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REVIEW ARTICLE

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Neurological symptoms due to COVID-19, are they really frequent?

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Abstract

Background: In December 2019, a pneumonia of unknown cause, led to the detection of the new SARS-CoV-2 with an alarming increase in cases worldwide and important critical challenges for public health. In addition to the clinical signs and symptoms initially described, there are reports of a possible neuroinvasive potential of SARS-CoV-2 and associated neurological complications, although this appears to be an uncommon phenomenon. Objectives: To analyze the frequency of neurological symptoms associated with COVID-19. Material and methods: Retrospective study, of a bibliographic review by means of a non-systematic search for keywords related to COVID-19, neurotropism and neurological symptoms reported in the literature from January 2020 to October 2020. Results: The number of patients with this type of complications compared to the number of infected and hospitalized patients could be relatively low and some of the associated neurological symptoms could be more related to the systemic and indirect impact of SARS-CoV-2 on the brain than with a parenchymal invasion. Conclusions: Although there are reports of neurological complications in patients with COVID-19, it is not known with certainty if SARS-CoV-2 is neurotropic in humans. It remains to be clarified whether the possible invasion of SARS-CoV-2 is partially responsible for the acute respiratory failure of patients, as well as to demonstrate the association of neurological symptoms with the presence of SARS-CoV-2 within the CNS. Timely analysis and isolation of the virus in the CNS is crucial to establish the neurological spectrum of the virus, the underlying pathophysiological mechanisms, and its possible long-term neurological sequelae.

Keywords: *COVID-19; SARS-CoV-2; neurological symptoms; neurocritical; neurotropism*

Introduction

In December 2019, patients with pneumonia of unknown etiology were associated with a wholesale seafood market in Wuhan, China [1]. This resulted in the detection of the new coronavirus 2 responsible for the severe acute respiratory syndrome (SARS-CoV-2) [2] with high transmissibility via the upper respiratory route [3] leading to Coronavirus Disease 2019 (Covid-19) [4] with unprecedented demand and burden of health care services and high morbidity and mortality worldwide [5]; the World Health Organization declared the pandemic in March 2020 [6]. The situation evolved rapidly with an alarming increase in cases worldwide, to date, the pandemic has spread to more than 185 countries and there are more than 11,317,637 cases, with 531,728 deaths worldwide, exponentially increasing over time [6-8] and it has posed major critical challenges for public health, research and the international medical community [5]. Along with the virus, the increasing information on Covid-19 has been exponential, with the publication of a large number of articles related to the pandemic; however, our lack of knowledge of this new virus and paper and report overpublishing has resulted in the retraction of more than 30 articles on the subject as far as September 2020 [9]. Some data can be worse than none, information overload, emotion, stress, fatigue and the desire and the pressing need for solutions and treatments can lead us to believe and trust any published result [10]. Although even case reports result in useful and valuable information that strengthens future research, we must be cautious when making decisions, not establish conclusions which have not been validated and promote well-designed studies. The journals and we, ourselves, have a great responsibility with the publications and with the interpretation of the information [10].

Materials and methods

Retrospective literature review study by non-systematic search of keywords related to Covid-19, neurotropism and neurological symptoms reported in the literature in PubMed and SciELO databases from January 2020 to October 2020.

Practice by Covid-19

An increasing number of reports of Covid-19 patients with neurological problems, in addition to emerging experimental models evidencing neuroinvasion, raises concern that SARS-CoV-2 is a new underdiagnosed neuropathogen [11]. Coronaviruses (CoV) are positive-sense RNA viruses, with a characteristic crown-shaped appearance, that can infect humans and different animal species[12-13]. SARS-CoV-2 is the seventh coronavirus known to infect humans[12]. In addition to the clinical signs and symptoms initially described with mainly respiratory and systemic involvement, there are several reports of neurological complications. Headache, dizziness, delirium, encephalopathy, confusion and altered consciousness, ataxia, seizures, ischemic stroke, postinfectious myelitis, neuropathic pain, acute peripheral polyneuropathy, myopathy, neuromuscular disorders and alterations in imaging studies among others have been described, especially in more severely ill patients[14-21].

The virus does not appear to concentrate in cerebrospinal fluid (CSF), blood or urine [22], however there is a report that SARS-CoV-2 specific RNA was not detected in the nasopharyngeal swab, but in a CSF examination in a patient with meningitis. Therefore, it is recommended not to exclude Covid-19 infections when clinical suspicion is high, even if the reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 from the patient's nasopharyngeal swab is negative [23].

RT-PCR study for SARS-CoV-2 in CSF samples was negative in the majority of reported cases with severe neurological complications [18], suggesting that most SARS-CoV-2-related neurological complications are probably not related to direct viral entry into the central nervous system (CNS) [24].

Sensitivity analysis of detection sources by RT-PCR showed that bronchoalveolar lavage fluid is most sensitive (93%), followed by sputum (72%), nasal swab (63%), fibrobronchoscope brush biopsy (46%), pharyngeal swabs (32%), stool (29%) and blood (1%); multiple testing of different sites improves sensitivity and reduces the possibility of false negative results [25].

Neurotropism

The first data showing that a coronavirus could infect the CNS date back to 1980, when the virus was detected in brain tissue at autopsy of a patient with multiple sclerosis (MS) [26]. The coronaviruses that cause Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV-1) cause CNS and peripheral disease [27-28], and have approximately 50% and 80% homology with SARS-CoV2, respectively. Based on these data and neurological symptoms found in Covid-19, it has been postulated that SARS-CoV-2 could have neurotropic properties, and although neurological syndromes were reported in association with MERS-CoV and SARS-CoV-1 [28], the extent of the epidemics and the number of patients with SARS-CoV2 are very different [13]. It has been suggested that the neuroinvasive potential of SARS-CoV-2 may influence the respiratory failure and

higher mortality rate of Covid-19 patients, but it remains to be clarified whether the possible invasion of SARS-CoV-2 is partially responsible for the patients' acute respiratory failure [21]. Observations in animal models do not necessarily reflect how a virus behaves in humans. In experimental studies, viral strains are sometimes selected for their neurotropic properties, and large quantities of virus are often required to induce CNS disease after peripheral inoculation[29]. Although murine models develop CNS infection after intranasal inoculation with MERS-CoV, this virus has never been detected in the CNS of humans [13, 30].

Potential mechanisms of neuroinvasion

SARS-CoV-2 virus invasion or damage to the CNS could occur in several ways: injury from direct infection, hematogenous from infection of the vascular endothelium, neuronal retrograde transsynaptic transfer, hypoxic injury, immunological [27, 29, 31, 32], via a surface protein with high binding affinity to the human angiotensin-converting enzyme 2 (ACE-2) receptor [11, 19, 32] or by leukocyte migration across the blood-brain barrier (BBB) using immune cells (in a process known as "Trojan horse") that are naturally able to migrate across the BBB during inflammation [33]. Preliminary reports indicate that the Trojan horse mechanism does not appear to contribute to the brain invasion of SARS-CoV-2 [29].

Interleukins

Hospitalized patients with Covid-19 may present numerous toxic metabolic disorders such as increased cytokines, severe inflammation and sepsis, probably at levels similar to other critical illnesses, which are likely to contribute significantly to toxic metabolic encephalopathy, inflammation and brain damage[27, 32].

Levels of D-dimer, proinflammatory cytokines such as interleukin (IL) IL-2, IL-6, IL-8, IL-10 and tumor necrosis factor-α were significantly higher in persons killed by Covid-19[16]. Previous studies of other coronaviruses, SARS-CoV-1 and MERS, have shown that both viruses directly induced neuronal death in the respiratory center of the bulb of animal models through a positive regulation of the IL-1, IL-6 and TNF alpha cytokine response[30] possibly through an inflammatory response or autophagy [34], however further studies are needed to determine if this is applicable to the new SARS-CoV-2 virus and humans[11]. Neurological complications of SARS-CoV-2 infection are high among people with severe and critical illnesses[24], although cytokine levels reported in Covid-19 patients do not differ significantly from those found in patients with other forms of ARDS, trauma, or cardiac arrest[35], which detracts from the importance of the cytokine storm concept.

Angiotensin-converting enzyme type 2 (ACE-2)

Angiotensin-converting enzyme 2 (ACE-2) is a cellular receptor that exists in a variety of organs, including endothelium, nervous system, and musculoskeletal system[32]. SARS-CoV-2 has a peak protein surface unit 1 with high binding affinity for the human ACE-2 receptor [36].

Because of their high similarity, it has been proposed that, like SARS-CoV, SARS-CoV-2 exploits the ACE-2 receptor to enter cells [19, 37]. The ACE-2 receptor can be expressed in CNS in glial cells, thalamic nuclei, cerebellum, inferior olivary nuclei, ventrolateral bulbar, and nucleus of the solitary tract, two areas closely involved in the regulation of the respiratory cycle[19, 38, 39], raising the need to investigate the possible potential for CNS infection and the contribution of neurological tissue damage to Covid-19 morbidity and mortality.

Neurological symptoms

Neurological symptoms can be divided into three groups: related to CNS involvement, peripheral nervous system (PNS) involvement and symptoms related to musculoskeletal disorders (MSD) or neuromuscular junction (NMJ)[13], some of which are observed more frequently with increasing disease severity [12].Table 1

The retrospective study by Mao L, et al. in Wuhan in 214 patients with positive RT-PCR to SARS-CoV-2, reported 36.4% of patients with neurological manifestations; CNS 25%, PNS 9% and MSD 11% [14]. Their data suggest that patients with more severe systemic presentations were more likely to have neurological symptoms, including acute cerebrovascular disease (5.7% *vs* 0.8%), altered consciousness (14.8% *vs* 2.4%), and musculoskeletal injury (19.3% *vs* 4.8%), compared with milder forms of infection[14]. Other authors report that patients with neurological symptoms, specifically anosmia/ageusia present in a less severe form of the disease [40].

Helms et al. reported neurological findings in 8 out of 58 patients (14%) on admission to the ICU and associated ARDS due to SARS-CoV-2 with encephalopathy, agitation, confusion and corticospinal tract signs[18].

The most frequently reported CNS symptoms were nonspecific general symptoms such as dizziness (16.8%), headache (13.1%)[14], as well as confusion (9%)[15].

Case reports of neurological syndromes such as encephalopathy, encephalitis/meningoencephalitis, Guillain-Barré syndrome (GBS) and stroke have also been published[12,28].

Table 1. Main neurological symptoms reported.

Location	Symptoms	Reported percentage	Reference
	Neurological symptoms in general	14% 36%	Helms, et al. Mao, et al.
Sistema Nervios Central (SNC)		25%	Mao, et al.
	Dizziness	16.8%	Mao, et al.
	Delirium	20-70%	O'Hanlon and Inouye
	Confusion/alteration of consciousness	7.5 - 31% 9% 37%	Sharifian-Dorche, et al. Chen N., et al. Mao, et al.
	Headache	8% 13%	Chen N, et al. Mao, et al.
	Convulsive crises	0.6%	Lu L., et al.
	Leukoencephalopathy and/or cerebral microhemorrhages	0.84%	Agarwal, Jain, et al.
	Ischemic cerebrovascular attack	0.9% 2.8% 5% 1.6%	Yaghi S., et al. Mao, et al. Li Y., et al. Merkler, et al.
	Hemorrhagic cerebrovascular attack	1%	Li Y., et al.
Peripheral Nervous System (PNS)		9%	Mao, et al.
	Hyposmia	5.1% 88%	Mao, et al. Lechien JR, et al.
	Dysgeusia/hypogeusia	5.6% 88%	Mao, et al. Lechien JR, et al.
Musculoskeletal disorders (MSD) or neuromuscular junction (NMJ)		11%	Mao, et al.
	Guillain-Barré syndrome (GBS)	%ND 52 pacientes de 36 estudios	Sharifian-dorche, et al.
	Multiple sclerosis (MS)	ND-NR	
	Myasthenia gravis	ND-NR	

NA – NR: Not Available – Not Reported

Anosmia and ageusia

PNS damage in Covid-19 is mainly represented by dysgeusia/hypogeusia 5.6% and hyposmia in 5.1% [14] and is considered a testimony to the neuroinvasion potential of SARS-CoV-2, although that hypothesis remains speculative[29].

In most patients, anosmia disappeared on its own within 3 weeks [41]. The Lechien study reported olfactory and gustatory dysfunction in 88.5% and 88.0% of patients, respectively [42] among adults with mild or moderate Covid-19.

Impaired consciousness, encephalopathy and delirium

Keeping a state of consciousness is extremely complex. The ascending reticular activating system (ARAS), one of the systems responsible for consciousness in humans, originates in the brain stem and connects with the thalamus and cortex[43]. In encephalopathy, attention and arousal are impaired and, confusion, lethargy, delirium or coma occur [27].

Impaired consciousness was reported in 37% of hospitalized patients with Covid-19 in the study by Mao et al. in Wuhan[14].

Sharifian-doreche et al. reported a decreased level of consciousness and encephalopathy in 7.5%-31% of Covid-19 patients in 22 articles involving 454 patients[13].

Delirium is a known complication of respiratory illnesses, such as pneumonia, especially in older adults [44]. Reports indicate that up to 20-30% of patients with Covid-19 will have or develop delirium or mental status changes during the course of their hospitalization and up to 60-70% in cases of severe disease [44].

The mechanisms of altered consciousness, encephalopathy and delirium may be multifactorial such as advanced age, comorbidities, fever, direct neurological infection, parenchymal damage, cerebrovascular involvement, hypoxic encephalopathy and toxic-metabolic, seizures/post-ictal status, systemic hyperinflammation, dehydration and water-electrolyte imbalance, immune dysregulation and excessive immune response, sepsis with multi-organ dysfunction/failure, medications or toxic-metabolic alterations[24,27,44]. Table 2.

Table 2. Possible neurophysiological factors of alteration of consciousness, encephalopathy and delirium associated with COVID-19 infection.

Possible mechanisms of alteration of consciousness, encephalopathy and delirium	Reference
Advanced age, comorbidities, fever, direct neurological infection, parenchymal damage, cerebrovascular involvement, hypoxic and toxic-metabolic encephalopathy, seizures/post-ictal status, systemic hyperinflammation, dehydration and water-electrolyte imbalance, immune dysregulation and excessive immune response, sepsis with multi-organ dysfunction/failure, drugs or toxic-metabolic alterations	Zubair, et al., 2020 O'Hanlon and Inouye, 2020 Najjar, et al., 2020
Autoimmune response directed toward the CNS post infection	Sonneville R., et al, 2019
Cytokine effect and systemic impact of organ dysfunction	Tsail, et al., 2020 Zubair, et al., 2020
Brain hypoperfusion	Najjar, et al., 2020
Toxic encephalopathy secondary to hypoxemia	Wu Y., et al., 2020 Chen T., et al., 2020 Solomon, et al. 2020

Direct SARS-CoV-2 infection of RCT-2 expressing endothelium of the neurovascular unit, which could cause endothelitis and vascular injury and contribute to cerebral hypoperfusion, remains unproven [24].

Acute necrotizing hemorrhagic encephalopathy (ANHE)

Acute necrotizing hemorrhagic encephalopathy (ANHE) is a rare complication of viral infections, high levels of proinflammatory cytokines in CSF can cause degradation and increased BBB permeability, which in turn can lead to viral invasion [13, 45].

A presumptive case of Covid-19-associated ANHE demonstrated hemorrhagic lesions enhancing the rim within the thalamus, medial temporal lobes and subinsular regions on brain magnetic resonance imaging (MRI) [45].

Leukoencephalopathy and/or cerebral microhemorrhages, which have also been reported, are multifactorial and are associated with critical illness, increased mortality and worse functional outcome in patients with Covid-19 [46].

In a retrospective review, 115 out of 4131 patients with Covid-19 admitted to 3 hospitals, who underwent CMR, 35 (30.4% of 115 and 0.84% of 4131 patients) had leukoencephalopathy and/or cerebral microhemorrhages, which had worse functional outcome at discharge compared to patients without these findings. An association was also found between the number of days patients were connected to a ventilator with possible cerebral hypoxia and ischemic injury due to prolonged shock and refractory hypoxia, thrombocytopenia and elevated D-dimer; these findings suggestive of a worse neurological status and the possibility of brain damage and encephalopathy [46].

Encephalitis, meningoencephalitis

There are case reports of meningitis/encephalitis associated with the new virus, however, evidence and direct evidence confirming its association is often lacking [28,29] and its consistent presence in the CNS has not been demonstrated.

Xiang et al. report the presence of SARS-CoV-2 by genome sequencing in CSF from patients with clinical viral encephalitis and Covid-19 [47].

Moriguchi et al. reported a case where SARS-CoV-2 RNA was isolated from CSF in a patient with meningitis/encephalitis who presented with seizures during transfer to hospital, impaired consciousness with Glasgow Coma Scale (GCS) score of 6 (O4 V1 M1) and neck stiffness. CT scan with no evidence of cerebral edema. CMR 20 hours after admission showed right lateral ventriculitis and encephalitis mainly of the right mesial lobe and hippocampus [23].

Many pathogens, including coronaviruses, can induce an autoimmune response directed toward the CNS after resolution of an infection (acute disseminated encephalomyelitis-EMDA)[48]; it is often difficult to distinguish encephalitis, meningitis, and neurological symptoms induced by metabolic, vascular, or autoimmune disorders occurring during or after a severe infection [29].

Seizures

Some patients with Covid-19 may be more predisposed to develop seizures or status epilepticus as an initial manifestation; however, it is unclear whether the infection is directly responsible for the seizures or whether epileptiform activity affects the outcome in these patients [49].

Seizures can also lead to impaired consciousness and have been reported in other CoV infections[13]. Subclinical seizures have been reported in 10% of patients with critical illness [50], and patients with primary seizure disorder are at increased risk for seizures and status epilepticus in the setting of severe infection [27]. In Covid-19, only 48 patients out of 20 studies were reported to have seizures [13].

Viral CNS infections and subsequent activation of neuroinflammatory pathways lower the seizure threshold and potentially facilitate epileptogenesis in certain individuals [51]. Accumulation of inflammatory markers associated with SARS-CoV-2 infection may cause local cortical irritation precipitating seizures[52]. In viral infections and critically ill patients, metabolic and electrolyte imbalances, hypoxia, fever, inflammatory/infectious processes, and increased cytokines may contribute to seizures or electroencephalogram (EEG) disturbances[13,24,39].

A report of 304 patients diagnosed with Covid-19 documented only 2 patients with "seizure-like symptoms" due to an acute stress reaction and hypocalcemia, with no evidence to suggest an additional risk of acute symptomatic seizures in persons with Covid-19 [53].

Guillain-Barré syndrome and variants

Guillain-Barré syndrome (GBS) can occur after a respiratory or gastrointestinal illness. Sharifian reported 52 patients from 36 studies with different variants of GBS in association with Covid-19 [13]. Toscano G, et al. reported 5 cases of GBS in Italy

who developed symptoms 5 to 10 days after the onset of viral symptoms by Covid-19 [54]. A clinical case of acute transverse myelitis was reported in Wuhan, but CMR and CSF were not available [55].

Multiple sclerosis and neuromuscular disorders

Patients with Multiple Sclerosis (MS) or neuromuscular disorders receiving therapies that have immunosuppressive effects may be at increased risk of developing severe Covid-19 disease. Patients with myasthenia gravis or Lambert Eaton myasthenic syndrome may have respiratory muscle weakness, which may put them at increased risk for serious complications [27].

Drugs

Numerous different drugs are currently used to treat patients with Covid-19 [27]. Neurological symptoms in some of these patients may be pharmacological side effects[13]. Potential neurotropism may depend on viral and host factors (including immunosuppression due to disease or medications) that may influence the severity of the disease [56].

Neurological adverse effects of chloroquine and hydroxychloroquine include irritability, psychosis, peripheral neuropathy and neuromyopathy. Hydroxychloroquine exacerbates symptoms and is contraindicated in myasthenia gravis. It also lowers the seizure threshold and interacts with several antiepileptic drugs, such as lacosamide and lamotrigine [27].

Tocilizumab is a monoclonal antibody against the IL-6 receptor that can attenuate cytokine release in patients with severe inflammatory disease. Neurological adverse effects include headache and dizziness and there are rare reports of multifocal cerebral thrombotic microangiopathy[27].

Vascular injury due to acute ischemic and acute hemorrhagic stroke

Patients with cerebrovascular disease continue to arrive in overcrowded emergency rooms. The Covid-19 pandemic has been detrimental by generating bottlenecks of access and delay of management time [57].

It is currently thought that SARS-CoV-2, together with host immune mechanisms, may be associated with increased risk of acute cerebrovascular disease[32,58]. Cerebrovascular attacks (CVA) are an uncommon complication of CNS viral infections (11), but further studies are needed to determine whether their incidence is higher in this type of patients. It has been reported that IVCA can occur in patients with severe Covid-19[14]; especially when there is D-dimer elevation, thrombocytopenia and hypercoagulable state [59, 60, 61]. It is speculated that cytokine elevation could increase vascular permeability, edema and generalized inflammation, in addition to triggering "hypercoagulation cascades", with small and large clots affecting multiple organs including the brain [32, 62].

In the context of SARS-CoV-2 infection, patients with vascular risk factors may be at increased risk of ischemic stroke (IVCA) as they face complications such as hypotension, shock, arrhythmogenic cardiomyopathy, heart failure and disseminated intravascular coagulation (DIC) that can potentially contribute to hypoperfusion, embolic mechanisms of stroke and large vessel occlusion [11].

Some researchers have found 31% rates of thrombotic complications in critically ill patients hospitalized in ICU with SARS-CoV-2 pneumonia [63] and more acute large vessel strokes have been observed in young adults under 50 years of age with Covid-19 [64].

Some authors have reported a lower volume of LVCA admissions and less thrombolysis and mechanical thombectomy during the Covid-19 pandemic compared to previous studies [65, 66, 67], probably due to patients not attending hospital centers, so it is critical to encourage patients to continue to seek emergency care and ensure early management [57].

The study by Mao et al reported that 0.8 to 5.7% had acute strokes depending on the degree of involvement, being higher in the most severe cases (6 cases out of 214 patients -2.8% in total) [14].

A report of 221 patients from Wuhan, China, found a 5% incidence of acute IVCA and a 1% incidence of cerebral hemorrhage [68].

Although the Merkler study shows that patients with Covid-19 were more likely to suffer an acute LVCA than patients with influenza, the percentage is relatively low, 31 out of 1916 patients with Covid-19 (1.6%) *vs* 3 out of 1486 patients with influenza (0.2%). Covid-19 patients also had a higher prevalence of risk factors such as hypertension, diabetes, and coronary artery disease [58].

3 out of 13 patients with Covid-19 infection who underwent CMR for unexplained encephalopathy had IVCA without focal signs (23%) [18].

Of 3556 patients hospitalized with Covid-19 in New York, 0.9% had IVCA[69]. Most cases in which ACVI has been reported, patients had several underlying comorbidities that made them more susceptible to thromboembolic events [69]. Thus, the pathophysiology of the increased risk of cerebrovascular disease during Covid-19 infection is likely to be multifactorial[27].

Subarachnoid hemorrhage (SAH)

In addition to thrombotic complications, bleeding is an important cause of morbidity in patients with Covid-19 [59]. Subarachnoid hemorrhage (SAH) is a neurological emergency and carries significant morbidity and mortality. It presents with elevated sympathetic drive and inflammation resulting in cardiac and pulmonary dysfunction that may manifest as dyspnea, hypoxia, fever, and bilateral pulmonary infiltrates due to neurogenic pulmonary edema that may mimic Covid-19 infection [49].

Whether endothelial/epithelial ACE-2 receptor involvement by SARS-CoV-2 increases the likelihood of vasospasm/thrombosis leading to late cerebral ischemia is undefined [49].

Some reports indicate a reduction in SAH, despite seasonal change and hemorrhagic cerebral vascular events [70].

The study by Al-Samkari, et al. found an overall bleeding incidence of 4.8%. All but one major hemorrhage occurred in critically ill patients, with an incidence of 5.6% [59].

Autopsies

Autopsy reports of patients with Covid-19 showing histopathological findings, such as cerebral edema and neuronal degeneration, suggest toxic encephalopathy secondary to hypoxemia may be the etiology of confusion, especially in severe cases [16,32,71].

The histopathological examination report of brain samples from 18 patients by Solomon, et al. reported hypoxic changes and no evidence of encephalitis or other specific brain changes attributable to the virus. Virus was detected at low levels in 6 brain sections of 5 patients. Positive tests may have been due to in situ virions or viral RNA in blood [71].

Regarding the high similarity between SARS-CoV and SARS-CoV-2, it remains to be known whether possible neuroinvasion of SARS-CoV-2 plays a role in acute respiratory failure in Covid-19 patients. Therefore, knowledge of possible neuroinvasion may have guiding significance for the prevention and treatment of SARS-CoV-2-induced respiratory failure [21].

Discussion

Although there are reports of neurological complications in patients with Covid-19, it is uncertain whether SARS-CoV-2 is neurotropic in humans[27]. The high similarity between SARS-CoV and SARS-CoV-2 could support the neuroinvasive potential of SARS-CoV-2, although this appears to be a rare phenomenon [24].

Of more than 2.5 million people infected with SARS-CoV-2, 93 cases of neurological manifestations (about 5/100 000) had been published as of May 2020 [28], so the number of patients with such complications compared with the number of infected and hospitalized patients may be relatively low.

When faced with acute neurological abnormalities during an infectious episode, it is often difficult to separate the neurological symptoms induced by the brain infection and those due to the impact of the host immune response on the CNS[29]. Patients with Covid-19 often suffer from severe hypoxia and viremia [72], which have the potential to cause toxic encephalopathy [32].

Pouga reports that only 4 out of 21 publications analyzed provided evidence of the presence of SARS-CoV-2 in the CNS. In most cases, the neurological symptoms reported in the literature were more related to the indirect impact of SARS-CoV-2 on the brain than to a parenchymal invasion [29].

Patients with severe Covid-19 infections, hypoxia and associated sepsis can lead to different neurological presentations that can be observed in any of the critical conditions[13].

Cases should be reported according to clear clinical case definitions, both systematically and transparently, and being honest about negative or missing results[28]. To this end, working groups have been established such as the CoroNerve Study Group (CoroNerve.com)[28] and the global consortium of Neurological Disfunction in COVID-19 (GCS-NeuroCOVID) study of the Neurocritical Care Society and the Latin American Brain Injury Consortium (LABIC) that implemented a pragmatic Level 1 study to establish the phenotypes and prevalence of neurological manifestations of Covid-19 [73].

Strict protection of all health professionals involved in the care of each patient through the use of PPE will ensure their safety and satisfy the healthcare needs of future patients with this and other conditions [74, 75].

Conclusions

Although there are reports of neurological complications in patients with Covid-19, it is uncertain whether SARS-CoV-2 is neurotropic in humans. It remains to be clarified whether the possible invasion of SARS-CoV-2 is partially responsible for the acute respiratory failure of patients, as well as to demonstrate the association of neurological symptoms with the presence of SARS-CoV-2 within the CNS. Timely analysis and isolation of the virus in the CNS is crucial to establish the neurological spectrum of the virus, the underlying pathophysiological mechanisms and its possible long-term neurological sequelae.

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