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Neurological changes post-covid-19 infection: signs and symptoms that remain

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Abstract

Since 2019, humanity has faced the pandemic outbreak of COVID-19 disease, caused by the new coronavirus, SARS-CoV-2. Respiratory symptoms of the disease were investigated and monitored worldwide, however, the nervous system lesions induced by COVID-19 did not receive as much attention. The aim of this study was to highlight the neurological alterations after infection of the new coronavirus, thus highlighting the symptoms that remained after Infection by SARS-CoV-2. The review shows relevant data on drugs and SARS-CoV-2, neurological alterations, complications and adverse effects related to COVID-19. At the time of writing this article, in mid-2022, SARS-CoV-2 is still spreading in several countries and infecting the population, leaving many people with temporary or permanent sequelae because of COVID-19.

Keywords: SARS-CoV-2; COVID-19; Clinical trial; Neurological alterations; Symptoms; Post-COVID-19 sequels.

1. Introduction

In December 2019, in Wuhan, Hubei Province, China, a new coronavirus "SARS-CoV-2" was discovered, responsible for causing the disease "COVID-19"[1-3]. The first viruses of the coronavirus family were discovered in 1937 and only in 1965 came to be called coronavirus (Cov), due to their microscopic morphology being similar to a crown, which can be explained by the presence of viral spicules (S proteins) on the surface of the virus membrane, being pathogens to humans, causing mild respiratory infections, moderate and even severe[4-6]. Among the various types of Cov, there are three types responsible for respiratory infection:

SARS-CoV, Mers-CoV and the new SARS-CoV-2[7].

SARS-CoV-2 is a 26 to 32 kb-sized positive single-tape RNA virus that exhibits a fold of the oligosaccharide type[8,9], a member of the *Coronavirinae* subfamily, which includes: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, within these classifications, SARS-CoV-2 is identified as Betacoronavirus[10,11]. The virus, presents lipids and glycoproteins S that are of paramount importance for its infectivity and virulence and also have the function of directing where the virus will enter and where it will stay in host cells[12,13].

The route of transmission of SARS-CoV-2 is through respiratory droplets from one sick person to another healthy person, these droplets can also contaminate surfaces and people can be infected or even by direct contact[14,15].

When a person is infected, the most common symptoms include dyspnea, runny nose, cough, fever, pneumonia in more severe cases[16] and people with comorbidities such as hypertension and obesity are more likely to be infected[17]. Because it is a highly contagious virus, it spread rapidly around the world, because of this, the World Health Organization (WHO) declared a global pandemic on March 11, 2020[18], thus a global health concern[19]. According to the Centers for Disease Control and Prevention (CDC), by June 2022, more than 86 million cases had been confirmed in the United States and 1,011,013 deaths[20]. In relation to Brazil, in mid-June 2022, 32 million more confirmed cases, with 670,229,000 deaths[21], causing chaos and terrible economic crisis in Brazil[22].

It should be noted that SARS-CoV-2 has caused several outbreaks of highly contagious respiratory diseases worldwide, especially severe acute respiratory syndrome (RSAR). Another relevant factor is that the respiratory symptoms of the disease were monitored and studied deeply, however, lesions of the central nervous system (CNS) and peripheral nervous system (PNS) induced by COVID-19 did not receive much attention[23]. Thus, it is essential to mention that patients with severe and mild neurological manifestations of COVID can leave long-term sequelae, with serious personal, social and economic costs[24]. It is in this context that the present study aims to highlight the neurological alterations after infection of the new coronavirus, thus highlighting the signs and symptoms that remained after Infection by SARS-CoV-2.

2. Study Design

The design of the scientific research was to evidence qualitative data researched in reliable databases such as SciELO, PubMed and Lilacs, in addition to the Ministry of Health, Centers for Disease Control and Prevention and Pan American Health Organization, allowing to understand the complexity and details of the data obtained on the main updated approaches of alternative drug therapies for COVID-19, as well as the main aspects of neurological alterations and complications associated with SARS-CoV-2 infection.

3. Brief Description of The New Coronavirus

COVID-19 is a disease caused by the virus called SARS-CoV-2, which belongs to the Betacoronavirus class[25-27]. Its transmission occurs through respiratory droplets, with an incubation period of approximately 5 days and an average of 11.5 days for the onset of the first symptoms of the disease[28,29]. For SARS-CoV-2 to

infect a cell, it uses surface receptors TMPRSS2 and angiotensin-converter enzyme 2 (ACE-2), which are present in airway cells, vascular endothelial cells, and macrophages in the lung. After entering the host cell, its viral cycle occurs, inducing the cell to undergo pyptosis, resulting in the release of ASC oligomers, ATP and nucleic acids. Thus, it triggers pararine signaling in epithelial cells and alveolar macrophages, leading to local inflammation mediated by IL-6, IP-10, MIP1-alpha, MIP1-beta and MCP1. These molecules signal the anaphylaxis and diapedesis of circulating monocytes and lymphocytes, releasing Interferon-gamma (IFN gamma) in the infection zone, promoting positive feedback, which can lead to the accumulation of immune cells and the exacerbated production of inflammatory mediators at the site of inflammation of the respiratory tract[28-30].

Because it is a contemporary disease, symptoms and abnormalities challenge science, demonstrating intense clinical manifestations involving the lower respiratory tract and even other organs. There is a greater concern for people with chronic-degenerative diseases, in whom they are most vulnerable. The diagnosis of coronavirus is made through the detection of virus RNA by molecular biology technique (RT-PCR), IgM and IgG antibodies, serological tests and chromatographic column tests[31].

4. Main Approaches to Alternative Drug Therapy

Among the existing drugs, there is a huge pharmacological possibility in the testing phase, such as the case of arbidol, favipiravir, remdesivir, chloroquine/hydroxychloroquine and azithromycin (Table 1).

Table 1. Main studies with drugs used for COVID-19 intervention.

Authors	Country / Year	Title	Intervention / Treatment	Initial outcome / Action
Dong et al.[32]	China / 2020	Discovering drugs to treat coronavirus disease 2019 (COVID-19).	Adults received arbidol orally 200 mg/day (3x) for 10 days.	Study shows that arbidol can inhibit SARS-CoV-2 infection[33].
			Clinical trial with favipiravir.	It prevents the activity of RNA polymerase[34]. Study reveals that it may have potential antiviral action on SARS-CoV-2.
Wang et al.[35]	China / 2020	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*.	Remdesivir and chloroquine in vitro for the control of COVID-2019 infection.	They potentially blocked virus infection at low micromolar concentration.

Colson et al.[36]	France / 2020	Chloroquine and hydroxychloroquine as available weapons to fight COVID-19.	Chloroquine 500 mg/day (2x) in COVID-19 patients with mild, moderate, and severe symptoms.	Reduction of symptoms and pneumonia associated with COVID-19.
Gao et al.[37]	China / 2020	Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies.	Use of chloroquine in a randomized clinical trial in hospitals in China.	It has been shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China.
Liu et al.[38]	China / 2020	Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*.	Assay with cell cultures and administration of different doses of HCQ.	The in vitro study reveals that HCQ can inhibit SARS-CoV-2 infection.
Gautret et al.[39]	France / 2020	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.	600mg/day of HCQ and azithromycin was added to the treatment.	The combination of HCQ with azithromycin potentiated drug therapy, thus showing viral load reduction in COVID-19 patients.
Singh et al.[40]	India / 2020	Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries.	They investigated all studies related to the administration of HCQ and COVID-19 in the PubMed database.	It showed significant improvement in some parameters in patients with COVID-19.

Note: RNA (ribonucleic acid); HCQ (hydroxychloroquine).

5. Central and Peripheral Neurological Changes

The new coronavirus can target the CNS, affecting neurons and glial cells as a result, can cause a variety of neurological pathologies. Because of this, it can be considered that this invasion of SARS-CoV-2, due to the great biological possibility of the CNS being infected by respiratory viruses, where there is evidence that the virus causes neurological damage and complications[41]. In the SARS outbreak in 2002 and 2003, neurological complications were reported in patients affected by the disease, presenting as symptoms associated with septic and cardiogenic shock and prolonged immobilization[42,43]. Unlike the 2002-2003 outbreak in the COVID-19 pandemic, the main symptoms are dry mouth, dizziness, decreased level of consciousness, headache and convulsion, emphasizing that these symptoms are present both in patients with a history of neurological disorders and in patients who do not have pre-existing neurological complications[44-46].

In the mildest cases, it is common to have taste disorders (dysgeusia) and olfactory (anosmia), headache, irritability, altered level of consciousness and nausea, and in patients who progress to intensive care units (ICU), more severe symptoms such as clonia, agitation, hyperreflexia, signs of the corticospinal tract and confusion are highlighted[28,47,48].

It is of paramount importance to highlight that COVID-19 in people with comorbidities, such as Hypertension (SAH) and Diabetes Mellitus (DM), predisposes this group of people to acute cerebrovascular diseases. Patients with SAH have few respiratory symptoms; however, they are more predisposed to have neurological manifestations, such as consciousness disorder and acute cerebrovascular disease, which appear more often at the onset of the disease, about 3 to 4 days after the onset of respiratory symptoms[49-53].

5.1 Case of Neurological Complication by other Human Coronaviruses

Among the other types of human coronaviruses, types OC43, 229 and SARS-CoV have neuroinvasive capacity, whose viral RNA has already been detected in the human brain[54]. A 1-year-old child with severe combined immunodeficiency was diagnosed with deadly encephalitis caused by coronavirus OC43[55], whose investigation of the disease was carried out through reverse transcriptase-polymerase chain reaction (RT-PCR) in brain biopsy and viral RNA sequencing techniques. The study revealed a microglial, lymphocytic infiltrate, predominantly T lymphocyte strain and detected oc43 coronavirus nucleocapsid in neurons[56].

5.2 Neurological Complications Associated with COVID-19

The incidence of neurological complications is not yet fully described, but it is known that patients with COVID-19 in severe condition are more likely to present neurological symptoms than patients in mild condition. Some autopsy studies have shown that in patients who died of COVID-19, they had cerebral edema and neuronal degeneration[57].

In a retrospective study, it was reported that of the 214 patients integrated with COVID-19 in a Wuhan hospital, about 36.5% of the patients had some neurological manifestation, characterizing as CNS involvement (24.8%), PNS (10.7%) and musculoskeletal (10.7%)[45]. The most frequent neurological symptoms in the patients studied were vertigo (16.8%), hyposmia (2.3%), hypogeusia (5.6%) and headache (13%)[58].

5.2.1 Smell and Taste Disorder

Anosmia and hypogeusia are reported in patients with COVID-19, whose prevalence of disorders in 12 European hospitals has been analyzed, with a total of 417 patients with mild to moderate COVID-19. The patients answered a questionnaire about olfactory and gustatory changes based on nutritional and health examination, whose most frequent symptoms were myalgia, cough and loss of appetite. In addition, about 85.5% and 88% of patients reported smell and taste disorders, respectively, and 12% reported that olfactory dysfunction was the initial symptom. In addition, 18% of the patients presented norinorrea or nasal obstruction[59].

5.2.2 Encephalopathy

Encephalopathy is a transient brain dysfunction that presents as an acute or subacute dysfunction of the level of consciousness. The risk of worsening of mental status associated with COVID-19 is higher in people of advanced age and with previous cognitive degeneration, as well as in SAH and previous comorbidities[45,60]. Patients who already have some neurological damage and acute respiratory symptoms are at higher risk of encephalopathy as initial symptoms of COVID-19[61]. One of the explanations for COVID-19 associated encephalopathy may be metabolic, toxic, drug or hypoxia effect, in addition there may be related indirect mechanisms, such as subclinical crises. A case of a patient with COVID-19 with severe encephalopathy is reported in one study, leaving the person unable to even follow verbal orders. In this case, an electroencephalogram was performed, which reported bilateral slow and diffuse waves in the temporal region[60]. Cerebral edema was evidenced at necropsy in patients who died of COVID-19, and it was also detected that there is no inflammation of the cerebrospinal fluid (CSF). The treatment in this case is to treat hypoxia, control fever and use antiepileptic drugs[57].

5.2.3 Encephalitis

In addition to the SARS-CoV-2 virus, it would be of great importance to include some differential diagnoses of encephalitis along with neurotropic viruses. Encephalitis presents some symptoms such as headache, fever, epileptic seizures, altered level of consciousness, and behavioral disorders. When an early diagnosis can be made, it is very important for the survival of the patient, in which these symptoms may also be present in patients with COVID-19 with hypoxia or severe pneumonia, being easily confused[62].

5.2.4 Rare Complications Associated with SARS-CoV-2 Infection

As rare as it is, acute necrotizing encephalopathy may occur in patients with COVID-19, which has already been described in some viral infections, such as influenza virus infection. Not much is known, but the literature reports that the pathogenicity of this complication is related to the cytokine storm caused by COVID-19[63]. In addition to this case, Guillain-Barré syndrome may occur concomitantly with COVID-19, which has been reported in a 62-year-old patient presenting as symptoms of motor asthenain in the lower extremities, the clinical symptoms of COVID-19, fever and dry cough days later[64].

5.2.5 Cerebrovascular Complications

Patients of advanced age and who have already presented some vascular risk may have a higher risk of having cerebrovascular complications after COVID-19 contamination than young and without comorbidities[65]. In Wuhan, a retrospective study was conducted with 221 patients with COVID-19, among which it was analyzed that 1 (0.5%) had thrombosis in venous sinus, 1 (0.5%) had cerebral hemorrhage and 11 (5%) had a consequence of ischemic stroke, and the risk factors for having a stroke was to be elderly, with a mean age of 71.6 years, having severe COVID-19, having a previous history of comorbidities such as SAH, DM, cerebrovascular disease, or having an inflammatory and procoagulant response, resulting in a mortality of 38%[66].

In addition, it is known that SARS-CoV-2 binds to the angiotensin-2-converter enzyme (ACE2), transferring its genetic material to the cell, initiating the virus replication process[67-69]. This leads to increased vascular permeability, pulmonary edema and neutrophil accumulation, as well as worsening pulmonary function[70]. In addition to these factors, it is important to mention the mild and severe forms. The mild form presents symptoms of fever, dry cough and fatigue, in addition to diarrhea, myalgia, headache, odinofagia, anosmia, ageusia and runny nose. Severe form is characterized by dyspnea, aquipnea, a fall in oxygen saturation, and pulmonary infiltrate. It is important to highlight critical cases, such as signs of circulatory shock and respiratory failure, which can lead to multiple organ dysfunction[71-75].

5.3 Peripheral Involvement

Peripheral complications caused by COVID-19 are closely related to the topography of the lesion. Thus, the disease has the ability to generate, broadly, peripheral neurological alterations ranging from myositis to severe myasthesis, rhabdomyolysis, to myopathy/polyneuropathy of critical disease[76].

5.4 Myopathy

Patients hospitalized with COVID-19 frequently reported fatigue and myalgia and, in addition, elevated levels of creatine kinase protein (CK) were observed, indicating that the disease may generate viral myositis[77]. In critically ill patients, myopathy is also related to prolonged hospital stay[78].

6. Conclusion

It can be concluded that SARS-CoV-2 mainly attacks the respiratory system, generating primordial symptoms of COVID-19. Other symptoms are becoming frequent, such as neurological changes. The main neurological manifestations reported may vary from mild conditions such as myalgia, headache and hyposmia to more critical conditions, such as encephalopathy, cerebrovascular accident and Guillain-Barré syndrome. Viral factors and host factors are of great importance in explaining different levels of neurovirulence, CNS invasion and neurotropism. Therefore, this study provided up-to-date information on SARS-CoV-2 associated with neurological alterations to improve the reader's knowledge and understanding of pathophysiology, possible treatments and possible neurological complications caused by COVID-19.

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Declaration of potential conflict of interest

The authors declare that they have no conflict of interest.

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