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## **COVID-19 neuropsychiatric repercussions: Current evidences on the subject**

da Silva Júnior RT *et al.* COVID-19 neuropsychiatric repercussions

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### <sup>1</sup> **Abstract**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected the entire world, causing the coronavirus disease 2019 (COVID-19) pandemic since it <sup>1</sup> was first discovered in Wuhan, China, in December 2019. Among the clinical presentation <sup>1</sup> of the disease, in addition to fever, fatigue, cough, dyspnea, <sup>1</sup> diarrhea, nausea, vomiting, and abdominal pain, infected patients may also experience neurological and psychiatric repercussions during the course of the disease and as a post-COVID-19 sequelae. Thus, headache, dizziness, olfactory and gustatory dysfunction, cerebrovascular disorders, neuromuscular abnormalities, anxiety, depression, and post-traumatic stress disorder can occur both from the infection itself and from social distancing and quarantine. According to current evidence about this infection, <sup>8</sup> the virus has the ability to infect the central nervous system (CNS) <sup>1</sup> via angiotensin-converting enzyme 2 (ACE2) receptors on host cells. Several studies have shown the presence of ACE2 in nerve cells and nasal mucosa, as well as transmembrane serine protease 2, key points for interaction with the viral Spike glycoprotein and entry

into the CNS, being olfactory tract and blood-brain barrier, through hematogenous dissemination, potential pathways. Thus, the presence of SARS-CoV-2 in the CNS supports the development of neuropsychiatric symptoms. The management of these manifestations seems more complex, given that the dense parenchyma and impermeability of brain tissue, despite protecting the brain from the infectious process, may hinder virus elimination. Still, some alternatives used in non-COVID-19 situations may lead to worse prognosis of acute respiratory syndrome, requiring caution. Therefore, the aim of this review is to bring more current points related to this infection in the CNS, as well as the repercussions of the isolation involved by the pandemic and to present perspectives on interventions in this scenario.

**Key Words:** SARS-CoV-2; COVID-19; Central nervous system; Quarantine; Neurologic disorders; Mental disorders

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**Core Tip:** Severe acute respiratory syndrome coronavirus 2 infection may also involve neurological and psychiatric manifestations, both by the viral action itself and by social distancing and quarantine. Headache, dizziness, cerebrovascular disorders, olfactory and gustatory dysfunction, neuromuscular abnormalities, anxiety, depression, and post-traumatic stress disorder may occur in this setting. Supporting these repercussions, this virus is able to reach the central nervous system by the interaction between the angiotensin-converting enzyme 2 and the transmembrane protease serine 2 expressed also in the host nerve cells, and the viral spike glycoprotein. Finally, the management of these patients is more complex and we review the current evidence on the subject.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has affected the whole world, causing fear and concern due to its transmissibility and severe life-threatening conditions. This pandemic infectious disease was first discovered in Wuhan, China, in December 2019<sup>[1]</sup>. Since then, the number of cases has increased, spreading rapidly globally and becoming a major pandemic disease<sup>[2]</sup>. By February 1, 2022, WHO has confirmed more than 370 million cases worldwide, leading to 5658702 deaths<sup>[3]</sup>.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a  $\beta$ -coronavirus with positive spherical single-stranded RNA and Spike proteins that project on the surface of the virion, which is characterized by its crown-shaped morphology<sup>[4]</sup>. Common symptoms are fever, fatigue, cough, dyspnea, diarrhea, chest tightness, nausea, vomiting, sputum production, anorexia, pharyngalgia, hemoptysis, and abdominal pain<sup>[5]</sup>. Frequently, SARS-CoV-2 contamination is associated with the nasopharyngeal and pulmonary tracts. However, important findings show that manifestations of this virus can be found in the central nervous system (CNS).

Neurological alterations have been described in patients with COVID-19, which varies from mild to fatal effects and can occur in severe or asymptomatic infection<sup>[6]</sup>. On other hand, the global effects of the SARS-CoV-2 infection results in various viral-related physical and mental health problems<sup>[7]</sup>. Thus, physical and social isolation, financial stress, and fear of contagion contribute in this scenario<sup>[8]</sup>. Therefore, this infection can present neuropsychiatric repercussions, such as headache, dizziness, anosmia, ageusia, neuromuscular dysfunction, anxiety, and depression<sup>[9]</sup>, shown in Figure 1, in addition to other symptoms related to physiological and psychiatric changes, such as post-traumatic stress disorder (PTSD) and neuropsychiatric syndromes<sup>[8]</sup>. These manifestations seem to be caused as much by the infection itself as by social distancing and quarantine, which means that specific therapy should be used according to each case, seeking the most efficient healing process. Therefore, this review aims to describe the reported CNS manifestations associated with COVID-19, in order

to help professionals who treat these patients, review the way the virus reaches the CNS and the intervention possibilities available so far in the literature.

## **METHODOLOGY**

For this minireview, the authors surveyed relevant and current articles published in the United States National Library of Medicine (PubMed). The descriptors used were COVID-19; SARS-CoV-2; coronavirus; angiotensin-converting enzyme 2 (ACE2); central nervous system; neuroimmune; cytokine storm; pathophysiology; neuroinvasion; neurological symptoms; neurological manifestations; olfactory dysfunction; gustatory dysfunction; ischemic stroke; hemorrhagic stroke; guillain-barré syndrome; neuropsychiatric symptoms; mental health; mental suffering; psychiatric disorder; quarantine. The eligibility criteria were based on the discussion of aspects related to the neuropsychiatric repercussions of SARS-CoV-2 infection, dealing with everything from viral neuroinvasive mechanisms to neurological and psychiatric manifestations, whether due to the infection itself or to the need for full isolation in the read full-text. Thus, 26.035 articles were found in the database, in which 109 comply with the aforementioned criteria and are included. For exclusion criteria, articles that did not address the topics in the title and/or abstract, and written in languages other than English were eliminated. Moreover, the search was complemented by a manual search of the references of the included articles to identify additional references, 13 of which were added later, totaling 122 articles included in this review.

## **COVID-19 NEUROPSYCHIATRIC REPERCUSSIONS: CURRENT EVIDENCES**

### ***SARS-CoV-2 neuroinvasive mechanisms***

One of the main mechanisms for the neurological invasion of SARS-CoV-2 is through ACE2 receptors on host cells<sup>[6,10]</sup>. Several studies have demonstrated ACE2 protein in human brain vessels, mainly in dopaminergic neurons, astrocytes, oligodendrocytes, and neurons<sup>[11-13]</sup>. ACE2 has also been observed in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb<sup>[11,13]</sup>. One study



reported that ACE2 is more expressed in neuronal cell bodies than in axons and dendrites<sup>[14]</sup>. Thereby, during the infection, the transmembrane protease serine 2 (TMPRSS2) activates the spike (S) glycoprotein on the SARS-CoV-2 envelope, which allows the virion to bind to ACE2 receptors<sup>[12,15]</sup>. TMPRSS2 is also found in oligodendrocytes and astrocytes located in substantia nigra, cortex, and in the endothelial cells of cerebral capillaries<sup>[6,14]</sup>, and is fundamental in the priming and activation of S proteins, that leads to membrane fusion. This interaction is responsible for SARS-CoV-2 entry on the CNS<sup>[14,16]</sup>. Later, the virus may affect the nervous system by disturbing the renin angiotensin system<sup>[11]</sup>. This process is exacerbated by the slower circulation in the brain capillaries, which intensifies the interaction between the viral S glycoprotein with the ACE2 on brain cells<sup>[9,16]</sup>. Thus, CoV interacts with ACE2 expressed in the capillary endothelium, causing neuronal death and neurodegeneration<sup>[9,18]</sup>.

Compared with SARS-CoV, SARS-CoV-2 presents higher affinity to ACE2<sup>[15]</sup>. This enzyme is also known as a cardiocerebral vascular protection factor, and influences blood pressure regulation and anti-atherosclerosis mechanism, in view of its vasoconstrictor function and pro-inflammatory effect<sup>[9,19]</sup>. When the virus binds to the enzyme, it may cause elevated blood pressure and increase the risk of arterial wall rupture, cerebral hemorrhage, and ischemic stroke<sup>[13,17]</sup>. On other hand, ACE2 and TMPRSS2 have been detected in the nasal mucosa, one of the main mechanisms of entry into the brain<sup>[15,20]</sup>. Once the infection of the olfactory system happens, the virus may be internalized in the nerve by endocytosis *via* the olfactory bulb and be transported retrogradely and disseminated to the brain *via* the cribriform plate<sup>[6,12,20]</sup>.

SARS-CoV-2 may also affect the CNS indirectly, as the virus provokes alveolar and lung tissue damage<sup>[17,21]</sup>. This inflammation and edema caused by lung invasion disturbs oxygen exchange and results in hypoxemia. Thus, this scenario may lead to increased anaerobic metabolism in brain cells, brain hypoxia with vasodilation, hyperemia, ischemia, and brain edema and injury<sup>[17,20,21]</sup>.

As previously mentioned, the virus can access the CNS through the olfactory nerve and also through the hemoretinal route. However, there is another potential pathway that allows CNS infection, which is *via* the blood-brain barrier (BBB), which occurs through hematogenous dissemination<sup>[22]</sup>. The BBB is one of the body's protections against disturbances in the nervous system. It is composed of endothelial cells, astrocytes, microglia and neurons, which act together. Under normal circumstances, these cells have a very accurate regulation of what enters and leaves the nervous system. However, in pro-inflammatory situations, such as that caused by SARS-CoV-2, this homeostasis is disturbed, which may be the genesis of the virus entry into the CNS<sup>[23-25]</sup>.

One of the factors that has been extensively studied currently is what causes this damage to the BBB, enabling infection in the CNS. The most likely one is the hyperinflammatory situation caused by the cytokine storm<sup>[1]</sup>. When viral replication occurs, damage-associated molecular patterns, that induce inflammatory states in neighboring cells through Toll-like receptors, are released. These receptors promote several cytokine production pathways. However, in COVID-19, there is hypercytokinemia. The main cytokines involved in this exacerbated process are TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-9, and the granulocyte-macrophage colony-stimulating factor. These cytokines ultimately potentiate the activation of immune system cells, creating a cycle of an increasing and perpetuating inflammation<sup>[26,27]</sup>. These processes are represented in Figure 2. Severe patients can also present elevated levels of IL-17, compared to non-severe patients<sup>[28]</sup>. A comparative study showed a particularly strong inflammatory response triggered with the activation of this cytokine<sup>[29]</sup>.

This cytokine storm damages the vascular endothelial cells of the CNS, affecting the integrity of tight junction proteins in the BBB, allowing the virus to enter. In addition to increased cytokines, the virus itself has cytopathic power, which can lead to pathogenic inflammation with cellular damage in the CNS, including edema, ischemia, bleeding and neurodegenerative disorders<sup>[1,30]</sup>. In pathological situations, the migration of cells

from the immune system to the CNS is increased and in severe SARS-CoV-2 infection, it is even greater. This is supplanted in histopathological examinations of the brain parenchyma where large numbers of macrophages and lymphocytes were found<sup>[27]</sup>.

Another factor that corroborates this increase in cell migration is that in the presence of damage to endothelial cells, the number of intercellular adhesion molecules increases. This favors the entry of the virus into the CNS, which is transported by cells of the immune system through a mechanism known as the “trojan horse”, in which the virus enters the nervous system inside the host cell<sup>[31,32]</sup>.

### **NEUROLOGICAL REPERCUSSIONS**

SARS-CoV-2 infection can reach the CNS through the olfactory tract and access the cortex, basal ganglia and midbrain, which may be affected during propagation<sup>[33]</sup>, supporting the existence of neurological symptoms as headache, anosmia, dysgeusia, dizziness and impaired consciousness<sup>[34,35]</sup>.

#### ***Headache and dizziness***

Although this symptom is very nonspecific, several studies have reported the prevalence of headache in patients infected with SARS-CoV-2. The symptom may be present at the beginning of the disease, or even be the initial presentation of the clinical picture, as it may also be present after the resolution of the infection<sup>[9]</sup>. In addition, this symptom may be related to other diseases present in the patient and, therefore, the prevalence varies greatly according to the work<sup>[36]</sup>. One study<sup>[28]</sup> indicated a combined prevalence of headache around 8% of patients, while others reported higher numbers such as 20%<sup>[37]</sup> and 25%<sup>[38]</sup>, as well as a variation from 0.6% to 70.3%<sup>[39,40]</sup>. Accordingly, among the neurological effects reported in COVID-19 infection, especially headache, may be the result of complications of the viral infection, the host immune response, the presence of severe installed disease or even the drug therapy used<sup>[41]</sup>.

The prevalence of dizziness is estimated to be around 8%<sup>[42]</sup> to 9%<sup>[5]</sup>, which indicates a combined overall prevalence of 8.77% in a systematic review that analyzed



neurological symptoms<sup>1</sup> in patients infected with SARS-CoV-2<sup>[43]</sup>. As with headache, studies vary in determining the period in which dizziness appears in the clinical picture. However, a retrospective and observational case series reports dizziness as the main neurological symptom<sup>[44]</sup>. This is not a surprise, after all, since dizziness is historically reported in patients with viral infections. This symptom has been proposed to result from the neuroinvasive potential of the virus, such as direct injury by binding to the ACE2, or even by hypoxia and coagulation disorders<sup>[45]</sup>. Because it is nonspecific, it is important that the healthcare team perform a thorough investigation to determine its cause, given that it can be due to acute labyrinthitis, acute otitis media, vestibular neuritis, or even stroke due to COVID-19<sup>[46,47]</sup>.

#### *Disturbances of consciousness*

In retrospective studies that analyzed the incidence of neurological symptoms<sup>1</sup> in patients with COVID-19, a range of 3.3% to 19.6% was reported for disturbances of consciousness/delusion<sup>[48,49]</sup>. The cause of this involvement is still poorly understood, and may even be related to post-inflammation inflammatory state, meningoencephalitis and encephalopathy, or may just be a sequela after a traumatic event<sup>[48]</sup>. Thus, a long-term follow-up is necessary for these patients, so that the real cause of this condition can be investigated with a detailed clinical history and serial imaging examinations.

#### *Acute cerebrovascular disease*

Viral neuroinvasion and subsequent central neuronal injury have been proposed to<sup>1</sup> contribute to the pathogenesis of the disease. The interaction of SARS-CoV-2 with ACE2 receptors may be related to the episodes of intracerebral hemorrhage found in some cases, resulting in receptor inactivation and consequent dysfunction in blood pressure regulation<sup>[50]</sup>. In patients who already have pre-existing vascular risk factors, ischemic stroke is related to late complications in the severity of COVID-19 infection. The elderly with alterations in vascular hemodynamics resulting from age or associated pathology,

once again, are groups that deserve special attention for the involvement of these injuries<sup>[51-54]</sup>.

Studies have observed that patients presented neurological symptoms on average 3 to 4 d after the onset of respiratory symptoms, with hemifacial paresis, dysarthria, hemiparesis, loss of level of consciousness, hemiparesthesia and ataxia being symptoms found less frequently<sup>[51,52,55,56]</sup>. One study reported that the sex-based distribution of patients affected by COVID-19 shows that female patients report more central nervous system-related symptoms than males. This sex-based difference may be attributed to humoral and innate immune responses to viral infections that are more pronounced in women than in men<sup>[54-57]</sup>. Yet, autopsy results from COVID-19 patients showed that brain tissue was hyperemic and swollen and that some neurons degenerate<sup>[55,58]</sup>.

### *Olfactory and gustatory dysfunction*

Although they are now among the most well-known symptoms during SARS-CoV-2 infection, olfactory dysfunctions (OD), mainly hyposmia and anosmia, were initially seen as less relevant conditions in the pandemic context. Thus, OD throughout the pandemic became part of the symptoms that carry a warning sign of a possible ongoing infection, even when they appear in isolation<sup>[59]</sup>.

Hyposmia, reduced sense of smell, and anosmia, the complete loss of smell, are common in patients with COVID-19. The OD can be evidenced subjectively, when the patient reports any degree of alteration, or objectively, when specific tests are applied in order to evidence the conditions of each individual. These parameters have guided researchers worldwide to carry out studies in which OD was evaluated in patients with COVID-19. In this context, a meta-analysis involving 3563 patients found that 47% of individuals had a self-reported loss of smell. In addition, researchers show that OD is more frequent in women and young patients. However, despite the relationship with the infectious condition, studies suggest that OD is not related to the severity of the condition<sup>[59,60]</sup>.

The mechanisms that can cause OD have not yet been fully defined. In this context, studies point to several possibilities that can lead to olfactory impairment, such as conductive loss due to edema in the olfactory cleft, injury to the respiratory epithelium - due to the local inflammatory response with an increase in pro-inflammatory cytokines and chemokines such as IL-6 and IFN- $\gamma$ , or lesion in the olfactory bulb, with neuronal damage. Symptoms begin on average within the first week of infection, vary in duration, and can last for weeks or months<sup>[61,62]</sup>.

The impairment of smell has a direct impact on the quality of life of the individual, since it can make it difficult to recognize odors in food that indicate its disposal and odors associated with risks, such as flammable or toxic substances, for example. In addition, it can cause impairment in social interactions, and several studies associate olfactory dysfunction with a higher risk of developing depressive disorders<sup>[63]</sup>.

Gustatory dysfunction (GD), mainly hypogeusia and ageusia, are prevalent symptoms in infected individuals. They are mostly associated with OD, but they may manifest in isolation in some cases, as pointed out by a systematic review that revealed a combined prevalence of GD of 43.93% in SARS-CoV-2-positive individuals<sup>[64]</sup>. Like OD, GD is more prevalent in young and female patients<sup>[65]</sup>. Furthermore, similarly to OD, the causes of DG are still uncertain. There are several hypotheses mainly involving the ACE2 receptors present on the tongue, which, being fundamental for the virus, may cause local inflammatory reactions, compromising taste functions. In addition, taking into account the potential for damage to the nervous system, there are hypotheses that relate DG to dysfunction of cranial nerves VII, IX, and X<sup>[66]</sup>.

The gustatory function is able to identify sweet, salty, sour, bitter, and umami flavors. Among patients infected by SARS-CoV-2 with DG, sweet and sour tastes had the most altered sensitivity<sup>[65]</sup>. Among the DG, hypogeusia, mild to moderate, is more common than ageusia. For example, an Italian study with 72 participants found that hypogeusia occurred in 47.1% of cases, while ageusia occurred in only 1.4% of patients<sup>[67]</sup>. Like OD, GD is a common manifestation mainly in the first week of symptoms and has a

resolution in a variable period with most patients completely regressing in approximately 10 d<sup>[68]</sup>.

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### Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is considered a post-infectious and immune-mediated syndrome characterized mainly by manifestations such as rapid, progressive, and symmetrical limb weakness, impairment of tendon reflexes, which may be reduced or absent and to sensory impairment. Their subtypes are acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy, in addition to Miller Fisher syndrome, a variant. It is usually associated with respiratory or gastrointestinal infections caused by *Campylobacter jejuni*, the most common agent, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, Epstein-Barr virus, influenza A, and Zika virus, for example<sup>[69-71]</sup>.

However, during the COVID-19 pandemic, an increase in the number of GBS cases associated with individuals infected with SARS-CoV-2 was observed. In this context, a study conducted suggested an up to 2.6-fold increase in the baseline GBS case rate, from 0.93/100000/year to 2.43/100000/year. Furthermore, the authors noted that GBS associated with COVID-19 is more severe than those not associated with this virus<sup>[69]</sup>. In this sense, among patients positive for SARS-CoV-2, GBS is more prevalent in males and those aged over 60 years and, among the GBS subtypes, the most prevalent is AIDP<sup>[71-73]</sup>.

As with other conditions arising from SARS-CoV-2 infection, the onset of GBS-related symptoms is variable, but studies suggest that the onset of symptoms occurs approximately during the second week of infection, reinforcing the hypotheses of a post-infectious etiology of GBS. The causal mechanisms are still uncertain. However, there are hypotheses that relate the development of GBS to the cytokine storm that occurs during the second phase of infection, which usually occurs in the second week of infection, related to the elevation of cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , -6, -17 and IFN- $\gamma$ , which are capable of causing tissue damage. In addition, there are hypotheses that

relate GBS to autoimmune mechanisms by cross-reaction against ganglioside components of peripheral nerves, causing impairment of nerve structures and, consequently, the development of the syndrome<sup>[72,74,75]</sup>.

A summary of the hypotheses and mechanisms related to development of <sup>29</sup>the neurological manifestations of the SARS-CoV-2 infection, as well as prevalence/incidence of these repercussions, are shown in Table 1.

### *Manifestations after infection*

Neurological complications following COVID-19 infection are still poorly understood due to the recent onset of the pandemic and the question remains whether neurological symptoms are a definite sequelae or just a late effect of the disease. As the virus attacks and grows in lung tissue, alveolar gas exchange is disrupted due to systemic inflammation and edema, which can cause hypoxia and acid accumulation. A study describing the autopsy of 8 confirmed cases with SARS-CoV-2 infection reported brain swelling and severe neuronal damage<sup>[78]</sup>, as did another study, with 18 brain autopsies of patients testing positive for the viral infection, indicated alteration by hypoxia in the cerebellum and brain, with loss of <sup>13</sup>neurons in the cerebral cortex and <sup>1</sup>hippocampus<sup>[79]</sup>. In addition, recent studies have shown that the infection caused by SARS-CoV-2 affects the central nervous system and the peripheral nervous system, and also directly or indirectly damages neurons, which causes long-term neurological sequelae<sup>[80]</sup>.

### **PSYCHIATRIC REPERCUSSIONS**

Along with the physical damages caused by SARS-CoV-2 infection, quarantine and social distancing significantly impacted the mental health of the population. In this sense, studies have demonstrated that during this period there was an increase in the rates of psychiatric manifestations such as irritability, stress, insomnia and depression<sup>[81]</sup>, which can influence the individual's daily life even after the epidemic has ended.



### *Depression and anxiety*

The subjectivity of life demonstrates an impact in reference to the development of mental disorders which contributes to different mental suffering rates for each group of people<sup>[82]</sup>. The necessity of staying at home for long periods<sup>[83]</sup>, the vulnerability of the risk groups, increase in unemployment rates and publicity of false information contribute to both the illness of the population and increased number of suicides cases<sup>[84]</sup>. Other factors such as living alone, having children, being a student or a health worker, poor sleep quality, family support lack, less contact with friends and previous psychiatric history or substance abuse were also associated with the emergence of depression and anxiety<sup>[85]</sup>.

A study conducted with the Chinese population showed that of the 1.210 respondents, about 30% had severe to moderate anxiety symptoms and 17% had severe to moderate depression<sup>[83]</sup>. Similarly, an online cross-sectional study conducted in China included 1.456 participants and assessed factors that influenced the mental health of adults during the pandemic. Its results showed that loneliness, depression and anxiety were associated with more somatic symptoms and lower self-efficacy. In addition, depression was associated with fear of infection, excessive alcohol consumption, and longer screen time. Loneliness was associated with single, divorced or widowed marital status, low education, medication use and frequent going out<sup>[86]</sup>. Furthermore, a survey of the Belgian population aged 18 to 65 years reported that in just 2 wk of isolation the stress of individuals increased by about 25%<sup>[87]</sup>.

### *Post-traumatic stress disorder*

Literature reports also describe an increase in rates of PTSD in children, parents and even health care professionals after contact with infection, which demonstrates that subjective experience is also related to mental illness<sup>[88]</sup>. PTSD manifestations were related to higher perceived risk of infection, fear of infection, and self-assessment of higher negative influence due to the epidemic<sup>[86]</sup>. Corroborating, an electronic records cohort of 69 million individuals, of which 62.354 tested positive for infection, found that

patients with COVID-19 had a higher incidence of unprecedented psychiatric diagnoses between 14-90 d after infection compared to other illnesses such as respiratory tract infections, skin infection, large bone fracture, urolithiasis, and cholelithiasis. Interestingly, previous psychiatric diagnoses also appear to be an independent risk factor for COVID-19<sup>[89]</sup>.

### *Susceptibility to mental distress*

The unpredictability of the outcomes of a possible infection can also increase susceptibility to mental distress, especially in people considered to be in the risk groups, which shows that subjective experience is an important predictor of the onset of psychological problems<sup>[90]</sup>. Studies performed during the pandemic reported a higher prevalence of mental disorders, such as anxiety in people with comorbidities or depression in individuals diagnosed with type 2 diabetes mellitus, when compared to the general population<sup>[91]</sup>. Similarly, minority groups such as immigrants, individuals with low access to health care and low socioeconomic status are more prone to mental disorders, since not only does the pandemic contribute to increasing marginalization and discrimination of these groups, but they are also considered more susceptible to infection and deaths caused by COVID-19<sup>[92]</sup>. In addition, women were also more affected than men by major depressive disorders and anxiety<sup>[93]</sup>. Violation of women's human rights with increasing rates of domestic violence and restrictions on access to prenatal health care services also contribute to greater mental illness in this group<sup>[94]</sup>.

On the other hand, a preexisting mental health condition may be aggravated by the pandemic, as people diagnosed with mental disorders are considered more vulnerable to changes in their health status due to varying risk factors<sup>[95]</sup>. Interestingly, Pan *et al*<sup>[96]</sup> noted that people who did not have a psychiatric diagnosis of anxiety, depression, or obsessive-compulsive disorder prior to the pandemic reported an increase in symptoms related to these comorbidities. However, those individuals who already had a diagnosis of one of these disorders did not experience greater worsening of symptoms post-pandemic.

### *Mental health of the healthcare professionals*

Healthcare professionals who worked on the front lines in the pandemic are a particularly affected population at higher risk of developing psychological distress and mental health impairment<sup>[97]</sup>. In this context, a cross-sectional study of 3852 healthcare professionals assessed the mental health of professionals who worked in the COVID-19 pandemic and SARS outbreak. The authors reported that health care workers achieved moderate and severe scores for symptoms of PTSD, anxiety, and depression<sup>[98]</sup>.

A summary of highlights related to development of the psychiatric disorders in COVID-19 are shown in Figure 3.

### **INTERVENTIONS**

The management of SARS-CoV-2 infection seems more complex when it involves the CNS. The dense parenchyma and impermeability of brain tissue, despite protecting the brain from the infectious process, may also hinder virus elimination. Still, the treatment of patients with neurological complications from this infection requires caution, because some drugs used in non-COVID-19 situations can lead to worsening of the disease-related acute respiratory syndrome, such as corticosteroids and immunosuppressant<sup>[99,100]</sup>. Moreover, viral damage can affect renal, immunological, hematological, hepatic, pulmonary and cardiac organ systems, as well as lead to pharmacokinetic changes that influence the absorption, distribution, metabolism and/or excretion of medications, such as psychotropic drugs. Susceptibility to side effects may be increased and adjustments in treatment regimens should potentially be considered<sup>[101]</sup>, in addition to the pro-inflammatory, pro-thrombotic and arrhythmogenic implications of this infection<sup>[102]</sup>. Therefore, the approach to COVID-19 positive patients with neuropsychiatric repercussions still needs further long-term studies for evaluation and establishment of guidelines.

### *Neurological repercussions*

One study reports the requirement for appropriate neuroimaging protocols in coronavirus infections to detect encephalitis, leptomeningeal and vascular changes such as stroke, microhemorrhages and cerebral infarction<sup>[103]</sup>. It is important that appropriate therapies are applied at the correct time, and that assessment of adjacent comorbidities, as well as damage to other organs and general condition is done using the sequential organ failure assessment score, which influences the COVID-19 prognosis<sup>[104,105]</sup>. Severe individuals can present high levels of the inflammatory markers, as C-reactive protein and D-dímer, and administration of tissue plasminogen activator (rt-PA) in these patients with ischemic stroke predicted worse prognostic<sup>[44,106]</sup>. Thrombectomy can be used, evaluating the risks and benefits of therapy, and antiplatelet and anticoagulant agents remain uncertain. Thus, due to the lack of definitive studies, it is recommended to follow the existing guidelines<sup>[104]</sup>.

Patients with demyelinating conditions and mild infection may be acceptable to continue treatment and the interruption may be considered in the use of potent immunosuppressant with risk factors for severe disease, returning after four weeks or complete remission of symptoms<sup>[107]</sup>. The remission time of olfactory and gustatory dysfunction is controversial in literature, with studies reporting spontaneous resolution in one to three weeks<sup>[108]</sup>. On the other hand, the smell performance of SARS-CoV-2 positive patients with mild or no symptoms can also not recover completely after four months or more of acute infection<sup>[109]</sup>. Therefore, this treatment is still uncertain, but studies point to benefits of practicing olfactory training for those with persistent symptoms. In addition, some studies evaluate the role of local corticosteroids in recovery, but there is no consensus<sup>[110]</sup>. A study evaluating the efficacy of locally applied steroids in the form of fluticasone nasal sprays for olfaction disorders and triamcinolone paste for taste disorders reported that olfaction and taste function improved significantly in patients with COVID-19 within one week<sup>[111]</sup>. Treatment for GDs is rarely addressed in the currently published literature, so more studies are needed to understand the best therapeutic options, especially in cases in which



symptom regression does not occur as expected. Yet, there are different treatments that can be used against GBS, depending on the health structure and clinical context of each individual. Thus, among treatment possibilities, the use of intravenous immunoglobulins, plasmapheresis, or corticosteroids, alone or in combination, may be necessary<sup>[73,112]</sup>.

The management of headache during SARS-CoV-2 infection can be accomplished by administering previously established therapeutic regimens for the treatment of acute crisis<sup>[113]</sup>. <sup>9</sup> Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are already widely used drugs in the treatment of headache crises and, although they are demonstrated during infection, their use is questioned. Reports in the literature note that NSAIDs could be related to increased ACE2 levels<sup>[114]</sup>, which would contribute to ease <sup>8</sup> the entry of the virus into the host cell as more viral receptors would be expressed, and negatively impact the immune system through COX inhibition, decreasing neutrophil chemotaxis and leading to an inefficient response against the virus, and reducing the expression of lipoxins and resolving that contribute to the resolution of inflammation. However, there are not enough studies to prove or rule out these theories<sup>[115]</sup>. On other hand, the administration of triptans like sumatriptan has been shown to be quite effective in the treatment of migraine, but despite this, for the drug choice, it is also important to consider both the patient's pre-existing comorbidities and the severity of the infection at the time<sup>[116]</sup>. Other therapies such as the administration of paracetamol, which is considered a safe and effective drug in these cases<sup>[114]</sup>, neuroleptics such as chlorpromazine and neuromodulation devices can also be considered for treatment<sup>[113,117]</sup>. Lastly, the use of oral corticosteroids has also been related to improving migraine cases and managing the transition to cluster headache, however, studies have reported that these drugs could also contribute to perpetuating the replication of the virus<sup>[117]</sup>.

### *Psychiatric repercussions*



With regard to psychiatric manifestations secondary to SARS-CoV-2 infection, delirium is mainly related to the hyperactive/mixed variety associated with elevated anxiety, and isolation itself is considered a factor that can both trigger and/or increase delirium symptoms<sup>[118,119]</sup>. This makes management difficult and lower potency antipsychotics such as olanzapine and quetiapine are preferred<sup>[118]</sup> and haloperidol is the most considered for agitation control in delusional patients<sup>[101]</sup>. Immune modulation therapies for depression secondary to infection-initiated hyperinflammation are being investigated, such as IL-6 inhibitors and melatonin<sup>[120]</sup>, but more studies are required. On the other hand, technologies with online psychotherapies can support the pediatric population in this situation<sup>[121]</sup>, cognitive behavioral therapy and mindfulness-based cognitive therapy can also assist in stress reduction<sup>[122]</sup>.

Although low dosages of benzodiazepines are indicated in anxiety, these drugs have the potential for respiratory depression and the risk and benefits in patients with respiratory symptoms should be considered. Thus, according to the situation, gabapentin, hydroxyzine or lower doses of selective serotonin reuptake inhibitors (SSRIs) can be used, as well as non-pharmacological interventions, such as psychotherapy<sup>[101]</sup>. Treatment of PTSD typically involves SSRIs and serotonin-norepinephrine reuptake inhibitors, and the potential risks should be analyzed on a case-by-case basis. Paroxetine is not recommended due to the short half-life, anticholinergic side effect profile, and increased risk of drug interactions<sup>[102]</sup>.

## **CONCLUSION**

Thus, in this review we have described the SARS-CoV-2 ability to infect the CNS and to cause manifestations related to neurology and psychiatry. Some nonspecific symptoms, such as headache, may be part of the initial clinical presentation as also be present after the resolution of the infection. Viral interaction with ACE2 receptors may be related to the onset or worsening of episodes of cerebrovascular disorders and demyelinating conditions, and to the development of olfactory and taste dysfunction by migration through the olfactory tract, one of the virus pathways. Yet, mental illnesses such as

depression, anxiety, and PTSD may be caused by the social distancing and quarantine in both patients and health care workers who worked on the front lines, and these disorders may remain even after the pandemic has ended. Our work contributes to the elucidation of the disease pathogenesis, as well as the understanding of clinical presentation, since not all patients will present with a classic respiratory condition. Finally, the pandemic effects still need to be evaluated in the long term and <sup>7</sup> more studies are necessary to clarify guidelines and establish the adequate management of these individuals.

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