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Special Covid-19

Neurological manifestations and pathophysiological mechanisms of Covid-19

Cristiano **GAUJAC**[1]
Regiane Cristina **AMARAL**[2]

[1]*DDA, MSc, PhD - Universidade Federal de Sergipe/ Postdoctoral student in the Postgraduate Program in Dentistry - Dentistry Department, 49060-100 Aracaju – SE, Brasil*
[2]*MSc, PhD - Universidade Federal de Sergipe/ Teacher in the Postgraduate Program in Dentistry - Dentistry Department, 49060-100 Aracaju / Sergipe / Brasil*

Abstract
Background - Severe acute respiratory syndrome coronavirus-2 is a novel, highly infectious coronavirus and the etiologic agent of Covid-19. The course of Covid-19 can range from mild flu-like symptoms to severe, life-threatening symptoms, especially when comorbidities are present. Increasing studies have reinforced the association between SARS-CoV-2 and various neurological manifestations, although the pathophysiological mechanisms remain uncertain. Objective - The aim of this paper was to briefly describe current findings on the relationship between SARS-CoV-2 pathophysiology and major CNS and Peripheral Nervous System (PNS) manifestations. Methods and Material - This work consists of a literature review based on the study of academic papers. To this end, the Pubmed platform was used to search for scientific articles, using the keywords: covid-19, coronavirus, physiopathology, neuronal symptoms. Results - out of 114,660 articles found, 94 were selected for this review. Conclusions - Periodic reviews collaborate in the constant updating and summarization of findings. Understanding the pathophysiology of SARS-CoV-2 on the SN and the link between the systems may lead to earlier and earlier diagnoses of neurological involvement, guide therapeutic management, prevent sequelae, and preserve lives
Descriptors: Coronavirus Infections; Physiopathology; Neurologic Manifestations.

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel virus of the family Coronaviridae responsible for the severe acute respiratory syndrome (SARS) epidemic that erupted in Wuhan, China in late 2019.[1],[2] SARS-CoV-2 belongs to the same genus - Betacoronavirus - as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), memorable for infectivity in 2002 and 2013.[3],[4],[5] The contamination quickly spread worldwide[6] and prompted the World Health Organization (WHO) to declare Covid-19 pandemic (COronaVIrus Disease 2019).

The extent of Covid-19 symptoms can reach critical conditions such as SARS and multiple organ failure.[7],[8],[9] However, the most common are mild and flu-like - fever, cough and asthenia.[10] Hypertension, diabetes, cardiovascular and respiratory diseases, especially in those over the age of 60, are comorbidities predisposing to the worsening of the disease.[11],[12] Possible neurological manifestations include dizziness, headache, altered consciousness, cerebrovascular disease, loss of taste and loss of smell, with a higher prevalence in the Central Nervous System (CNS) (24.8% vs. 8.9%) and in critically ill patients (45.5% vs. 30.2%).[13]

Considering the influence that Nervous System (NS) manifestations may exert on the morbidity or mortality of Covid-19 patients, the aim of this paper was to briefly describe current findings on the relationship between SARS-CoV-2 pathophysiology and major CNS and Peripheral Nervous System (PNS) manifestations.

- *Neuroinvasion*

The means by which SARS-CoV-2 invades the SN is still unknown. Recent findings added to previous research on SARS-CoV, whose genome is 80% similar to SARS-CoV-2,[14] have suggested three main possible pathways:

- *Angiotensin-converting enzyme-2 pathway.*

Angiotensin-converting enzyme-2 (ACE-2) is the major receptor site for SARS-CoV-2 to enter host cells.[15] The spike protein of SARS-CoV-2 exhibits a 10-20-fold higher affinity for ACE-2 receptors than that of SARS-CoV.[16] Thus, various cells expressing ACE-2 receptors - airway epithelium, vascular endothelium, oral and nasal mucosa;[17],[18],[19] in addition to glia cells and neurons[20] - may be targets for SARS-CoV-2. Although plausible, the correlation between cellular expression of ACE-2 and susceptibility to infection is imprecise. SARS-CoV has already infected hepatocytes, cells without detectable expression of ACE-2,[21] but not human endothelial and intestinal cells.[22],[23]

- *Via the bloodstream*

Viremia is a process of systemic dissemination via the bloodstream well known in viruses such as influenza and previously suggested for SARS-CoV.[24] Presence of SARS-CoV-2 RNA in plasma has already been detected.[25] Thus, the circulatory stream could also drive SARS-CoV-2 to brain vessels. The interaction of SARS-CoV-2 with ACE-2 of endothelial cells may compromise the integrity of the Blood-Brain Barrier (BBB) and thus access the CNS.[20] A post-mortem analysis of several organs has identified dysfunction, lysis and death in infected endothelial cells.[26] Furthermore, vasoactive molecules and inflammatory cytokines can also permeabilize and open gaps in the endothelium.[27],[28]

- *Olfactory tract pathway*

Transgenic mice showed rapid

dissemination of SARS-CoV to the thalamus and brainstem after intranasal administration,[29] indicating the possible association of nasal cavity structures with virus transport to the CNS. Endocytosis in peripheral endings with retrograde axonal pathway and synaptic diffusion constitute a possible route for SARS-CoV-2 to reach the brain.[30] However, a recent study suggested that non-neuronal cells with ACE-2 receptors are the potential targets of SARS-CoV-2 in this region in anosmia.[31]

- *Neurological manifestations*

An association between Covid-19 pathophysiology and SN has recently been suggested by several studies and communicated through different research designs.

- *Encephalitis*

The immune response to SARS-CoV-2 may be able to inflame and swell the brain, producing alterations in consciousness.[32],[33] However, the simultaneous identification of inflammation and detection of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) to confirm the diagnosis of direct viral encephalitis presents several difficulties, which makes physical examination and assessment of brain inflammation important tools for diagnosis in the absence of viral detection in CSF.[33]

Despite the difficulty in isolating the virus present in CSF, Moriguchi et al.[34] reported the first case of encephalitis with detection of SARS-CoV-2 RNA in CSF. Another study diagnosed SARS-CoV-2-associated encephalitis with the aid of a serological test, which identified elevated levels of immunoglobulin (Ig) M for SARS-CoV-2 in CSF, culminating in the diagnosis of encephalitis in three patients.[35]

- *Encephalopathy*

Encephalopathy is a pathobiological brain process that can alter personality, behavior, cognition, or consciousness.[36] SARS in Covid-19 patients can lead to systemic effects such as hypoxia, hypotension, renal failure, and the need for high doses of sedatives, which are classically associated with encephalopathy.[37],[38]

- *Cerebrovascular manifestations*

Cerebrovascular accidents (strokes) are dangerous events that can result in permanent damage or death. Ischemic strokes incur between 0.9% and 2.7%, and achieve death in 38% of Covid-19 patients.[39] The cause may involve the development of a hyperinflammatory state and subsequent pro-thrombotic state.[26],[40]

The main elevations in markers of Covid-19 coagulopathy are in D-dimers, fibrin degradation products, and antiphospholipid antibodies.[41],[42] High levels of D-dimers and poor prognosis appear to be correlated.[43]

- *Headaches*

Headaches are the fifth most common symptom, present in 12% of Covid-19 patients.[44] The characteristics of Covid-19-associated headaches have peculiar features: in the first week, they are characterized as acute and tense, associated with other influenza symptoms; and in the second, coincident with a phase of intense immune response, diffuse, continuous, moderate, and expansive.[45] In 70% of patients with Covid-19 the headaches disappear within 3 days[46] while in others, they persist after one[47] or two[48] months following recovery from the disease.

The etiology of headaches in Covid-19 is uncertain, but it is believed that they may stem from attack on ACE-2 receptors that derange blood pressure and BBB;[32] direct invasion of trigeminal endings in the nasal cavity that activate the trigeminovascular system and promote migraine-like symptoms;[49] and influence of pro-inflammatory cytokines on neuroinflammation and hypoxia.[50] In addition, the immune response and levels of pro-inflammatory mediators may also correlate with post-recovery headaches, given that the SARS-CoV-2 virus is able to remain in body fluids for more than 6 weeks.[51]

- *Anosmia and Ageusia*

Loss of smell and taste are commonly interrelated manifestations of PNS and frequent as an initial or single symptom in Covid-19.[52] In patients with mild or moderate disease, olfactory and gustatory changes occur in 86% and 82% of cases, respectively.[53] The early manifestation of anosmia may contribute extensively to recommend diagnostic testing.[54] Expression of ACE-2 in the olfactory epithelium suggest that anosmia results from epithelial damage.[31] Ageusia, in turn, may represent a manifestation secondary to olfactory dysfunction[55] or arise from dysfunction of the cells of the tongue and mucous membrane of the oral cavity that express ACE-2 receptors.[56]

- *Neuropathic pain*

Neuropathic pain is a relatively uncommon (2.3%),[13] but distressing neurological manifestation in patients with Covid-19. Neuropathic pain, despite its peculiar attributes, has received little attention from researchers.

In one case described, pain occurred in a 49-year-old woman who developed reactivation of Varicella-Zoster Virus (VZV) along dermatome V2. The patient denied previous anosmia and ageusia, and despite the prescription of antiviral medication, she

developed burning sensations in the skin and allodynia, as well as sinus and dental pain. After 4 weeks of the first rash, she still experienced severe neuralgia in the left cheek region, which improved after prescription of gabapentin and topical anesthetic use.[57]

Trigeminal neuropathy associated with covid-19 was reported in a 39-year-old male who presented with orofacial skin lesions associated with all three branches of the trigeminal nerve, intraoral mucosal lesions. The patient reported acute pain in the left hemiface, hypogeusia, and a history of childhood chickenpox. His blood markers were normal, IgM was positive for VZV, and MRI examination showed enhancement of the left trigeminal nerve. After the fifth day of intravenous antiviral medication, the progress of the lesions had already been halted.[58]

A third case of neuropathic pain occurred in a woman, 40 years old, who presented with respiratory symptoms, body pain, anosmia, and ageusia. On the second day of hospitalization, she developed pain in the dorsal region bilaterally and in the cervical region, which differed from neuropathic pain presentations commonly associated with herpesviruses, constant in nature, with a burning sensation, exacerbated to light touch and heat. Family history of similar episodes or herpetic lesions were absent. Laboratory tests, including characteristic biomarkers in Covid-19 - IL-6, fibrinogen, D-dimer, lactate dehydrogenase, creatine kinase, and C-reactive protein - were normal. The patient's pain properties led to the prescription of gabapentin, successfully controlling the pain.[59]

Reactivations of viruses of the Herpesviridae family are frequent in patients with Covid-19.[60] Stress and low immunity in patients may contribute to the remodulation of Herpes Simplex type 1 (HSV-1) and VZV surface ligands latent in the individual and manifestation of characteristic symptoms.[61],[62]

The main suggestions about sensory involvement of the face concern the interaction of the virus with structures in the nasal cavity where the ophthalmic and maxillary branches of the trigeminal nerve are located.[30],[31]

- *Post-Infectious Manifestations*

Some neurological manifestations associated with Covid-19 have been classified as post-infectious based on their typical onset after the acute phase of the disease.

- *Acute Hemorrhagic Necrotizing Encephalopathy*

Acute hemorrhagic necrotizing encephalopathy (ENHA) is a rare disease characterized by multiple, symmetrical lesions in the thalamus and other brain sites.[63] The possible first case of Covid-19-associated ENHA was in a woman who developed mental changes. Computed tomography (CT) scans showed symmetrical hypoattenuation within the medial thalamus bilaterally. Magnetic resonance imaging (MRI) showed multiple hemorrhagic lesions with a ring enhancement pattern throughout the brain.[64]

Another case was reported in a 59-year-old woman with aplastic anemia. Brain MRI showed multiple symmetrical hemorrhagic lesions and diffuse inflammation. The patient did not respond to steroid treatment and died on the eighth day of hospitalization.[65]

Virhammar et al.[66] also reported a case of the disease, but with detection of SARS-CoV-2 RNA in CSF. An intriguing fact was that the detection occurred 19 days after the onset of Covid-19 symptoms and after two prior negative tests. The features observed on MRI were bilateral pathological signs in the central thalamus, subinsular regions, temporal lobes and brainstem.

- *Acute Disseminated Encephalomyelitis*

Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating CNS disorder.[67] The autopsy of a 71-year-old man who died from complications of Covid-19 revealed several neuropathological lesions indicative of demyelinating and vascular origins. Also, hemorrhagic lesions in the gray matter were present in the cerebral hemispheres with surrounding axonal damage.[68]

Another EMDA affected a 40-year-old woman with Covid-19. CT scan showed ill-defined areas of hypoattenuation in the white matter and MRI showed extensive ill-defined areas in the subcortical region and deep white matter consistent with demyelination.[69]

- *Guillain-Barré syndrome*

Guillain-Barré syndrome (GBS) is an autoimmune, paralytic, PNS neuropathy with variant forms.[70] Toscano et al.[71] reported a series of 5 cases where all had presented with Covid-19 symptoms between 5 and 10 days prior to GBS symptoms. Three patients had findings consistent with the axonal variant of GBS and two with a demyelinating process, but none with SARS-CoV-2 in the CSF. Other authors have reported a form of GBS with bilateral facial paralysis.[72],[73]

- *Miller-Fisher syndrome*

Miller-Fisher syndrome (MFS) is a variant of GBS characterized by loss of coordination, loss of tendon reflexes, and external ophthalmoplegia.[74] Gutiérrez-Ortiz et al.[75]

described a case of MFS in a 50-year-old patient, whose CSF exhibited albumin-cytological dissociation and anti-ganglioside antibodies (GD1b-IgG) in addition to a case of cranial polyneuritis.

- *Kawasaki Disease*

The first case of an association between Kawasaki Disease (KD) and Covid-19 was reported in a child who, in addition to KD, also presented with fever and respiratory symptoms.[76] KD is a vasculitis of small- and medium-caliber vessels, commonly coronary arteries, and the most common cause of acquired heart disease in children.[77] Its etiology is unknown, although the incidence increases during seasonal viral epidemics.[78]

Since the irruption of Covid-19, a multisystemic inflammatory syndrome mimicking KD has appeared throughout the world. In the Paris, France region, the incidence of patients with KD increased by almost 500% in the two weeks following the first peak of Covid-19.[79] In Bergamo, Italy, the incidence multiplied 30-fold compared to the monthly incidence of the previous 5 years.[80]

Complications such as heart failure, coronary dilatation, pericarditis, myocarditis have been reported.[81] Besides cardiac ones, neurological complications such as cerebral vasculopathies and meningeal symptoms can also occur.[80]

Multiple clinical and laboratory findings diverge from traditional KD, and the criteria for diagnosing complete KD exclude up to 50% of patients.[79] The main distinctions from classic KD are the higher mean age of affected patients; the frequency and severity of myocarditis, abdominal pain and diarrhea; and the high levels of IL-1, TNF-α and IL-6, C-reactive protein and ferritin.[81]

DISCUSSION

SARS-CoV-2 is a Betacoronavirus and the cause of Covid-19. Commonly the symptoms of Covid-19 are mild.[10],[44] Aggravations and deaths are prevalent in the elderly and people with comorbidities such as hypertension and diabetes,[11],[12] while neurological manifestations, in turn, are prevalent in critically ill patients.[13]

The detections of neuronal and endothelial infection in an autopsy,[82] as well as viral RNA in CSF,[34][66] reinforce the idea that SARS-CoV-2 can invade the CNS and cause the manifestations directly. The possible low-level expression of ACE-2 also in human brain vascular wall cells[82] could interfere with the permeability of the BBB and facilitate the access of the virus to the brain to cause damage directly. Although endothelial infection of peripheral vessels is possible,[83] involvement of brain vessels still remains without evidence. Even if the virus does not access the CNS through ACE-2 of the cerebral endothelium, the action of cytokines produced to combat it on the permeability of the EHB could opportunize its invasion.

On the other hand, neurological disorders seem to be more often multifactorial, following hypoxia, immune and metabolic abnormalities.[84] The interaction with ACE-2 receptors and the intense immune response are two key pieces to describe the multiple systemic derangements in Covid-19. Functional impairment of ACE-2 receptors in the body can influence hydro-electrolyte balance, dysregulate blood pressure, intensify inflammation, and increase airway vascular permeability.[85] The action of mediators of the immune response can compromise the EHB, allowing infection of brainstem cells and eliciting cardiorespiratory difficulties and hypoxia,[86] systemic effects that rebound on the brain.[87] In addition, the action of the mediators themselves on the CNS can accentuate neuroinflammation and neurologic symptoms.[88] Neurologic manifestations of SARS-CoV-2 are seen in severe cases of Covid-19.[89]

Encephalitis may arise from the immune response, which is capable of inflaming and swelling the brain, or from direct mechanisms.[32],[33],[34] Encephalopathy may result in hypoxia, hypotension, renal failure, and the need for high doses of sedatives.[37],[38] The intense inflammatory response may be associated with a coagulopathy in Covid-19 patients and thus trigger cerebrovascular manifestations.[41],[42]

Headaches in Covid-19 may arise from the attack on ACE-2 receptors;[32] activation of the trigeminovascular system in the nasal cavity;[49] neuroinflammation and hypoxia by cytokines;[50] and from the immune response and the levels of pro-inflammatory mediators (post-recovery).[51] Facial neuropathic pain may be associated with trigeminal nerve disorders in the nasal cavity,[30],[31] but when associated with HSV-1 and VZV reactivation, other factors such as stress and low immunity of the Covid-19 patient may also be involved.[61],[62]

Ageusia can arise from dysfunction of cells in the oral cavity that express ACE-2[56] or be secondary to olfactory dysfunction.[55] Anosmia can arise from neuronal[30] or non-neuronal infection.[31] These are symptoms that have marked this disease presenting a strong suggestion for seeking medical attention, being "almost" pathognomonic for this pathology.

Post-infectious manifestations and KD may also be associated with SARS-CoV-2, as do some other viruses that increase their incidences, as well as with the inflammatory response, including the autoimmune one, as occurs in GBS and its variants.[63],[67],[70],[74],[81]

Finally, understanding the mechanisms and effects of SARS-CoV-2 on the SN is of fundamental importance for early diagnosis and appropriate management. Other neurological manifestations are likely to occur as this disease progresses.[89] Considering that a variety of nonspecific neurological signs and symptoms may denote SN involvement in Covid-19, it is essential that clinicians carefully investigate the possible involvement of the SN and its extent when encountering incipient suggestive effects such as dizziness, altered level of consciousness, seizure, neuropathic pain, as well as sensory and motor deficits, increasing the chances of early diagnosis and better prognosis.

CONCLUSION

Growing evidence points to an association between SARS-CoV-2 and neurological manifestations. New findings have unfolded previous ones, increasing the understanding of the pathophysiology of the virus, and for this reason, periodic reviews collaborate in the constant updating and summarization of findings. Given that the neurologic manifestations of Covid-19 may result from the direct or indirect action of the virus, understanding both the unique pathophysiology of SARS-CoV-2 and the link between the systems may shorten the time to diagnosis of neurologic involvement, guide treatment, prevent sequelae, and preserve lives.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

CORRESPONDING AUTHOR

Cristiano Gaujac
Rua Claúdio Batista - Cidade Nova,
49060-108 Aracaju - SE, Brasil
Phone: (79) 9.8139-1479
email: cgaujac@gmail.com

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