nivel mundial. En febrero de 2020, la Organización Mundial de la Salud denominó a esta manifestación clínica enfermedad por coronavirus 2019, COVID-19. Al 21 de junio de 2020, el número global de infectados por COVID-19 era de 8'708,008 con 461,715 fallecidos. Es bien sabido que el sistema respiratorio es la estructura más afectada por el virus, algunas revisiones sistemáticas, numerosos estudios experimentales y los informes de casos han demostrado el neurotropismo potencial del SARS-CoV-2, que implica complicaciones neurológicas que afectan el sistema nervioso central y periférico. Durante los brotes de coronavirus entre 2002-2003 y 2012 (SARS-CoV-1 y MERS-CoV), se produjeron casos con complicaciones neurológicas. Tradicionalmente, los coronavirus afectan al reino animal, concretamente a las especies de mamíferos. Comprometen el sistema respiratorio y, en algunos casos, el sistema nervioso. Se considera que las mutaciones en el genoma vírico permitieron que el virus trascendiera a la especie humana con el paso del tiempo. Esta transición se produjo gracias a huéspedes intermediarios, generalmente mamíferos de Asia Oriental y Oriente Medio. En algunos países, debido a sus costumbres locales, como el suministro de alimentos o el uso actual de estos huéspedes intermedios con fines de movilidad, ha puesto en peligro a los seres humanos. Han llevado a la especie humana a sufrir brotes respiratorios y gastrointestinales a lo largo de los años, sin dejar de lado el compromiso neurológico. Esta revisión pretende analizar las consecuencias neurológicas secundarias a*

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its effects in the current pandemic, its clinical presentation, and the potential occurrence of sequelae.

**Keywords:** coronavirus, neurological disease, COVID-19.

*la infección por SARS-CoV-2, las características neuroinvasivas del virus, sus efectos en la pandemia actual, su presentación clínica y la potencial aparición de secuelas.*

***Palabras clave:*** *coronavirus, enfermedad neurológica, COVID-19.*

## INTRODUCTION

Coronaviruses are a type of virus belonging to the family *Coronavirinae* that usually affect the animal kingdom. Its name comes from its crown-shaped structure[1] because its ultrastructural characteristics resemble a solar corona, according to observations made by June Almeida in 1967 when observing images of the avian bronchitis virus.[2] Since then, an increasing number of coronaviruses have been responsible for respiratory and enteric infections in bovid, suid, equid, felid, canid and avian species. Coronaviruses have been previously known to cause nervous system involvement, being reported as a porcine hemagglutinating encephalomyelitis in 1962 in Canada that decades later became a worldwide endemic zoonosis reported in Michigan and Ohio, USA, in 2015.[3]

## THE CORONAVIRUSES

These viruses are highly transmissible and adaptable to different media, achieving genetic mutations in their evolution that allowed them to be transmissible to humans, causing acute respiratory and enteric disorders, in addition to showing, over time, a remarkable ability to invade the nervous system. The evidence that supports this fact was observed during known outbreaks of the virus. The first outbreak occurred in Guangdong, China, in 2002-2003; the virus known as SARS-CoV-1 originated in bats and passed to humans through some Southeast Asian mammals, such as the Chinese ferret-badger, the Asian palm civet and the raccoon dog. A subsequent coronavirus outbreak, known as MERS-CoV, occurred in Saudi Arabia in 2012 with a higher mortality than the previous virus (9.6 versus 34.4%), also originated in bats and passed to man by camels and dromedaries.[4]

SARS-CoV-1, MERS-CoV and SARS-CoV-2 are all beta coronaviruses that share some interesting protein sequences that are considered homologous in their ultrastructure. The RNA genome of these viruses is the largest known to humankind and consists of 3 main proteins: S (spike), M (membrane) and E (envelope) proteins. The spike glycoprotein is the fusion protein that determines binding to the host, its potential, cellular tropism and the pathogenesis of the disease.[5] Specifically, the spike (S) surface protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor.[6,7] After binding, the virus fuses its envelope to the host cell membrane, and its nucleocapsid is delivered into the cell.[8]

Another element that is similar among these beta coronaviruses is the generation of a so-called "cytokine storm", which affects clinical disease severity, with proinflammatory cytokines IL-1B, IL-6, IL-12, IFN-γ, IP-10 and MCP-1 predominant for SARS-CoV-1; IFN-γ, TNF-alpha, IL-15 and IL-17 predominant for MERS-CoV; and IL-1B, IFN-γ, IP-10 and MCP-1 predominant for SARS-CoV-2 (in addition to T-helper-1 [Th1] and T-helper-2 [Th2], which are potent cytokines that suppress inflammation, which differs from SARS-CoV-1 and MERS-CoV). This "storm" triggers a cascade of pathophysiological events during acute illness and leads to death.[9]

For other authors, SARS-CoV-2 is a beta coronavirus whose genetic characteristics differ significantly from those of SARS-CoV-1 and MERS-CoV, and this is reflected in a mechanism of action that interestingly involves the nervous system.[10,11] Matías considers that the presence of fusion (S) and ORF3b and ORF8 accessory proteins represent structural differences to be taken into account in the novel SARS-CoV-2, as these structural differences may be responsible for the presence of neurodegenerative diseases.[12] Upon entering the host, the viral genome encodes 2 precursor polypeptide chains, which in turn are processed into 16 nonstructural proteins (NSP) by viral proteinases, playing a critical role in the replication and transcription of viral RNA[11,13] as well as in the immune response (ORF3b).[11,14]

## MECHANISMS OF NEUROINVASION

The frequency of neurological symptoms and complications has increased in the course of the current pandemic, and this is evidenced in the literature, as well as the clinical variety and hypotheses about its mechanisms and routes to reach the nervous system. On the host side, the expression of ACE2 receptors determines viral tropism, and its presence is critical in some organs and systems, such as the airway epithelium, small intestine, lung, kidney, endothelium and nervous system.[6] The brain has a high expression of ACE2 receptors,[15] and in the same sense, the affinity of SARS-CoV-2 for these receptors that are present in neurons and endothelial cells is greater than for SARS-

CoV-1; therefore, its neuroinvasive capacity is greater.[16] In the nervous system, ACE2 receptors are mainly expressed in neurons, oligodendrocytes and astrocytes, with high concentrations in the medial temporal lobe, posterior cingulate cortex, olfactory bulb, ventricles, substantia nigra, motor cortex and sympathetic pathway in the brainstem.[17]

From the pathophysiological point of view, there are several hypotheses that attempt to explain the dissemination to the nervous system. This has been demonstrated in animal tests after virus inoculation in various forms, with the transnasal form being the most widely used. Axonal transport and transneuronal dissemination from olfactory and trigeminal nerve endings in the nasal epithelium is one of the hypotheses.[16] There are varieties of coronavirus with proven neuroinvasive potential (avian bronchitis, hemagglutinating encephalomyelitis HEV67, murine hepatitis, MERS-CoV, and HCoV-OCR43).[18] One of them, HEV67, after reaching the transnasal pathway and infecting the nasal mucosa, respiratory epithelium and small intestine, disseminates from its corresponding peripheral nerve endings by retrograde axonal transport and reaches the dorsal root ganglion and, from there, the spinal cord.[6,19] In this sense, transmission from the olfactory epithelium via the cribriform plate to the olfactory bulb should also be included. Likewise, endocytic or exocytic transmembrane pathways facilitate the spread of the virus interneuronally.[20] At the intraneuronal level, retrograde or antegrade rapid transport occurs via microtubules, with which the pathogen reaches different levels of the central and peripheral nervous systems.[18,21] Similar findings have been observed with the HIV, herpes, and HCoV-OCR43 viruses.[21]

During the COVID-19 outbreak, anosmia and ageusia with or without respiratory symptoms have been reported, considering that access through the olfactory membrane and its subsequent arrival at the nervous system through the lamina cribosa, as mentioned, is one of the pathways.[22-25] However, there is still debate whether this is truly a mechanism because there are studies that report that the nasal epithelium expresses ACE2 receptors, while olfactory sensory neurons do not.[26,27] Another possible access route of the virus to the nervous system should be considered, such as through organs that normally lack a blood-brain barrier, such as the periventricular organs, or through the autonomic ganglia and the dorsal root, which also lack a blood-brain barrier.[20,28]

The vascular endothelium and its wide distribution throughout the body express ACE2 receptors at high levels, make it susceptible to SARS-CoV-2, such that infection and transport through its cells is a possible mechanism that allows the virus to reach the nervous system once the blood-brain barrier has been altered by the acute inflammatory mechanisms underlying this pathology.[29] In fact, Varga demonstrated that SARS-CoV-2 produces a systemic endothelial infectious state or systemic vascular endotheliitis characterized by endothelial microvascular dysfunction that leads to vasoconstriction, ischemia, edema and, ultimately, a procoagulatory and prothrombotic state relevant to the development of cerebrovascular events.[30-32] The virus packed in vesicles dilated by endocytosis or exocytosis thus gains access to the nervous system, and the infection develops in an already inflamed endothelium. On the other hand, infected leukocytes can cross the blood-brain barrier and reach neural tissue by a mechanism known as a Trojan horse.[12]

## Role of the renin-angiotensin-aldosterone system in SARS-CoV-2 infection

The renin-angiotensin-aldosterone system (RAAS) is a sophisticated cascade of vasoactive peptides that regulate a series of processes in human physiology. Severe acute respiratory syndrome of coronavirus 1 (SARS-CoV-1) and SARS-CoV-2, which have been responsible for SARS epidemics in 2002-2003 and the most recent and current COVID-19 pandemic, respectively, are interrelated with RAAS through angiotensin-converting enzyme 2 (ACE 2), an enzyme that physiologically activates RAAS but also functions as a receptor for both SARS viruses.[33,34] The interaction between SARS viruses and ACE2 has been proposed as a potential factor of their infectivity.[34,35]

Renin converts angiotensin, a liver protein, into angiotensin I, which in turn is converted to angiotensin II in the pulmonary endothelium by angiotensin-converting enzyme (ACE). Angiotensin II produces multiple physiological effects: it stimulates the pituitary gland to secrete vasopressin, thus retaining water; activates the AT1 receptors of vascular smooth muscle, thus producing vasoconstriction; and promotes the secretion of aldosterone in the adrenal gland, whose action is to retain water and sodium, eliminating hydrogen and potassium.

Recently, the discovery of a mechanism of angiotensin II degradation by an ACE homolog, known as ACE2, offers the opportunity to study another aspect of RAAS regulation. Angiotensin II can be degraded by at least 3 metabolites: a) des-aspartyl-angiotensin II (angiotensin III), which has similar functions to angiotensin II but is less effective due to its accelerated metabolism *in vivo*; b) angiotensin IV, which can cause vasodilation and natriuresis; and c) angiotensin 1-7, which can be formed directly from angiotensin II by the action of ACE2 *(Figure 1)*. Angiotensin 1-7 has opposite functions to angiotensin II; that is, it is a vasodilator and antiproliferative agent. ACE2 also degrades angiotensin I to angiotensin 1-9, which is an inactive peptide.[36] The SARS-CoV-1 and SARS-CoV-2 viruses bind to the ACE2 enzyme receptor and use it to enter the cell, causing this enzyme,

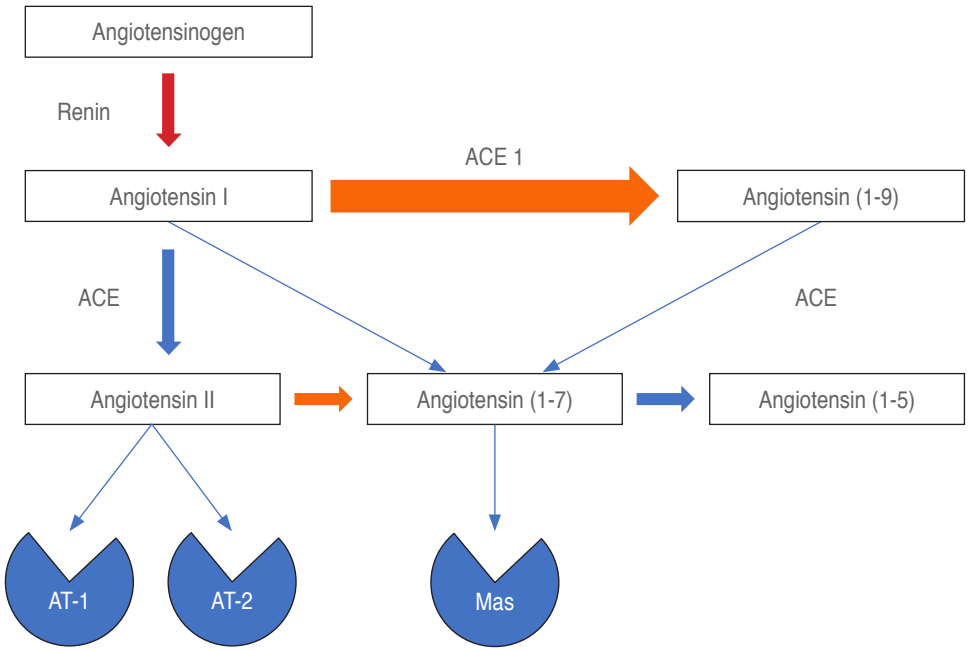


**Figure 1:**

Renin-angiotensin-aldosterone system.

which also acts as a transmembrane receptor, to not perform its function; thus, angiotensin II and angiotensin I accumulate, promoting RAAS hyperactivity. This leads to acute lung injury, vasoconstriction and increased vascular permeability (effects of angiotensin II) and to a decrease in the effects of angiotensin 1-7, which, as previously mentioned, are counterregulatory to those of angiotensin II, all of which are associated with the systemic inflammatory syndrome caused by the virus alone.[36]

Comparatively, the subunit of the receptor binding domain (RBD), or S1 or spike protein, that is present in the virus and binds to the ACE2 receptor is quite similar between SARS-CoV-1 and SARS-CoV-2, having a sequence identity of approximately 74%. It is theorized that this difference of 26% is what allows SARS-CoV-2 to have 10 to 20 times more affinity for the ACE2 receptor, explaining its infective capacity.[37]

In skeletal muscle, there is evidence of local production of angiotensin II from angiotensin I.[38] Consistent with this, ACE activity has been detected in skeletal muscle; its expression was found in the plasma membrane of its cells at the level of the capillary endothelium, suggesting the presence of a functional RAAS in this organ.[39,40] The main peptide generated by ACE is angiotensin II, which mediates its effects by binding to G protein receptors located in the plasma membrane. The main receptors involved in the effects of angiotensin II are AT-1 and AT-2 *(Figure 1)*.[41,42] Although the evidence regarding the expression of AT-1 and AT-2 receptors in skeletal muscle is contradictory, some studies have shown that their expression and regulation occur under normal and pathological conditions.[43,44]

ACE 2 constitutes an alternative step from angiotensin I and II, forming an intermediate component, angiotensin 1-7, which has counterregulatory properties. The competitive occupation of the ACE2 receptor contributes pathophysiologically to the deleterious effects of COVID-19 infection.[36]

Transcription of the AT-1 gene has been detected in human fetuses and adults, while transcription of the AT-2 gene has been detected only in skeletal muscle of normal fetuses.[45] These data support the presence of a classic local RAAS (ACE, angiotensin II and AT receptors) in skeletal muscle and its regulation under pathological conditions.[46]

## NEUROLOGICAL MANIFESTATIONS

From the clinical point of view, neurological manifestations and complications vary between authors, but there are some that are essential, among which are headache, dizziness, anosmia, ageusia, stroke and polyneuropathies. Some consider that recognizing clinical neurological manifestations is difficult in the context of severe disease; therefore, it remains uncertain whether these manifestations are concurrent or if they are directly produced by the viral infection.[47] Thus, it is critical to define the direct versus indirect neurotrophic effects induced by SARS-CoV-2 on the nervous system. Although neurological compromise by SARS-CoV-2 has been described significantly more in the adult population, children are also affected. In children, transmission occurs mainly through family, symptoms are milder, and their prognosis is better.[48] Historically, HCoV has produced clinical signs in children that vary between

encephalitis, meningitis, Guillain-Barré syndrome and encephalomyelitis.[40,49,50] Neurodegenerative diseases also coexist with HCoV infection, including Parkinson's disease, Alzheimer's disease and multiple sclerosis.[11] Headache, anosmia and ageusia should draw attention even in the absence of respiratory symptoms, without forgetting other frequent symptoms such as CVD, impaired consciousness, seizures, encephalopathy and coma.[6]

Mao et al. classify symptoms into 3 categories, namely, those that affect the central nervous system (headache, dizziness, ataxia, impaired consciousness, seizures and stroke, among others), peripheral nervous system (changes in taste, smell and vision, neuropathic pain and neuropathies); and musculoskeletal system. In their study, they evaluated 214 patients (average age, 57.2 years; 59.3% female) hospitalized for severe acute respiratory syndrome with a confirmed diagnosis of SARS-CoV-2 by RT-PCR in 3 hospital centers in Wuhan, China, between January and February 2020 (58.9% with nonsevere infection and 41.1% with severe infection according to their respiratory status). Neurological complications were reported in 36.4% of patients, distributed as follows: CNS, 24.8%; PNS, 8.9%; and musculoskeletal system, 10.7%, with the highest proportion of neurological complications occurring in the severely infected group.[51] The majority of neurological manifestations occurred early in the evolution of the disease (1 to 2 days) and in many cases with few or no typical symptoms of COVID-19, which is why in some cases the possibility of COVID-19 was not taken into account as a diagnosis, only after evolution and laboratory tests confirmed the infection.[11,23,51]

It is noteworthy that the Environmental Neurology Specialty Group of the World Federation of Neurology (ENSG-WFN) has called on neurological societies around the world to develop a national, regional and global neuro-epidemiological database for patients with COVID-19, with the goal of promoting research that allows us to understand the neurological impact of this pandemic.

## Manifestations in the central nervous system

### *Headache*

It is one of the most common complaints during the initial stage of the disease, along with respiratory and general symptoms that affect these patients. The mechanism is not yet clear, but it has been attributed to the acute inflammatory cascade precipitated by the "cytokine storm" that is also responsible for fever, fatigue, general malaise and respiratory symptoms. The neuro-inflammatory response could be related to the activation of nociceptive neurons during the different stages of infection, in which the release of cytokines by macrophages is proposed as a base mechanism, and could even be responsible for pain in other areas of the body.[52] Otherwise, it is part of the clinical presentation of meningitis, encephalitis, intracranial hypertension, vasculitis, anxiety or depression in the present context, and its prevalence can reach one-third in some studies,[53] although it is variable according to each author: 6.5%,[54] 8%,[55] 12.1%,[56] and 13.1%.[51] Many of the figures for this symptom are linked to others, such as fever or impaired consciousness and fatigue.

### *Impaired consciousness*

As with headache, impaired consciousness can be concurrent with general symptoms or represent a specific neuroinfectious disease. When the latter is considered, possible underlying mechanisms are related to direct parenchymal injury, demyelinating disease, seizure disorder or toxic-metabolic encephalopathy.[12] The acute inflammatory process with the abundant presence of cytokines is postulated to alter the permeability of the blood-brain barrier and cause direct viral injury. In this sense, the occurrence of acute hemorrhagic necrotizing encephalopathy demonstrated on MRI as ring hemorrhagic lesions in the bilateral thalamus, medial temporal and subinsular lobes[4] or meningoencephalitis with signs of ventriculitis, temporal signal abnormalities and atrophy of the hippocampus on MRI[57] are examples of encephalopathic processes by COVID-19. Clinically, these patients present with headache, fever, myalgia, seizures, neck stiffness, CSF pleocytosis and a range of impairment of consciousness from confusion and delirium, to coma. In encephalopathy, the level of consciousness impairment is very important and can be rarely accompanied by only some of the aforementioned manifestations, with a normal brain CT and an EEG showing changes typical of diffuse encephalopathy.[58,59]

Demyelinating lesions have been tested in other types of coronavirus, such as the murine hepatitis virus, in which the host that survives severe acute encephalitis exhibits chronic brain demyelination reminiscent of sclerosis, which has been used as a model of multiple sclerosis.[60] Human coronavirus RNAs have been amplified from the CSF and brain tissue samples from patients with multiple sclerosis.[61-63] On the other hand, in toxic-metabolic encephalopathy, it is important to consider risk factors, including age, comorbidity (diabetes mellitus, hypertension, kidney or liver disease, hydroelectrolyte imbalance, and malnutrition), cognitive status, infection and sepsis, previous dementia, poor functional state and frailty. All of these combined with the cytokine cascade affect attention and consciousness, leading the patient to confusional states, lethargy, delirium and coma as representative abnormalities of encephalopathy.[64,65]

### Seizures

As mentioned above, seizures can lead to impaired consciousness, but they have also been reported in approximately 10% of patients with critical illness. Seizures occur in patients with coronavirus infection and in those with pre-existing epilepsy affected by SARS-CoV-2, as reported in the literature.[66] However, the frequency of seizures in the present pandemic has been reported as isolated cases rather than as part of a specific clinical picture; in fact, they are reported concurrently with cases of encephalopathy and impaired consciousness, in patients generally severely affected and with associated fever, fatigue, general malaise and stiff neck.[57] Perhaps the low frequency of meningoencephalitis with associated seizures is the result of the high mortality of patients with ventilator-dependent COVID-19 by direct neuroinvasion to the respiratory centers in the brainstem.[3]

### Cerebrovascular disease

The procoagulatory and prothrombotic states caused by SARS-CoV-2 infection establish a basis for the development of cerebrovascular disease. Reports in the literature are variable, and many of them have been isolated cases. In their study of 214 patients, Mao et al. found an incidence of 2.8%, most of which was in the severely compromised group, the majority being large vessel ischemic stroke. It also reports that these cases occurred in older patients, with cardiovascular risk factors and higher levels of CRP and D-dimer.[51] This procoagulatory state has been described in other studies, and it is very pathophysiologically reasonable due to endotheliitis, vasospasm, edema and inflammation promoted by the acute state of COVID-19 infection.[30,51,60,67] Klok et al.[68] found a 31% incidence of thrombotic complications in a series of 184 patients in 3 intensive care units (ICUs) in the Netherlands, including PTE, deep vein thrombosis, ischemic stroke and myocardial infarction. Venous thrombosis represented 27% and arterial thrombosis represented 3.7%, attributing diffuse intravascular coagulation, excessive inflammation, hypoxia and immobilization as precipitating factors. Standard doses of thromboprophylaxis were provided.

In a study of 221 patients in Wuhan, Li et al. reported a 5% incidence of ischemic stroke, mostly in the large vessels, with a mortality of 38%, where thrombosis was the predominant finding.[60] Varga et al. found changes in endotheliitis in 3 patients in Zurich, Switzerland.[30] Therefore, the acute state with very high inflammatory and coagulability markers is a factor of paramount importance in the development of large vessel disease, in some cases regardless of age.[69] In this regard, a study highlights that patients in their 50s can be affected, highlighting the importance of the base endothelial mechanism.[70] Risk factors for ischemic stroke linked to SARS-CoV-2 are severe and critical disease in older patients with underlying vascular symptoms such as hypertension, diabetes, hyperlipidemia, smoking and history of previous stroke or TIA, with increased levels of D-dimer favoring thrombotic disease.[71,72] Systemic infection of the vascular endothelium and its subsequent damage then promotes the risk of stroke due to endotheliitis itself, thrombosis and vasculitis. Regarding the latter, cerebral arteries and venules can be compromised, and a hemorrhagic event can result, although its frequency has been lower in all series.[6] Arterial hypertension continues to be the most common cause of intracerebral and subarachnoid hemorrhage in these patients.[71,72] Some guidelines have been developed locally, formulating early recognition and prevention measures as well as treatment for patients infected with SARS-CoV-2, including intravenous thrombolysis and endovascular therapy for stroke.[73-75]

### Frontotemporal dysfunction

In their study of 58 patients severely affected by COVID-19 and admitted to 2 ICUs in Strasbourg, France, Helms et al. found neurological compromise in 58% of them, manifested as agitation, pyramidal signs with hyperreflexia, clonus, bilateral extensor plantar reflex, delirium, hyperthermia and, in some of these cases, seizures. In addition, ischemic changes were observed in 3 of them on brain MRI. However, changes in bilateral frontotemporal hypoperfusion was evident in 11 patients, and 8 of them had diffuse bifrontal slowing on electroencephalography. Of the 45 patients who survived, 33% had a dysexecutive syndrome suggestive of frontal compromise expressed clinically by inattention, disorientation and poorly organized movement.[76] Syndromes with mixed clinical presentation and related to frontal dysfunction with changes in behavior, in motor initiation and/or execution, in attention and orientation, in ideation and thought or in mental health may be present in patients affected by SARS-CoV-2. Discarding frontotemporal dysfunction syndrome would be appropriate.[4]

### Myelitis

In Wuhan, China, Zhao et al. reported a case of a 66-year-old male patient with an acute picture of fever, malaise and pneumonia, with laboratory studies of the acute phase of inflammation markedly abnormal. He presented with acute flaccid paralysis of the lower limbs associated with urinary and intestinal incontinence, with a sensitive level at T10, complete loss of muscle strength in the lower limbs and partial loss in the upper limbs, with the latter partially recovering with treatment. In brain studies with CT, small lacunar infarcts were demonstrated in the basal ganglia and paraventricular

nuclei. They highlighted possible infectious causes of myelitis (TB, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, Epstein-Barr, influenza and parainfluenza viruses, adenovirus, coxsackievirus, cytomegalovirus and respiratory syncytial virus). They then considered the possibility of myelitis as a direct result of SARS-CoV-2 interacting with ACE2 receptors on the cell membrane in the spinal cord along with the "cytokine storm" caused by the disease.[77]

## Manifestations in the peripheral nervous system

The information available on the involvement of the peripheral nervous system (peripheral nerve and muscle) is comparatively less with respect to the number of reports of CNS involvement. The vast majority of the information found in the literature currently corresponds to case reports. In the following lines, we will try to review the evidence found. The symptoms reported in many of the systematic review and meta-analysis articles correspond to nonspecific symptoms for peripheral involvement, such as the sensation of dizziness, headache and myalgia,[9,55,56,78] and some more specific symptoms, such as altered taste and smell (dysgeusia and anosmia/hyposmia),[51,79-81] neuropathic pain,[51] diplopia, ataxia, areflexia[76] and hearing loss,[82] are the most common neurological symptoms in patients with severe COVID-19.[51] As previously mentioned, in the retrospective study of Mao et al. with 214 patients,[51] 10.7% of the patients had a peripheral nervous system lesion.

### *Disorders of smell and taste*

The presence of olfactory (anosmia, hyposmia) or taste (hypoageusia, dysgeusia) alterations has been proposed as a common symptom among patients with COVID-19 infections.[79,80] The spread of this infection in Europe has revealed a new atypical presentation of the disease: olfactory and taste dysfunctions. Many viruses can lead to this type of dysfunction through inflammation of the nasal mucosa and the development of rhinorrhea, the most common agents being rhinovirus, parainfluenza, Epstein-Barr virus and some coronaviruses;[83,84] however, the olfactory dysfunction linked to infection by COVID-19 seems not to be particularly associated with rhinorrhea.[79] Additionally, it has not been presented with other symptoms, such as fever or cough, which makes it difficult to suspect COVID-19 infection.

Faced with numerous reports from otolaryngologists throughout Europe, the YO-IFOS (Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies) decided to conduct an international epidemiological study (France, Spain, Italy and Belgium) to characterize the olfactory and taste disorders of patients infected with COVID-19 and to establish the prevalence of these symptoms. A total of 417 patients from 12 European hospitals were recruited by completing questionnaires based on smell and taste (National Health and Nutrition Examination Survey) and a short version of the sQOD-NS (Questionnaire of Olfactory Disorders-Negative Statements). This study showed that 85.6% reported olfactory dysfunction and 88.0% reported taste dysfunction. Olfactory symptoms appeared before other symptoms in 11.8% of cases; another significant finding was that among 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% had hyposmia or anosmia. With this high prevalence, it was suggested that sudden anosmia or ageusia needed to be recognized by the international scientific community as an important symptom of COVID-19 infection.[79]

Anosmia seems to be not only an indicator of the presence of the disease but also a prognostic indicator. Yan CH et al.[85] reported a series of 169 patients with a positive test for SARS-CoV-2, of which 128 had provided information on olfactory and taste involvement. An adjusted analysis showed an inversely proportional relationship between the presence of these symptoms and the need to hospitalize the patient: those who reported anosmia/hyposmia were 5 times more likely to be managed on an outpatient basis, and those without olfactory symptoms were 10 times more likely to need hospitalization. Thus, anosmia/hyposmia could be considered a clinical marker inversely related to disease severity. In general, the prevalence of anosmia was 75 of 128 patients (58.6%).

The pathophysiological mechanisms that lead to these alterations remain unknown; however, some explanations have emerged, the first of which proposes that it is the effects of generalized inflammation of the olfactory apparatus. Another theory is based on data obtained with viruses that cause injury to olfactory neurons by infection of nerve endings, transport in vesicular structures and transsynaptic passage.[21,86,87] In a study conducted in mice and published by ACS Chem Neuroscience,[88] it was shown that the ACE2 receptor that is essential for viral infection is expressed in the support cells located on the apical side of the olfactory epithelium, being absent or present in a very small proportion in the sensory neurons of said epithelium. The olfactory epithelial support cells, as well as glial cells, provide an anatomical and physiological substrate for neurons, containing Lrp2/Megalin proteins necessary for the internalization of odoriferous particles and their rapid clearance in the microenvironment of olfactory receptors.[89] This process, affected by the virus, could be one of the causes of the olfactory decrease in COVID-19 patients.

### *Guillain-Barre syndrome*

Acute demyelinating inflammatory polyneuropathy (AIDP), also known as Guillain-Barré syndrome, is a potential

and emerging complication of COVID-19. Under usual conditions, in approximately 2/3 of Guillain-Barré syndrome cases, neurological symptoms appear after a transient infectious process of either the respiratory tract or less commonly of the gastrointestinal system. Infectious agents associated with this syndrome include HIV,[90] Herpes Zoster,[91] hepatitis B,[92] West Nile,[93] *Campylobacter jejuni*[94] and ZIKA.[95] Neurological complications, including Guillain-Barré syndrome, have also been reported in other beta coronaviruses, such as SARS and MERS.[96] It is believed that this occurs through mechanisms of molecular mimicry in which infecting viruses share epitopes similar to the components of peripheral nerves, which stimulates autoreactive T or B cells. The antibodies produced by the immune system against the viruses cross-react and bind to components of the peripheral nervous system, causing neuronal dysfunction,[6] or do so as part of an inflammatory response syndrome.[97] However, the mechanism by which SARS-CoV-2 produces neuropathy still needs to be clarified.

Zhao et al.[98] reported the first case of Guillain-Barré syndrome associated with COVID-19 in a 61-year-old woman who had returned from Wuhan to Shanghai, China. Her reason for consultation was lower limb weakness and severe fatigue, and she reported no fever or respiratory symptoms. The physical examination showed symmetric weakness and areflexia of both lower limbs that progressed from 4/4 to 3/5 in 3 days. Laboratory tests showed the presence of lymphocytopenia and thrombocytopenia. CSF analysis showed a normal cell count with an increase in proteins (124 mg/dL). Neuroconduction studies showed slowing of distal latencies and absence of late responses (F wave) consistent with demyelinating neuropathy.

Since then and until the time of this review, 12 cases of Guillain-Barré syndrome in patients with COVID-19[98-102] have been reported in the literature, some of which required mechanical ventilation. The interval between the onset of viral disease and the development of peripheral neurological symptoms was on average 10 days. Many patients present with paresthesias and associated progressive flaccid quadriparesis,[7,103] Toscano,[100] in the first series of patients with this complication in Italy, reported 5 patients with Guillain-Barré syndrome from 3 hospitals in northern Italy during the present pandemic. Neurophysiological studies were consistent with axonal-type Guillain-Barré syndrome in 3 cases and demyelinating-type Guillain-Barré syndrome in 2 cases.

### *Miller-Fisher syndrome/cranial polyneuritis*

Miller-Fisher syndrome is characterized by the presence of an acute onset of external ophthalmoplegia, ataxia and decreased tendon reflexes. Gutiérrez-Ortiz et al.[76] reported 2 patients with clinical manifestations of COVID-19 with an associated severe acute respiratory syndrome. The first patient was a 50-year-old man who presented with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor nerve palsy, ataxia, areflexia, albuminocytological dissociation and a positive test for GD1b-IgG antibodies. Five days later, he developed a cough, general malaise, headache, low back pain and fever. The second patient was a 39-year-old man who presented with ageusia, bilateral abductor paralysis, areflexia and albuminocytological dissociation. Three days later, he developed diarrhea, fever and poor general condition. The oropharyngeal smear test for coronavirus (reverse polymerase transcriptase - PCR) was positive in both patients; tests using CSF were negative.

Similar cases were reported by researchers from Weill Cornell Medical College in New York, USA,[104] describing 2 cases. The first was a 36-year-old man with left ptosis, diplopia and bilateral distal paresthesia in the lower limbs who developed fever, cough and myalgia 4 days later. The diagnostic tests were positive for COVID-19. MRI showed T2 hyperintensity and thickening of the left oculomotor nerve. The second case was a 71-year-old woman with painless diplopia who had developed cough and fever days prior to admission. MRI showed thickening of both optic nerves. CSF analysis was normal. A growing body of evidence shows that neurotropism is a common feature in coronaviruses.[7] Animal models show that SARS-CoV and MERS-CoV can enter the CNS possibly through the olfactory nerves and rapidly spread to specific areas of the brain, including the thalamus and brainstem.[7] This may explain the symptoms of anosmia in many patients with SARS-CoV[105] and could be applied in this case to the optic nerve.

### *Myopathies*

Skeletal muscle involvement as a peripheral complication of SARS-CoV-19 infection has been suggested[106] due to the presence of symptoms of fatigue (26-51%) and myalgia (36%) associated with the increase in creatine phosphokinase (CPK) in 33% of cases;[107,108] however, there are no reports of EMG or histopathological studies that corroborate it. Mao et al.[51] reported muscle injury in 17 (19.3%) severely compromised patients and in 6 (4.8%) non severely compromised patients. They defined muscle injury as a patient who had myalgia and high CPK levels (> 200 U/L). Rhabdomyolysis was reported in patients with renal failure during the SARS-CoV epidemic in 2003,[108] and there are 2 reports[109,110] of this complication during COVID-19 infection. An important aspect to take into account because no electrophysiological or histopathological studies were reported is that it is difficult to exclude that these patients could have a critical illness neuropathy or myopathy in

addition to their muscle damage.[111] It is not clear whether muscle damage is due to the direct effect of the virus on muscle tissue or due to the immune response mediated by the infection that causes an increase in proinflammatory cytokines as a result of muscle damage. It is important to note that patients in the severely compromised group in the Mao study additionally showed an increase in liver enzymes and renal function tests, which could have contributed to this presentation.[51]

We should not overlook the importance of the RAAS in skeletal muscle function. As we have already expressed, there is evidence on the expression of RAAS in skeletal muscle; therefore, ACE receptors at this level could affect activity in normal tissues or in pathological states. An example of this is the increased expression of these receptors, which has been demonstrated in muscle biopsies of patients with Duchenne muscular dystrophy, or the functional improvement seen in response to ACE inhibition in dystrophic monkeys.[112,113]

## LABORATORY FINDINGS

Regarding laboratory tests related to the group of patients with neurological manifestations, it is reported that those with CNS complications have lower lymphocyte and platelet levels along with higher urea nitrogen levels than those without CNS involvement. For the group of patients affected in the PNS, no specific data were found, except general laboratory data for the disease. Those with lesions of the skeletal muscle system report significantly higher levels of creatine kinase with high neutrophilia and lymphocytopenia along with markedly increased C-reactive protein and D-dimer. In addition, muscle involvement is associated with a greater likelihood of multiorgan injury with serious hepatic involvement (lactic dehydrogenase, elevated alanine amino transferase and aspartate amino transferase) and renal involvement (increased ureic nitrogen and creatinine).[30,51]

## CONCLUSION

It is clear that the information on neurological involvement in patients with COVID-19 is heterogeneous; currently, this information is based on case reports because it comes from a pandemic outbreak. However, as evidenced in the literature, neural injury impacts mortality and the possible generation of sequelae and disability. This makes it necessary to conduct epidemiological studies that provide more solid information that allows us to understand the neuroinvasive potential of SARS-CoV-2 and the frequency and severity of complications of this nature. Undoubtedly, this will serve as a basis for the approach to take with these patients from the neurological and rehabilitation points of view.

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