Neurological complications of coronavirus and COVID-19

Francisco J. Carod-Artal

Introduction. Clinical and experimental studies have shown that the coronavirus family has a certain tropism for the central nervous system. Seven types of coronavirus can infect humans.

Development. Coronaviruses are not always confined to the respiratory tract, and under certain conditions they can invade the central nervous system and cause neurological pathologies. The potential for neuroinvasion is well documented in most human coronaviruses (OC-43, 229E, MERS and SARS) and in some animal coronaviruses (porcine haemagglutinating encephalomyelitis coronavirus). Neurological symptoms have been reported in patients affected by COVID-19, such as headache, dizziness, myalgia and anosmia, as well as cases of encephalopathy, encephalitis, necrotising haemorrhagic encephalopathy, stroke, epileptic seizures, rhabdomyolysis and Guillain-Barré syndrome, associated with SARS-CoV-2 infection.

Conclusions. Future epidemiological studies and case records should elucidate the real incidence of these neurological complications, their pathogenic mechanisms and their therapeutic options.

Key words. Coronavirus. COVID-19. Encephalitis. Encephalopathy. Neurotropism. SARS-CoV-2. SARS.

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Introduction

In December 2019, an epidemic outbreak of viral pneumonia associated with a new coronavirus began in the Chinese city of Wuhan; it was originally referred to as the Wuhan virus or new coronavirus 2019 [1]. What was initially a local epidemic outbreak has transformed into a global pandemic of uncertain and tragic consequences. In February 2020, an official taxonomic name was established for the new virus, coronavirus (CoV) type 2 associated with severe acute respiratory syndrome (SARS) (SARS-CoV-2), and the disease that it causes, COVID-19 (coronavirus disease 2019). The World Health Organization declared the epidemic as a public health emergency of international interest on January 30, 2020, and subsequently as a global pandemic [2].

This article reviews the available data on the neurological complications of coronaviruses in general and SARS-CoV-2 in particular. For this, a search was conducted in PubMed (April 7, 2020) with the descriptors COVID-19 (2,863 articles), SARS-CoV-2 (1,089 articles) and their combinations with the term complicaciones neurológicas (15 and seven articles, respectively).

Coronavirus

Coronaviruses are encapsulated viruses and have one of the largest genomes among positive-sense single-stranded RNA viruses, with a length ranging between 26 and 32 kilobases. The term coronavirus stems from the peculiar crown-shaped appearance of its envelope, visible by electron microscopy, which is surrounded by spike-shaped membrane glycoproteins. Coronaviruses belong to the subfamily *Orthocoronavirinae*, family *Coronaviridae*, order Nidovirales. The family *Coronaviridae* consists of four genera: alpha-, beta-, delta- and gamma-coronavirus [3].

Coronaviruses are causative agents of respiratory, hepatic, intestinal and, occasionally, neurological pathologies. They have a wide distribution in nature and can affect humans and other species (birds and mammals, including bats, felines, rodents and pigs) [3]. In addition to SARS-CoV-2, six other coronaviruses infect humans: alphacoronaviruses 229E and NL63 and betacoronaviruses HKU1, OC43, severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and Middle East respiratory syndrome-associated coronavirus (MERS-CoV). Coronaviruses have remarkable genetic diversity and a high capacity to recombine, which explains the interspecies leap of emerging coronaviruses that have affected humans in recent decades [4].

Epidemiology and transmission routes

The first strains of human coronavirus were identi-

fied in the 1960s. Before the appearance of SARS, only several strains of alphacoronavirus (229E) and betacoronavirus (OC43) were known.

SARS-CoV was detected in Guangdong, southeast China, and caused a pandemic between 2002 and 2003 with more than 8,000 confirmed cases and 774 deaths in 37 countries. *Rhinolophus* (bat) was the reservoir in which positive anti-SARS-CoV antibodies were detected. The intermediate reservoir was civets, from which the virus jumped to human beings. The initial symptoms were viral syndrome, followed by respiratory symptoms (cough and dyspnoea), which in 20% were complicated by SARS. Some patients had multiorgan failure. Mortality was 10% [5].

MERS-CoV was first detected in the Middle East (Jordan and Saudi Arabia) in 2012, and there were 2,500 confirmed cases and 858 deaths. The clinical picture was a respiratory syndrome complicated by SARS, gastrointestinal symptoms and renal failure. MERS-CoV originated in bats of the species *Pipistrellus* and *Perimyotis* and in turn was transmitted to camels (intermediate reservoir) and, through zoonotic transmission, to humans. In Saudi Arabia, nosocomial transmission occurred in various hospitals, and numerous health personnel and relatives of patients were infected. In the 2015 South Korean outbreak, there was more efficient transmission between people [6].

Human coronaviruses 229E, OC43, NL63 and HKU1 are endemic worldwide and are responsible for 15-30% of upper respiratory tract infections, rhinitis, laryngitis and pharyngitis, as well as otitis. Sometimes, they can cause more serious infections, such as bronchitis, bronchiolitis, exacerbation of asthma or SARS. The outbreaks associated with MERS-CoV and SARS-CoV 1 and 2 have caused high mortality in more vulnerable population groups, such as the elderly and immunocompromised people or those with serious diseases [6].

SARS-CoV-2 is transmitted through the respiratory tract through small droplets that disperse one or two metres when speaking or coughing. In hospitals and closed venues, larger aerosols can be formed, with a greater contagion capacity, in which the virus lasts for several hours. Transmission by fomites is possible because the virus remains viable on smooth surfaces for an indeterminate period. Experimental studies have shown that SARS-CoV-2 persists 24 hours on cardboard and 72 hours on stainless steel and plastic surfaces [7]. SARS-CoV-2 has been detected in the lung secretions, blood, faeces, saliva and urine of infected people.

Structure and replication

SARS-CoV-2 is a betacoronavirus that contains a single positive RNA strand. Its envelope, whose diameter oscillates between 60 and 140 nm, gives it a rounded or elliptical morphology. Its genome contains specific elements that facilitate the replication of the virus and the formation of essential structural proteins. The complete genome has been isolated from nine Wuhan patients and consists of a single-stranded RNA (29,903 base pairs) that is closely related (88%) with two betacoronaviruses isolated in bats [8]. Phylogenetic studies suggest that bats were the original host and reservoir [9]. The genomic sequencing of SARS-CoV-2 shares 96.2% and 89% homology, respectively, with the bat coronaviruses RaTG13 and ZXC21 and 82% homology with SARS-CoV. SARS-CoV-2 jumped to humans through an intermediate host, probably the pangolin. The SARS-CoV-2 genome comprises a variable number of open reading frames (ORFs), which are RNA sequences between two codons, one for translation initiation and the other for termination. The largest is called ORF 1a/b and encodes two polyproteins called pp1a and pp1b. The rest of the ORF encodes other accessory and structural proteins [8]. The remaining genome encodes four structural proteins that are necessary for the assembly and infectious capacity of SARS-CoV-2 (surface glycoprotein S, envelope E protein, membrane M protein and nucleocapsid N protein) as well as other accessory proteins that interfere with the immune response. Glycoprotein S is located on the outer surface of the envelope and forms a three-dimensional binding domain that facilitates the anchoring of the virus to the host cell receptor. It consists of two subunits: S1, which determines the tropism by the specific receptor, and S2, which is involved in the process of cellular and viral membrane fusion [10].

SARS-CoV-2 binds to the angiotensin converting enzyme II (ACE2) receptor and invades cells that express this receptor [11]. The ACE2 receptor is present in pneumocytes of the lower respiratory tract, which are the main target, vascular endothelial cells, kidney and smooth muscle. Glutamine residue 394 of the receptor binding domain is recognized by the lysine 31 residue of the ACE2 receptor [12]. After binding, a conformational change in the S protein occurs that facilitates the fusion of the SARS-CoV-2 envelope with the membrane of the infected cell and the entry of genomic RNA into the intracellular compartment. The receptor binding domain of SARS-CoV-2 is structurally similar to that of SARS-CoV.

Once inside the cell, a polyprotein translation process is activated; the polyprotein, in turn, is cleaved by proteolysis into minor proteins until forming a series of non-structural proteins of the viral transcriptase-replicase complex. It is a very dynamic process in which RNA polymerases synthesize subgenomic messenger RNA, which in turn is translated into viral proteins. The final assembly of genomic RNA and essential viral proteins in virions is performed in the endoplasmic reticulum and the Golgi apparatus. Virions are transported in vesicles and finally released to infect other cells in a new cycle [13].

Clinical manifestations

The average incubation period is five days (average range: 3-7, with a maximum of 14 days). During the viral replication phase, which lasts several days, subjects may present mild symptoms as a result of the effect of the virus and the innate immune response. The involvement of the lower respiratory tract occurs when the immune system fails to stop the spread and replication of the virus, and respiratory symptoms arise as a result of the cytopathic effect on lung cells [14].

The main clinical manifestations of COVID-19 are fever, dry cough, dyspnoea and acute respiratory stress. However, many infected subjects may be asymptomatic or present mild symptoms, such as headache, non-productive cough, fatigue, myalgia and anosmia.

Table I shows the frequency of symptoms for a series of 1,099 admitted patients with SARS-CoV-2 in Wuhan [15]. Some patients may develop SARS one week after the onset of symptoms, which can be fatal. The overall mortality is estimated at 8% and is due to respiratory failure with hypoxia or multiple organ failure.

The acquired immune system acts in a second response, and the viral load of SARS-CoV-2 is reduced. However, in some patients, a severe hyperinflammatory systemic reaction has been observed, possibly due to a cytokine release, and is reminiscent of haemophagocytic lymphohistiocytosis triggered by other viral infections (Table II) [16].

Elderly or seriously ill patients are the most vulnerable population group. Arterial hypertension (24%), diabetes mellitus (16%), ischaemic heart disease (6%), cerebrovascular disease (2.3%) and chronic obstructive pulmonary disease (3.5%) are the most common comorbidities in severe forms of COVID-19 [15].

Table I. Frequency of symptoms associated with COVID-19 (n = 1,099 patients). Adapted from [15].

Cough	68%	Sore throat	14%
Fatigue	38%	Chills	12%
Sputum production	34%	Nasal congestion	5%
Dyspnoea	19%	Nausea-vomiting	5%
Myalgia/arthralgia	15%	Diarrhoea	4%
Headache	14%	Conjunctival injection	1%

Table II. Characteristics of cytokine release syndrome.

Acute hyperinflammatory syndrome	
Fulminant and lethal hypercytokinaemia	
Usually, triggered by viral infections	
Present in 4% of sepsis cases	
Cardinal symptoms	Persistent fever
	Cytopenia
	Hyperferritinaemia
Pulmonary involvement and severe acute respiratory syndrome in at least 50% of cases	

Neurological complications

Respiratory viruses can penetrate the central nervous system (CNS) (neuroinvasion), affect both neurons and glial cells (a property known as neurotropism) and induce various neurological pathologies (neurovirulence) [17]. The hypothesis regarding the neuroinvasion and neurovirulence properties of SARS-CoV-2 is based on the following evidence:

- Extrapolated biological plausibility of CNS involvement by other respiratory viruses.
- Evidence of neurological damage by coronaviruses in other species.
- Animal models of CNS infection by human coronaviruses.
- Existence of neurological complications from other coronaviruses.
- Patients with COVID-19 who have presented neurological manifestations.

Infections of the central nervous system by other respiratory viruses

Viral infections of the respiratory system are a public health problem. The respiratory viruses that affect humans most frequently are influenza, orthopneumovirus (respiratory syncytial virus), human metapneumovirus and coronavirus. All of them have been associated with various neurological manifestations in people who suffer from severe respiratory disease [18]. Respiratory syncytial virus can cause encephalitis, epileptic seizures, cerebellitis and ataxia and has been detected in cerebrospinal fluid. The Hendra and Nipah viruses of the family Paramyxoviridae are causative agents of severe pneumonia and can cause encephalitis. The influenza virus can affect the CNS, and a wide variety of neurological complications have been described, including meningitis, encephalitis, necrotizing encephalopathy, myelitis and Guillain-Barré syndrome (GBS), among others [18].

Pathogenic coronaviruses that affect other species

Various coronaviruses can infect cattle and birds (porcine respiratory coronavirus, porcine haemagglutinating encephalomyelitis virus, bovine coronavirus and avian coronavirus), canids (canine respiratory coronavirus) and felines (feline coronavirus). Neurological complications (meningitis and spinal cord involvement) have been described in cats infected with a virulent feline coronavirus strain that has been isolated in brain tissue [19,20]. Porcine haemagglutinating encephalomyelitis virus shares 91% homology with human coronavirus OC43 and is capable of invading the porcine brain. It has been isolated from the brains of piglets suffering from encephalomyelitis. The inoculation of porcine haemagglutinating encephalomyelitis virus in the buconasal region caused the infection of epithelial cells in the respiratory tract and the small intestine, subsequently reaching the CNS by retrograde neuronal propagation via peripheral nerves [20,21]. Porcine haemagglutinating encephalomyelitis virus first affects the nasal mucosa, tonsils, lungs and small intestine in piglets, and then, it spreads retrogradely through the peripheral nerves to the neurons of the medulla oblongata, responsible for peristalsis of the digestive tract, causing vomiting. Mouse hepatitis virus is a subspecies of murine coronavirus, whose JHM and A59 strains have clear neurotropism and induce a demyelinating disease that resembles multiple sclerosis [20].

Animal and *in vitro* models of central nervous system infection by human coronaviruses

Arbour et al. demonstrated 20 years ago that the human coronaviruses OC43 and 229E are capable of inducing both acute and persistent infection in human neuronal cell lineages, oligodendrocytes and neuroglia [22-24]. Human coronavirus OC43 has been shown to be neuroinvasive and cause flaccid paralysis and demyelination in animal models [25]. In susceptible mice, OC43 coronavirus spreads from the olfactory bulb to the brain stem and spinal cord. CoV-OC43 RNA has been detected for one year in the CNS of mice with encephalitis induced by this virus. In a murine model, OC43 coronavirus has a selective tropism for neurons and is capable of using the axonal transport system as a means of neuron-to-neuron propagation [17]. Both passive diffusion of viral particles and axonal transport are neuron-neuron propagation strategies observed in cell cultures [26]. SARS-CoV infection can cause neuronal death in ACE2 transgenic mice [27]. In this animal model, SARS-CoV enters the CNS through the olfactory bulb, and the infection spreads transneuronally to other regions of the brain.

Neurological complications from other human coronaviruses

Among the various human coronaviruses, at least 229E, OC43 and SARS-CoV have demonstrated neuroinvasive capacity because viral RNA or nucleic acids have been detected in the human brain [20]. One case of fatal coronavirus OC43 encephalitis [28] has been described in a 12-month-old infant suffering from severe combined immunodeficiency. The diagnosis was made using brain biopsy samples and RNA sequencing techniques and reverse polymerase chain reaction (RT-PCR). An immunohistochemical study of the brain showed a prominent microglia reaction and T lymphocyte infiltration and detected the nucleocapsid of the OC43 coronavirus in neurons. The case of a 15-year-old adolescent suffering from acute disseminated encephalomyelitis associated with coronavirus OC43 has been published [29]. The resonance showed areas of demyelination in the subcortical white matter, cerebellum and spinal cord. OC43 coronavirus was detected in cerebrospinal fluid and in secretions of the nasopharynx by PCR. In the convalescent phase three weeks later, anti-OC43 antibodies in the serum increased from 1:160 (acute phase) to 1:640.

SARS-CoV can cause encephalitis, ischaemic stroke and polyneuropathy in patients with SARS

[30]. Viral RNA has been detected in the cerebrospinal fluid of a patient with encephalitis [31]. Epileptic seizures may be the first manifestation of SARS-CoV encephalitis in patients with SARS [32]. A necropsy study of eight patients who died from SARS-CoV confirmed the infection of neurons in the cortex and the hypothalamus [33], and SARS-CoV genomic sequences were detected in all cases by RT-PCR.

MERS-CoV can cause encephalomyelitis and vasculitis. Arabi et al. published a series of three patients who suffered from altered levels of consciousness, from confusion to coma, ataxia and multifocal motor deficit. MRI of the brain showed bilateral hyperintense lesions in T_2 sequences in the white matter and in subcortical areas of the frontal, parietal and temporal lobes, as well as in the basal ganglia and the corpus callosum. In two patients, cerebrospinal fluid showed an increase in proteins. All three patients had severe involvement of multiple organs (lungs, kidneys and cardiovascular system) and lymphocytopenia with decreased B and T lymphocytes [34]. Other neurological complications described during MERS-CoV infection are GBS, encephalitis of the brain stem [35], and cerebral haemorrhage in the context of thrombocytopenia and disseminated intravascular coagulation [36]. In a retrospective study of 70 patients with MERS from Saudi Arabia, 8.6% of patients suffered seizures [37]. In a series of 23 cases of MERS-CoV, four patients with GBS were described; the latency of neurological symptoms was between seven and 26 days after the onset of pulmonary symptoms. A case of GBS associated with co-infection by coronaviruses 229E and OC43 has been described in a paediatric patient [38].

Neurological complications associated with COVID-19

The incidence of neurological complications from SARS-CoV-2 is unknown. Patients with severe COVID-19 are more likely to have neurological symptoms than those with mild forms. Necropsy studies have shown the presence of cerebral oedema and neuronal degeneration in deceased patients with COVID-19 [39].

Nonspecific and possibly systemic neurological symptoms

Headache, myalgia, dizziness and fatigue are the most frequently described nonspecific symptoms. In a retrospective study of 214 admitted patients with COVID-19 in a Wuhan hospital, 36.4% presented some type of neurological manifestation, categorized as CNS involvement (24.8%), peripheral (10.7%) and musculoskeletal (10.7%) [40]. The most common neurological symptoms were dizziness (36 cases), headache (28 cases), hypogeusia (12 cases) and hyposmia (five cases). Neurological symptoms were more frequent in patients with severe COVID-19 (45.5% vs. 30%).

Headache is the most common symptom in people with COVID-19 in China. In the series by Guan et al. [15] of more than 1,000 patients with COVID-19, 13.6% reported headaches (15% of those with severe disease). The intensity of the headache is described as mild, even when the clinical details are incomplete. These studies do not mention whether patients had a history of primary headache (migraine) or meningeal signs. In the series by Guan et al., 15% of patients reported myalgia, 13.7% had elevated levels of creatine kinase (19% in severe cases), and two cases of rhabdomyolysis (0.2%) were cited in patients with non-severe COVID-19. Rhabdomyolysis, increased creatine kinase and multiple organ failure have also been described as late complications of COVID-19 [41].

Disorders of smell and taste

Anosmia and, secondarily, taste disorders seem to be very prevalent in people with COVID-19, even in the absence of nasal symptoms, and can appear suddenly [42]. The prevalence of olfactory and gustatory dysfunction was analysed in a case registry of 12 European hospitals. A total of 417 patients with mild to moderate COVID-19 completed the study. The patients answered questionnaires of taste and smell alterations based on a health and nutrition survey and the short version of the Questionnaire of Olfactory Disorders. The most frequent symptoms reported were cough, myalgia and loss of appetite; 85.6% and 88% of patients described smell and taste disorders, respectively, and olfactory dysfunction was the initial symptom reported by 12%. Eighteen percent of patients did not present with rhinorrhoea or nasal obstruction, but in this subgroup, 80% had anosmia or hyposmia [43].

Encephalopathy

Encephalopathy is a transient cerebral dysfunction syndrome that manifests as acute or subacute impairment of the level of consciousness. The risk of suffering an altered mental state associated with COVID-19 is higher in people of advanced age or with previous cognitive deterioration as well as in those who present vascular risk factors (hypertension) and previous comorbidities [40,44]. Patients

with previous neurological damage and acute respiratory symptoms are at a higher risk of encephalopathy as an initial symptom of COVID-19. Patients with COVID-19 suffer from severe hypoxia, which is a risk factor for encephalopathy [15]. In a study by Mao et al., 15% of patients with severe COVID-19 presented altered levels of consciousness, compared with only 2.4% of patients with mild disease [40]. The encephalopathy associated with COVID-19 may be due to toxic and metabolic causes and the effect of hypoxia or drugs. Another associated indirect mechanism is the presence of subclinical crises. The case of a patient with COVID-19 who presented an encephalopathic picture, unable to follow verbal orders, has been described. The electroencephalogram showed diffuse slow waves in the bilateral temporal region [44]. Pathological findings include cerebral oedema in the absence of inflammation of the cerebrospinal fluid. Cerebral oedema has been detected in necropsies of patients who died from COVID-19 [39]. Treatment is symptomatic and includes control of fever, treatment of hypoxia or use of antiepileptic medication.

Encephalitis

SARS-CoV-2 should be included in the differential diagnosis of encephalitis along with other neurotrophic viruses, such as the herpes simplex family, varicella zoster or West Nile virus, among others. The symptoms of encephalitis include fever, headache, epileptic seizures, behavioural disorders and altered levels of consciousness. An early diagnosis is crucial to ensure survival because these symptoms can also occur in patients with COVID-19 with severe pneumonia and hypoxia. A case of encephalitis was reported in a 56-year-old patient from Wuhan who was diagnosed with COVID-19 in January 2020 [45]. The patient was admitted to an intensive care unit and presented a decreased level of consciousness; therefore, a brain CT was performed, which was normal. The diagnosis of encephalitis was confirmed by the isolation of SARS-CoV-2 in the cerebrospinal fluid by genomic sequencing techniques [46]. A second case of meningoencephalitis was described in a 24-year-old Japanese male with symptoms of COVID-19 who presented generalized epileptic seizures and a decreased level of consciousness. SARS-CoV-2 RNA was not detected in the nasopharynx, but it was detected in the cerebrospinal fluid by RT-PCR. The analysis of the cerebrospinal fluid showed 12 cells/μL (10 mononuclear and two polymorphonuclear cells). In the brain resonance, hyperintense areas were observed in the right lateral ventricle, the mesial region of the temporal lobe and the hippocampus [47]. The patient required invasive mechanical ventilation due to pneumonia and multiple generalized seizures.

Acute haemorrhagic necrotizing encephalopathy

A case of acute haemorrhagic necrotizing encephalopathy has been reported in a patient with COVID-19 who presented symptoms of fever, cough and altered mental status. The diagnosis was made by detecting SARS-CoV-2 by PCR-TR in a nasopharyngeal sample. Brain CT detected a symmetrical and bilateral hypodense area in the medial thalamic nucleus. The resonance showed haemorrhagic lesions, of multifocal and symmetrical disposition, in annular form in the thalamus, the insula and the medial region of the temporal lobes, that were enhanced after the administration of contrast [48]. Acute necrotizing encephalopathy, although relatively rare, is a complication described in some viral infections, including influenza virus. The authors postulate that its pathogenesis is related to cytokine release syndrome, which is a described manifestation of COVID-19 [16].

Guillain-Barré syndrome

A case of GBS associated with SARS-CoV-2 infection was described in a 62-year-old patient who presented motor weakness in the lower extremities and clinical symptoms of COVID-19 with fever and dry cough a week later. The study of the cerebrospinal fluid showed an increase in proteins (124 mg/dL) and the absence of cells. The neurophysiological examination revealed an increase in distal latencies and an absence of F waves, indicating a form of demyelinating GBS. The authors suggest that the patient was infected with SARS-CoV-2 at the onset of GBS symptoms, as she had lymphopenia and thrombocytopenia. However, it cannot be excluded that the patient had coincidental symptoms of COVID-19 and GBS [49].

Cerebrovascular complications

Elderly patients with vascular risk factors seem to have a higher risk of developing cerebrovascular complications when developing COVID-19 than do younger people without comorbidities [50]. In a retrospective study of 221 patients with COVID-19 from Wuhan, 11 (5%) presented ischaemic stroke; one (0.5%) presented cerebral thrombosis of the venous sinuses; and one (0.5%) presented cerebral haemorrhage. The risk factors for having a stroke were advanced age (mean age: 71.6 years), severe COVID-19, previous history of hypertension, dia-

betes or cerebrovascular disease, or a marked inflammatory and procoagulant response (increased C-reactive protein and D-dimer, respectively) [50]. Mortality was 38%. In the series by Mao et al., five patients with stroke (80%, ischaemic) who had severe forms of COVID-19, with increased D-dimer levels, thrombocytopenia and multiple organ involvement, were described [40]. Regarding physiopathogenesis, SARS-CoV-2 binds to ACE2 receptors in endothelial cells, which can cause an increase in blood pressure. The increase in blood pressure, together with the presence of thrombocytopenia and coagulation disorders, can contribute to the increased risk of both ischaemic and haemorrhagic stroke in patients with COVID-19. Cytokine release syndrome may be another risk factor for cerebrovascular disease.

Uncertain pathogenic mechanisms

Several pathogenic mechanisms have been proposed to explain the neurological complications of COVID-19.

Propagation routes: haematogenous dissemination versus transsynaptic transfer

Direct invasion of the CNS, haematogenously or lymphatically, and retrograde dissemination from the peripheral nerve terminals are theoretically possible [51] and could occur both in the initiation phase and in the late phase of COVID-19. Currently, the exact route by which SARS-CoV-2 can penetrate the CNS is unknown [52]. Coronaviruses can disrupt the nasal epithelium, and in certain circumstances that are still not well understood, they can cross the epithelial barrier and reach the bloodstream or lymphatic system and spread to other tissues, including the CNS.

The retrograde transsynaptic pathway from peripheral nerve endings is biologically plausible. Although the olfactory bulb is quite efficient in controlling viral invasion, some coronaviruses seem to be able to penetrate the CNS through the cribriform plate of the ethmoid. Transsynaptic transfer is well documented for porcine haemagglutinating encephalomyelitis coronavirus and avian bronchitis virus [52].

Li et al suggest a possible retrograde pathway for SARS-CoV-2 through the mechanoreceptors and chemoreceptors located in the lungs and respiratory tract because the nucleus of the solitary tract receives sensory information from that location. According to this hypothesis, dysfunction of the cardiac-respiratory control centres of the medulla oblongata aggravate SARS and cause death [52]. Turtle does not support the neurogenic hypothesis of respiratory failure and argues that patients with COVID-19 pneumonia develop hypoxia and type 1 respiratory failure with low CO_2 levels and an increased respiratory rate. These patients can breathe spontaneously but with great difficulty and increased respiratory effort. In contrast, respiratory failure of neurological origin manifests as a reduction in respiratory rate, low levels of oxygen and high levels of CO_2 (type 2 respiratory failure) and the presence of other neurological symptoms [53]. Histopathological, virological and immunohistochemical studies are necessary to demonstrate whether there is specific tropism and neurological damage to respiratory control brain centres by SARS-CoV-2.

Regulation of the ACE2 receptor

The ACE2 receptor facilitates cell invasion by SARS-CoV-2 and its rapid replication [11]. The depletion of the ACE2 receptor of the cell membrane causes the harmful effects of angiotensin II to multiply and, consequently, acute deterioration of lung function. Downregulation of the ACE2 receptor could put the hypertensive and diabetic population at risk with COVID-19 due to increased angiotensin II. A hypothesis pending confirmation postulates that the use of ACE inhibitors, commonly used in such patients, leads to an increase in the expression of ACE2, making cells more vulnerable to infection by SARS-CoV-2. In a study on mortality risk factors in COVID-19, 40% of the deceased had some type of comorbidity, and arterial hypertension (30%) was the most common, followed by diabetes (19%) and coronary disease (8%) [54]. The neurovirulence of SARS-CoV2 could be related to the degree of ACE2 expression in the CNS. The ACE2 receptor is expressed in endothelial cells; therefore, it is necessary to further investigate its role in the etiopathogenesis of stroke associated with COVID-19. The virus could interact in the cerebral microcirculation through the S (spike) protein with ACE2 expressed in the capillary endothelium, infecting endothelial cells and replicating within them, and once the virus causes endothelial damage, it propagates to neurons [51].

Other factors: hypoxia, immune-mediated neurological damage

SARS-CoV-2 replicates and proliferates in pneumocytes and causes diffuse interstitial and alveolar

inflammatory exudate and, in the most severe forms, the formation of membranes; therefore, gas exchange in the alveoli is affected in a very pronounced way [55]. Hypoxia induces anaerobic metabolism in CNS cells, cellular and interstitial oedema, and ischaemia and vasodilation in the cerebral circulation. In this context, syncope, anoxic crisis and stroke can occur [55]. Host immune response may also play a role. Some patients with COVID-19 have died from a hyperinflammatory syndrome (cytokine release) and multiorgan failure [16]. Coronaviruses have the capacity to infect macrophages, astroglia and microglia, and experiments in cell lines have shown that glial cells are capable of secreting proinflammatory factors, such as interleukin 6, interleukin 12, interleukin 15 and tumour necrosis factor alpha, after infection by a coronavirus [18].

Neurological implications of a persistent infection

Is it possible that coronaviruses persist in CNS-resident cells and may be cofactors related to clinical exacerbations or the development of long-term neurological manifestations in genetically predisposed subjects? Several coronaviruses have been identified by serological techniques in a wide variety of neurological pathologies, such as Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis and optic neuritis [56-59]. Coronaviruses 229E, 293 and OC43 have been isolated from the cerebrospinal fluid and brains of patients with multiple sclerosis. A significantly higher prevalence of OC43 coronavirus has been described in the brains of patients with multiple sclerosis than in the brains of participants in a control group [57-59]. As a result of these findings, it was proposed that a persistent coronavirus infection could be an etiopathogenic factor in certain neurological diseases. The immune response after infection could participate in the induction or exacerbation of outbreaks of multiple sclerosis in susceptible individuals [17].

Exposure to human coronaviruses could be a risk factor for certain psychiatric diseases. A case-control study showed a higher prevalence of immune reactivity for the HKU1 and NL63 coronaviruses in patients with recent psychotic symptoms than in participants in a control group [60]. The significance of these findings is far from elucidated because exposure to these respiratory viruses is very prevalent throughout the lives of individuals, and their true role in the etiopathogenesis of these pathologies is unknown.

Implications for diagnosis and treatment

The aspects related to the degree of immune response, diagnosis and treatment of COVID-19 need to be evaluated in depth in future research. The antibody response follows a typical pattern: IgM antibodies disappear after 12 weeks of infection, while the anti-viral protein S and N-specific IgG antibodies persist for a longer time, thus playing a protective role. The clinical diagnosis of COVID-19 is based on epidemiological history, clinical manifestations and confirmation of exposure to SARS-CoV-2. In the current context, the diagnosis of COVID-19 should be considered in everyone who presents with fever, dry cough, fatigue and dyspnoea. Real-time RT-PCR and genomic sequencing techniques are the two tests used to confirm a COVID-19 diagnosis. The isolation and culture of the virus from blood and sequencing of the entire genome are limited in clinical practice due to the high cost and the need for technology. Therefore, real-time RT-PCR techniques have become the fastest and most efficient methods for detecting SARS-CoV-2 in the nasopharynx and respiratory secretions [51]. The University of Hong Kong and the Chinese Center for Infectious Disease Control recommend the use of primers specific for the ORF1 and N regions for SARS-CoV-2 detection by RT-PCR. This technique has high specificity, although its sensitivity ranges between 50 and 79% depending on the type of sample, the time from the onset of symptoms, and the number of clinical specimens collected. The detection capacity of SARS-CoV-2 should be improved because false negative cases have been described [61]. At present, detection systems for viral antigens and antibodies are being developed. The sensitivity of the anti-protein N IgG ELISA technique for SARS-CoV was 94.7%, higher than that for the anti-S IgG ELISA (59.9%) [62].

Currently, there is no anti-viral treatment that has demonstrated efficacy to cure COVID-19. Adenosine analogues, such as remdesivir, which acts on RNA-dependent polymerase and blocks the synthesis of viral RNA, are promising drugs for treating RNA virus infections. Other nucleotide analogues under evaluation are favipiravir, ribavirin and galidesivir. Chloroquine and hydroxychloroquine can effectively inhibit SARS-CoV-2 *in vitro.* The efficacy of therapy with serum from subjects in the convalescent phase, rich in anti-SARS-CoV-2 antibodies, is under study. Other therapeutic options include specific monoclonal antibodies that bind to the union-receptor domain of SARS-CoV-2 and antibodies that block the action of inflamma-

tory interleukins (such as tocilizumab) [63]. The World Health Organization has initiated the SOLIDARITY clinical trial to evaluate the efficacy of various drugs to treat COVID-19.

Finally, several vaccines are in the analysis phase and include live attenuated viruses, inactivated viruses, recombinant DNA and vaccines based on proteins and specific subunits of SARS-CoV-2. Until these therapeutic options are available, the main measures are prevention, isolation and social distancing, hygienic handwashing measures and the use of masks for risk groups.

Discussion

The initial descriptions of people who suffer from COVID-19 and who present neurological symptoms raise important questions. First, what are the pathogenic mechanisms underlying neurological damage, are they related to specific host factors at the individual level, or are they due to factors associated with neurovirulence and neurotropism of SARS-CoV-2? Some symptoms, such as headache, are nonspecific manifestations of viral infection by SARS-CoV-2, but in some cases, they could lead to certain more serious pathologies, such as meningitis or encephalitis. The actual degree of neurotropism of SARS-CoV-2 has yet to be elucidated. The presence of SARS-CoV-2 in the cerebrospinal fluid of patients suffering from COVID-19 and encephalitis should be demonstrated, and analysis and sequencing of the virus in brain tissue samples from necropsies should be performed. In the context of the current epidemic, there may be limitations for performing an MRI or lumbar puncture in a patient with COVID-19 with neurological manifestations or an altered mental status. Patients presenting with COVID-19 and altered levels of consciousness should receive appropriate neurological assistance and undergo neurological exams, including neuroimaging studies, electroencephalography and cerebrospinal fluid studies, when appropriate.

The data regarding encephalitis associated with other coronaviruses suggest that the presence of lymphopenia may be a risk factor in immunosuppressed subjects. Patients with cancer, systemic autoimmune diseases or immunosuppressive treatment are risk groups for COVID-19 and neurological complications. In the field of neurology, the treatment of pathologies such as neurosarcoidosis, polymyositis, cerebral vasculitis, neuromyelitis optica, myasthenia gravis and multiple sclerosis is especially relevant because people with these diseases may be taking corticosteroids or a wide range of immunosuppressive treatments and biological agents. Neurologists and relevant scientific societies should develop plans and guidelines for the prevention of exposure to the virus and re-evaluate the doses and treatment cycles for these diseases during the COVID-19 era. Recently, the Madrid Demyelinating Diseases Group reviewed the indications to maintain or modify immunomodulatory and immunosuppressive treatments in multiple sclerosis in the context of the COVID-19 pandemic [64]. In Scotland, a contingency plan has been developed to identify neurological patients in immunosuppressive treatment and at added risk of COVID-19. Social distancing and shielding are recommended to protect vulnerable populations from COVID-19 and avoid contagion (Table III). Proactive measures of contact with patients are recommended through telemedicine, telephone and online consultations and by sending educational and informative material to patients [65,66].

The quality of the case series on COVID-19 and CNS involvement is important. For epidemiological

Table III. Patients at high risk of severe COVID-19 for whom social distancing and additional protection and self-isolation measures (shielding) are recommended. Adapted from [66].

Patients who have received an organ transplant
Cancer patients undergoing chemotherapy
Patients with lung cancer who have received or are receiving radical radiotherapy
Patients with lymphoproliferative disease, such as leukaemia, lymphoma or myeloma in any phase of treatment
Patients receiving biological treatments for or monoclonal antibodies against cancer
Patients receiving other cancer therapies that affect the immune system, such as protein kinase inhibitors
Patients who have received a bone marrow or stem cell transplant in the last six months or who are still receiving immunosuppressive drugs
Patients with severe chronic lung disease: cystic fibrosis, severe asthma, and severe chronic obstructive pulmonary disease
Patients with rare diseases and innate errors of metabolism
Homozygous patients with sickle cell anaemia
Patients with interstitial lung disease; sarcoidosis
Patients who receive immunosuppressive treatments that significantly increase the risk of infection [a]
Pregnant women with severe heart disease, either congenital or acquired

[a] Relevant aspect in neurology.

Table IV. Possible neurological complications that should be evaluated in epidemiological studies of COVID-19.

Encephalopathy and other complications of the central nervous system (crisis, delirium) in the context of a systemic infection or respiratory failure associated with COVID-19	
Central nervous system infection	Acute encephalitis/meningitis
	Encephalomyelitis
	Acute transverse myelitis
(Possibly) immune-mediated syndromes	Mononeuritis/involvement of the cranial nerves
	Guillain-Barré syndrome and variants (Miller Fisher)
	Post-infectious transverse myelitis
	Acute disseminated encephalomyelitis
	Necrotizing encephalomyelitis
	Acute cerebellitis
	Post-encephalitic parkinsonism
	Post-COVID-19 chronic fatigue syndrome
Neurological complications associated with cytokine release	
Cerebrovascular complications	Transient ischaemic attack
	Ischaemic stroke
	Haemorrhagic stroke
Neuromuscular complications	Myalgia
	Rhabdomyolysis
Neuro-ophthalmological complications	

and research purposes, the proposed model is recommended to categorize the neurological complications of other neurotrophic viruses [67,68] (Table IV).

Finally, it is necessary to propose a global vision for COVID-19 in the field of neuroinfection. The way in which SARS-CoV-2 can affect the clinical expression of other viral, bacterial or parasitic coinfections in the CNS is unknown. In specific tropical regions, co-circulation of SARS-CoV-2 with dengue, chikungunya, Zika or Japanese encephalitis viruses can occur. Coinfection and co-circulation of influenza, enterovirus and herpes viruses can occur together with SARS-CoV2 in a global setting. The impact of COVID-19 in patients suffering from human immunodeficiency virus infection or chronic parasitic diseases, such as malaria, schistosomiasis, neurocysticercosis, tuberculosis, chronic meningitis or simply malnutrition, is unknown.

Conclusions

Viral factors (mutations in specific genes that increase the virulence of SARS-CoV-2) and factors associated with the host (advanced age, comorbidities, and immunosuppression), as well as the interaction between virus and host, are the appropriate conditions that can explain the different levels of neurotropism, CNS invasion and neurovirulence of SARS-CoV-2 in humans. The actual incidence of neurological complications and their type and severity are uncertain; therefore, future epidemiological and research studies should clarify these gaps in our current knowledge.

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Complicaciones neurológicas por coronavirus y COVID-19

Introducción. Estudios clínicos y experimentales han demostrado que la familia de los coronavirus tiene un cierto tropismo por el sistema nervioso central. Siete tipos de coronavirus pueden contagiar al ser humano.

Desarrollo. Los coronavirus no siempre permanecen confinados en el tracto respiratorio, y en determinadas condiciones pueden invadir el sistema nervioso central y causar patologías neurológicas. La capacidad potencial de neuroinvasión está bien documentada en la mayor parte de los coronavirus humanos (OC-43, 229E, MERS y SARS) y en algunos coronavirus animales (coronavirus de la encefalomielitis hemaglutinante porcina). Se han descrito síntomas neurológicos en pacientes afectos por COVID-19, como cefalea, mareo, mialgias y anosmia, así como casos de encefalopatía, encefalitis, encefalopatía necrotizante hemorrágica, ictus, crisis epilépticas, rabdomiólisis y síndrome de Guillain-Barré, asociados a la infección por el SARS-CoV-2.

Conclusiones. Futuros estudios epidemiológicos y registros de casos deben elucidar la incidencia real de estas complicaciones neurológicas, sus mecanismos patogénicos y sus opciones terapéuticas.

Palabras clave. Coronavirus. COVID-19. Encefalitis. Encefalopatía. Neurotropismo. SARS. SARS-CoV-2.