

Short Review

COVID-19: Are we Underestimating its Neuroinvasive Potential? Review of Literature

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Abstract

Even though the primary symptoms of COVID-19 are fever, cough, diarrhea, fatigue and pneumonia, and initially neurologic symptoms had not been reported, after ten months of pandemic we can affirm that neurological disease is extremely frequent, being present in more than 36% of the patients. Central nervous system manifestations (as headache, altered level of consciousness, acute cerebrovascular disease or parkinsonism), peripheral nervous system manifestations (as anosmia or dysgeusia), skeletal muscular injury manifestations (as rhabdomyolysis) and mental disorders can appear in patients infected with SARS-CoV-2, even when they remain asymptomatic and do not develop respiratory or digestive symptoms of infection. Neurological involvement can determine the prognosis of the patient at short, medium and long term.

Keywords: COVID-19; SARS-CoV-2; Neurotropism; Encephalitis; Encephalopathy; Central Nervous System

Introduction

After the description of the first case for the new coronavirus SARS-CoV-2-2019 in Wuhan, China, it started to spread quickly in Europe and the rest of the world, infecting millions and killing by now more than half million people worldwide [1].

Clinical presentation of COVID-19 owns a wide spectrum. Even when initially typical respiratory symptoms like fever, cough, dyspnoea, fatigue, pneumonia or diarrhea seemed the more frequent [2], other dermatological or gastrointestinal manifestations were described. At the breakdown of the pandemic, no neurologic manifestations had been described associated to COVID-19 [3]. However,

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10 month after, we can affirm that patients with COVID-19 usually presents neurological symptoms that can vary from anosmia and dysgeusia to headache, dizziness, encephalopathy up to demyelinating lesions [4,5]. Viral neurotropism, endothelial dysfunction, coagulopathy and inflammation are plausible proposed mechanisms of this lesions in patients with COVID-19 [6].

This article review the available data in Pubmed (October, 2020) on the neurological complications described on SARS-CoV-2, with the words “NEUROLOGIC DISORDERS” and “COVID”, obtaining 2035 results and “Neurologic Complications” and “COVID”, with 551 results.

Pathogenic Mechanism of Neurological Affection

Influenza, respiratory syncytial virus, human metapneumovirus and coronavirus frequently affects humans. All of them have been associated with neurological complications [7]. Associated to Influenza virus, for example, exists cases of meningitis, myelitis, Guillain-Barré syndrome or necrotizing encephalopathy [7].

Human coronaviruses present neuroinvasive capacity, and have been published encephalitis, encephalomyelitis, epileptic seizures, ataxia or altered level of consciousness associated to MERS and SARS-CoV. Viral RNA could be detected in cerebrospinal fluid of the patients [8].

In the same way, SARS-CoV-2 can cause nerve damage by several pathways. Direct haematogenous or lymphatic dissemination, as well as retrograde dissemination from the peripheral nerve terminals are possible [7,9]. Coronaviruses can cross the nasal epithelium, and disrupt the epithelial barrier, reaching the bloodstream or lymphatic system and spread to other tissues, including the central nervous system (CNS). The rupture of the blood brain barrier (BBB) is associated with cytokine storm, slowing microcirculation at the capillary level or infection of myeloid cells [10], and secondary intracranial infections may cause headaches, projectile vomiting, visual loss, and limb convulsions among others [11].

VHS-1 or influenza virus have demonstrated their capability of reaching CNS through olfactory tract [10]. After an intranasal infection, SARS-CoV has shown to infect the respiratory tract in mice and to be neuroinvasive [12]. For some authors, this transneuronal way by olfactory tract can be the reason of the anosmia as first sign of infection of some patients [10].

Secondly, coronavirus affects lung tissue originating lung lesions and therefore, hypoxia. Some authors suggest a retrograde pathway through mechano and chemo receptors located in the lung and respiratory tract, which send information to the nucleus of the solitary tract. This could aggravate respiratory insufficiency by dysfunction of the cardiac and respiratory control centres of the medulla oblongata, causing death [13].

On third place, it can enter directly through the olfactory nerve to the CNS, and from there, to the blood circulation and the rest of the CNS, resulting in neurological disorders [11].

ACE2 Receptor

Angiotensin-converting enzyme 2 (ACE2) is a cardio-cerebral vascular protection factor existing in a variety of organs, including the nervous system and skeletal muscles, playing a major role in regulating blood pressure and anti-atherosclerosis mechanisms [11]. The ACE2 receptor (ACE2-r) facilitates cell invasion by SARS-CoV-2, favouring its rapid replication, which is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestine cells [13]. The brain express ACE2-r in glial cells and neurons, which makes them a potential target of SARS-Cov-2 [9]. Depletion of ACE2-r increases the harmful effects of angiotensin II. The common use of ACE inhibitors, commonly used in hypertensive and diabetic patients, produce an increase of the expression of ACE2, making cells more vulnerable to infection by SARS-CoV-2 [10]. Also, COVID-19 spike protein can interact with ACE2 expressed in the capillary endothelium, damaging the BBB and entering the CNS by attacking the vascular system [11].

Hypoxia

SARS-CoV-2 replicates in pneumocytes, causing diffuse alveolar and interstitial oedema, inflammatory exudation, and the formation of membranes in the most severe cases [10]. This alterations produce alveolar gas exchange disorders causing hypoxia in the CNS, increasing anaerobic metabolism in the mitochondria of brain cells [11]. Acid accumulation can cause cerebral vasodilatation, swelling of brain cells, interstitial oedema, obstruction of cerebral blood flow, and even headache due to ischemia and congestion, producing intracranial hypertension, bulbar conjunctival oedema, and even coma, inducing acute cerebrovascular disease or acute ischemic stroke [11].

Immune Injury

Nervous system damage caused by viral infection may be mediated by the immune system [11]. Severe COVID-19 infections are linked to development of a systemic inflammatory response syndrome (SIRS) that could be initiated by severe pneumonia and produce multiorgan failure. The ability of SARS-CoV-2 to infect macrophages, microglia, and astrocytes in the CNS is particularly important [7]. Experiments in cell lines have shown that glial cells are capable of secreting proinflammatory factors (interleukin 6, interleukin 12, and interleukin 15) and temporal necrosis factor, and neurotropic virus can activate glial cells inducing a pro-inflammatory state with cytokine storm. Furthermore, activation of immune cells in the brain will cause chronic inflammation and brain damage [11].

Neurologic Complications Associated to COVID-19

To the best of our knowledge, the first report of neurologic manifestations of patients hospitalized with COVID-19 was published by Ling Mao et al in April, 2020 [3]. They describe that more than 36% of the patient presented various neurologic manifestations, involving CNS, periferical nervous system and skeletal muscles. Patients with severe infection seemed more likely to develop neurologic manifestations [3,7]. Most of them appeared 1-2 after admission in hospital. An epidemiological survey on COVID-19 showed that the median time from the first symptom to dyspnoea was 5.0 days, to hospital admission was 7.0 days, and to the intensive care was 8.0 days. So, the latency period may be enough for the virus to enter and destroy the medullar neurons [13].

Mondolfi, et al. reported the presence of virus in neural and capillary endothelial cells in frontal lobe tissue in postmortem examination from a patient with COVID-19 [14]. However, the real incidence of neurological complications remains unknown [7].

Dysgeusia and Anosmia

Even when the most frequent symptoms of COVID-19 are fever, dyspnoea, cough, sputum production, myalgia, arthralgia, headache, diarrhea, rhinorrea and sore throat, in Europe started a detection of patients with olfactory and gustatory dysfunctions not associated with rhinorrhea [2,15].

Lechien, et al. found that 85.6% of the patients had olfactory dysfunction related to the infection, and of them almost 80% were anosmic and 20 % were hyposmic. 63% of patients continued with olfactory alteration after the resolution of other symptoms [15].

More than 88% of the patients reported Dysgeusia, clinically as changes in salty, sweet, sour, and bitter [15]. Anosmia can appear before the rest of the symptoms in more than 11% [2].

Hatipoglu, et al. found no anomalies of the olfactory bulbs and tract in MRI, and TC showing patchy ground glass opacities in some patients [15].

Encephalopathy and Encephalitis

Encephalopathy is a transient cerebral dysfunction with acute or sub acute impairment of consciousness, mainly due to inflammatory lesions in the brain parenchyma. Is a reversible brain dysfunction syndrome caused by factors pathogens that originate neuronal damage and nerve tissue lesions, systemic toxemia, metabolic disorders, and hypoxia during the process of acute infection [11].

It presents acute onset and the most frequent symptoms are headache, fever (mainly high), vomiting, convulsions, and consciousness disorders.

The probability of impairment consciousness is higher in people with co morbidities, advanced age, hypertension or previous cognitive alteration [3].

The main changes include cerebral oedema, and the clinical symptoms are diverse: headache, dysphasia, delirium or mental disorder. In the most severe cases we can find coma and paralysis [11].

COVID-19 patients, usually suffers from severe hypoxia, and almost 40% shows headache or disturb consciousness [3].

In addition, the great cytokine storm causes inflammatory injury and oedema of the brain, producing impaired consciousness and originating encephalitis [16,17]. Early diagnosis is critical [11].

Almost 15% of the patients with severe illness presented consciousness disturbance, and 2,4% with mild disease [3].

There are publications describing posterior reversible encephalopathy syndrome, developing motor aphasia, and a EEG with marked slowing and triphasic waves [18].

In the meningitis cases, SARS-CoV-2 was detected in cerebrospinal fluid [16], and resonance imaging showed abnormal findings of medial temporal lobe including hippocampus.

Acute hemorrhagic necrotizing encephalitis is another complication involving the Subcortical white matter, where patients maybe have absence of any other respiratory manifestations. Usually present with generalized tonic-clonic seizure, dysexecutive syndrome and cognitive impairment, and MRI images can show hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and sub insular regions. It may be fatal [19,20].

Treatment described for encephalopathy and encephalitis was symptomatic and included corticosteroids [18], mannitol [17], antibiotics and antiepileptic medication [16].

Acute Cerebrovascular Disease

Severe infection make patients more likely to develop neurologic acute cerebrovascular disease [3] (ACD), probably because the severe infection produce elevated levels of D-dimer and severe platelet reduction, which can favour acute cerebrovascular events [11]. The risk is higher in elderly patients with vascular risk factors. Li et al found that severe patients were more likely to develop neurological symptoms. The presence of the virus in the general circulation enables it to pass into the cerebral circulation, where the slow movement of the blood within the microcirculation can facilitate the interaction of the SARS-CoV-2 spike surface protein with ACE2-R expressed in the capillary endothelium, which maybe associated to endothelial apoptosis and neuronal damage [9,21]. The damage to the endothelial lining can facilitate the pass of virus to the brain [9]. The interaction with ACE2-r of neurons can initiate a cycle of viral budding accompanied by neuronal damage. In patients with COVID-19 infections, endothelial ruptures of cerebral capillaries that bleed usually have fatal consequences [9].

Being inflammation is an important factor in the pathophysiology of ACD, these patients present a hypercoagulable state favoured by elevated concentrations of IL-6 and IL-8 and others serum inflammatory factors as C reactive protein, responsible for molecular events triggered by coagulation abnormalities, favouring the chain of events that ends with the interruption of the blood supply and the hypoxia. In an imaging screening of patients with COVID-19 infection, ischemic stroke was found in 0.9%, accompanied by elevated troponin and D-dimer. D-dimer levels ≥ 2.0 $\mu\text{g/ml}$ is associated with a higher incidence of mortality [6]. On the other hand, patients with a history of ACD had 2.5 times more probabilities to develop severe infection [6,21]. This make the doubt of which patients can benefit from preventative or therapeutic anticoagulation or antiplatelet agents [6].

Non Specific Symptoms

As non specific symptoms we can find headache, myalgia, dizziness and fatigue. Mao et al found in a retrospective study in Wuhan, dizziness in 16.8% of the patients and headache in 13%, most of them occurred in 1-2 days since admission time to hospital [3]. In a survey in Turkey on 262 COVID-19 patients, they found mild intensity pain in 26.6%, moderate in 47.7%, severe in 23.4% and very severe (dependent to bed/hospital) in 2.3%. They thought that infection itself and drugs can be the triggers of headache, and concluded that bilateral headache, duration over 72 h, male gender, analgesic resistance, gastrointestinal symptoms and anosmia/ageusia increase the risk of having headache related to SARS-CoV-2 infection. The underlying mechanisms are not clear, but a direct invasion of trigeminal nerve endings in the nasal or oral cavity by the virus seemed one of the most reasonable mechanisms to them, according to their results showing the close relation between headache and anosmia/ageusia [22].

Myalgias and hyperkalemia are also frequents. Pathologic studies in skeletal muscle in COVID-19 patients shows presence of necrosis and atrophy. This has been related to myopathy of the critically ill and corticosteroid myopathy, but in animals models activation of ACE2 induces alterations in skeletal muscle with mitochondrial dysfunction and subsequent muscle atrophy. If activation of ACE 2 induces myopathy, and facilitates respiratory insufficiency must be elucidated [10]. We cannot forget that ICU patients may develop a post-intensive care syndrome and develop long-term sequelae as myopathy and critical illness neuropathy [23].

Rhabdomyolysis and Guillain-Barré Syndrome

Rhabdomyolysis is a life-threatening disorder that manifests with fatigue, myalgia, pigmenturia and acute renal failure [24]. Rhabdomyolysis has been described in many cases reports associated to COVID-19. It can appear as an initial presentation [25] or latter in the course of the illness [26]. Rhabdomyolysis is characterized by fatigue and focal muscle pain. Laboratory test will show elevation of creatine kinase and myoglobin, but as they are not routinely tested, it can be misdiagnosed, but early detection is essential to avoid acute renal failure. The treatment is based in aggressive hydration [26], diuretics and if necessary, hemodialysis [24,27]. Gefen, et al. describe a case in a pediatric patient [27].

Abu rumeileh et al. performed a systematic review of Guillain-Barré (GB) cases associated to COVID-19 until July 2020, including 73 patients of 52 articles. They conclude that most patient developed GB after the symptoms of COVID, but sometimes there was asymptomatic cases. The classic sensorimotor form and the acute inflammatory demyelinating polyradiculoneuropathy are the most typical presentation, with ascending weakness, loss of deep tendon reflexes, and sensory deficits, although rare variants like Miller Fisher syndrome were also reported [28]. Patients developed sensory symptoms (alone or with paraparesis or tetraparesis) in 72.2%, affectation of facial or oculomotor nerves in 16.7%. Most of the patients presented lower limbs or generalized areflexia, and in 37,5% ataxia was reported. Some patients also developed dysphagia and respiratory failure. Autonomic disturbances were infrequents. In cases of Miller-Fisher syndrome, they further showed facial palsy with paraesthesia or oculomotor disturbances. Is thought that the cytokine storm produced by SARS-CoV-2 is the cause for the dysimmune process that origins GB [28]. We can find some other reports of facial palsy in patients [29,30].

Neurodegenerative Disorders

Parkinson's Disease could be due initially to viruses or other pathogens [31]. The first evidence was the number of cases of Encephalitis lethargica (EL) after the influenza pandemic at the beginning of the XX century. Almost all patients with encephalitis developed parkinsonism afterwards [31-33], but the cause EL, after hundred years, is still unknown [33]. Even when influenza AH1N1 has not been demonstrated as the cause of post-encephalitic Parkinsonism, the association between influenza A and parkinsonism has been reported. Avian flu, Coxsackie, West Nile virus, Western equine encephalomyelitis, Japanese encephalitis B virus, Saint Louis encephalitis virus, and HIV among others can originate inflammation or hypoxic damage in the basal ganglia, developing transient or permanent parkinsonism [31,33].

Psychiatric

Since the beginning of the pandemic, increasingly neuropsychiatric symptoms have been reported. Anxiety, panic attacks, post-traumatic shock and depression have been described in patients with COVID-19 and in health workers [34]. In patients with SARS-CoV and MERS-CoV had already been described psychotic symptoms of new onset. Possible etiological factors can be the secondary effects of drugs, psychosocial stress [34], viral infection and the host immunologic response of the central nervous system.

During the influenza pandemia multiple psychiatric symptoms were described, as insomnia, depression, delirium, anxiety, mania, suicidality and psychosis [32].

According to influenza pandemia, seems that maternal infection increased schizophrenia risk in the newborn [32]. Placental dysfunction can be determined by immune activation of the mother, that produces change in normal cytokines and microglial activation, initiating the pathogenic process. Neuronal autoimmunity shows a model of infection-induced psychosis, implicating autoimmunity to schizophrenia-relevant protein targets including the N-methyl-D-aspartate receptor [35].

After this COVID pandemia, It's still unknown whether this neuropsychiatric complications will continue appearing in the next months or years.

Related to healthcare workers, seems that frequency and severity of symptoms are associated with proximity to COVID patients, but no serology test were made to them, so we cannot know if they were infected [32].

According to Parra et al, the number of acute psychotic syndromes in patients without a previous psychiatric history is increased in patients infected with SARS-CoV-2 [34].

As more frequent symptom, they found delusions highly structured, orientation/attention disturbances auditory and visual hallucinations. Disorientation in space and time and inattention can be considered as normal in severe ill patients, as many were in ICU and developed bilateral pneumonia originating important hypoxia. Disorientation disappeared quicker than delusional beliefs did [34].

Parra, et al. treated their patients with low doses of antipsychotics (olanzapine, aripiprazole, risperidone and haloperidol), with an optimal outcome.

Ferrando, et al. describe three cases of with new onset with severe anxiety, agitation, paranoia, disorganized thinking, and auditory hallucinations. All of them were asymptomatic, but positive for COVID-19.

About the reasons that could trigger these episodes, they stated that psychotic stress can trigger the psychotic episodes in psychiatrically vulnerable individuals, however, in some of the patients they highlighted the absence of concern about the pandemic. It seems more logical that the real cause was the cytokine storm associated to COVID, that resulted in a hyper inflammatory response, explaining psychotic and confusional symptoms and favouring ischemic events [34,36,37]. In high risk patient, this can be aggravated. Between secondary effects of corticosteroids and hydrocloroquina we can also find neuropsychiatric symptoms. Lopinavir, ritonavir and tocilizumab don't own psychiatric adverse effects [34].

Conclusions

Even when severe acute respiratory syndrome is the first cause of death by SARS-CoV-2, this virus present a great potential of central nervous system invasion and produce neurological disease. Some coronaviruses have demonstrated their capacity to spread via trans-synaptic to the medullar cardio respiratory centre from the mechanoreceptors, so, maybe part of the respiratory failure associated to COVID invasion of breathe centres. The cytokine storm that COVID develops, can breakdown the brain blood barrier, allowing the virus access to CNS.

As a neurotropic virus, it affects central nervous system (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure) peripheral nervous system (dysgeusia, anosmia, nerve pain) and skeletal muscle, being the affection greater in patients with severe infection.

In this review, we have tried to offer a global vision of all the neurological events described in the reported clinical cases.

We should be aware that a rapid deterioration of the patient can be related with a neurologic event. And always think on COVID-19 as a plausible cause of neurologic manifestations even when the patient is asymptomatic.

We cannot forget that autopsies studies are a key point to know the certain mechanism of neuroinvasion and the real damage on brain cells.

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