

Relationship between neuropsychiatric signs and symptoms and SARS-CoV-2 infection: an integrative review

Relação entre sinais e sintomas neuropsiquiátricos e infecção por SARS-CoV-2: uma revisão integrativa

Relación entre los signos y síntomas neuropsiquiátricos y la infección por SARS-CoV-2: una revisión integradora

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Tahissa Frota Cavalcante

ORCID: <https://orcid.org/0000-0002-7758-4273>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: tahissa@unilab.edu.br

Daniel Freitas Oliveira Damasceno

ORCID: <https://orcid.org/0000-0002-9664-6660>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: danielfreitas17@yahoo.com.br

José Erivelton de Souza Maciel Ferreira

ORCID: <https://orcid.org/0000-0003-2668-7587>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: eriveltonsmf@gmail.com

Raphaella Castro Jansen

ORCID: <https://orcid.org/0000-0002-4032-5825>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: raphaella.jansen@gmail.com

Eloise da Silva Barbosa

ORCID: <https://orcid.org/0000-0003-3312-2875>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: eloise.barbosa@hotmail.com

Rafaella Pessoa Moreira

ORCID: <https://orcid.org/0000-0003-2341-7936>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: rafaellapessoa@unilab.edu.br

Huana Carolina Cândido Morais

ORCID: <https://orcid.org/0000-0001-6435-1457>
University of International Integration of Afro-Brazilian Lusophony, Brazil
E-mail: huanacarolina@unilab.edu.br

Abstract

Introduction: Several viruses, including CoVs, can affect the nervous system, causing neuropsychiatric signs and symptoms. Because this is an unknown disease widely spread, there are few studies that deal with the effects of the SARS-CoV-2 on the nervous system. **Objective:** To describe the relationship between neuropsychiatric signs and symptoms and SARS-Cov-2 virus infection. **Methods:** integrative review conducted in the Pubmed Portal, Virtual Health Library, Cochrane and the academic researcher Science Direct. The works were analyzed qualitatively, with the narrative description divided into four thematic categories. **Results:** 1024 studies were found and 48 studies selected to compose this integrative review. There is a pathophysiological relationship of SARS-Cov-2 infection and the involvement of the Central Nervous System and Peripheral Nervous System through different pathways and mechanisms. **Conclusion:** Monitoring patients during and after COVID-19 can minimize the neuropsychiatric sequelae resulting from this disease, especially in elderly patients with comorbidities.

Keywords: Coronavirus; COVID-19; Neurologic-symptoms; Psychiatry; SARS Coronavirus.

Resumo

Introdução: Muitos vírus, incluindo CoVs, podem afetar o sistema nervoso, causando sinais e sintomas neuropsiquiátricos. Por se tratar de uma doença desconhecida e amplamente disseminada, existem poucos estudos que tratam dos efeitos do SARS-CoV-2 no sistema nervoso. **Objetivo:** Descrever a relação entre os sinais e sintomas neuropsiquiátricos e a infecção pelo vírus da SARS-CoV-2. **Método:** Revisão integrativa realizada no Portal Pubmed, Biblioteca Virtual da Saúde, Cochrane e no buscador acadêmico Science Direct. Os trabalhos foram analisados de forma qualitativa, com a descrição narrativa dividida em quatro categorias temáticas. **Resultados:** Foram encontrados

1024 trabalhos e selecionados 48 estudos para compor essa revisão integrativa. Existe uma relação fisiopatológica da infecção por SARS-CoV-2 e o acometimento do Sistema Nervoso Central e Sistema Nervoso Periférico por meio de diferentes vias e mecanismos. Conclusão: A monitorização dos pacientes durante e após a COVID-19 pode minimizar as sequelas de cunho neuropsiquiátricos decorrentes dessa doença, principalmente nos pacientes idosos com comorbidades.

Palavras-chave: Coronavirus; COVID-19; Psiquiatria; Sistema Nervoso; Vírus da SARS.

Resumen

Introducción: Varios virus, incluidos los CoV, pueden afectar el sistema nervioso y causar signos y síntomas neuropsiquiátricos. Debido a que se trata de una enfermedad desconocida muy extendida, hay pocos estudios que se ocupen de los efectos del SARS-CoV-2 en el sistema nervioso. Objetivo: Describir la relación entre los signos y síntomas neuropsiquiátricos y la infección por el virus del SARS-CoV-2. Método: Una revisión integradora realizada en el Portal Pubmed, Biblioteca Virtual de la Salud, Cochrane y en el buscador académico Science Direct. Los trabajos fueron analizados de forma cualitativa, con la descripción narrativa dividida en cuatro categorías temáticas. Resultados: Fueron encontrados 1024 trabajos y seleccionados 48 estudios para componer esa revisión integradora. Existe una relación fisiopatológica de la infección por SARS-CoV-2 y el acometimiento del Sistema Nervioso Central y Sistema Nervoso Periférico por medio de diferentes vías y mecanismos. Conclusión: El seguimiento de los pacientes durante y después del COVID-19 puede minimizar las secuelas neuropsiquiátricas resultantes de esta enfermedad, especialmente en pacientes ancianos con comorbidades.

Palabras clave: Coronavirus; COVID-19; Psiquiatria; Sistema-Nervioso; Virus del SRAS.

1. Introduction

In December 2019, in Wuhan, China, an epidemic of cases of atypical pneumonia caused by a new coronavirus emerged, called SARS-CoV-2. Due to the high transmissibility of this virus, the infection quickly took on worldwide proportions and, currently, the Corona Virus Disease 2019 (COVID-19) pandemic has been an intense public health problem with impacts on all spheres of society (Brito & Silva, 2020).

With the erratic behavior and the rapid spread of the SARS-CoV-2 virus, the problem has become a worldwide public health emergency (WHO, 2020). Currently, it is known that several viruses, including CoVs, can affect the Central Nervous System (CNS) and the Peripheral Nervous System (PNS), causing several neuropsychiatric signs and symptoms. The increasing reports based on clinical data from patients infected with SARS-CoV-2 reveal the presence of signs and symptoms such as headache, delirium, psychosis, altered consciousness, hyposmia or anosmia, dysgeusia, and hypogeusia or ageusia (Parry et al., 2020).

Because this is an unknown disease widely spread, there are few studies that deal with the effects of the SARS-CoV-2 on the Nervous System. It is important that studies are developed to better explain the clinical manifestations and complications of COVID-19, among them, neuropsychiatric signs and symptoms manifested in the acute phase of the disease and/or that persist as sequelae of the infection.

Health professionals who are currently involved in the prevention, early detection and treatment of COVID-19 can use the synthesized knowledge on the subject for decision-making. Furthermore, it can contribute to the creation of multidisciplinary outpatient health services for the follow-up of patients with neuropsychiatric sequelae of COVID-19.

Therefore, the following research question arose: What is the relationship between neuropsychiatric signs and symptoms and SARS-CoV-2 infection? In the context of a SARS-CoV-2 pandemic, evidence-based practice encourages the use of research results into healthcare practices. In view of the aforementioned, the present study aims to describe the relationship between neuropsychiatric signs and symptoms and SARS-CoV-2 infection.

2. Methodology

This study is about an integrative review of the literature, with the objective of establishing the relationship between sinus and neuropsychiatric symptoms and infection by SARS-CoV-2. The study was elaborated in the following stages: theme

definition; elaboration of the guiding question; literary search; delimitation of study selection criteria; reading of studies; organization of studies; synthesis of the information found; interpretation of results and presentation of the review (Sousa et al., 2017).

The following libraries and databases were selected for the bibliographic search: the Brazilian Virtual Health Library (BVS in Portuguese), which covers the LILACS, BDEF, WHO-IRIS, PAHO-IRIS, and SCIELO databases; Pubmed, which covers the Medical Literature Analysis and Retrieval System Online (Medline) database; Cochrane; and Science Direct. The use of these different databases was intended to expand the scope of the research and, thus, to minimize possible bias. In order to survey the studies in these databases, different descriptors were initially defined to be used in each database.

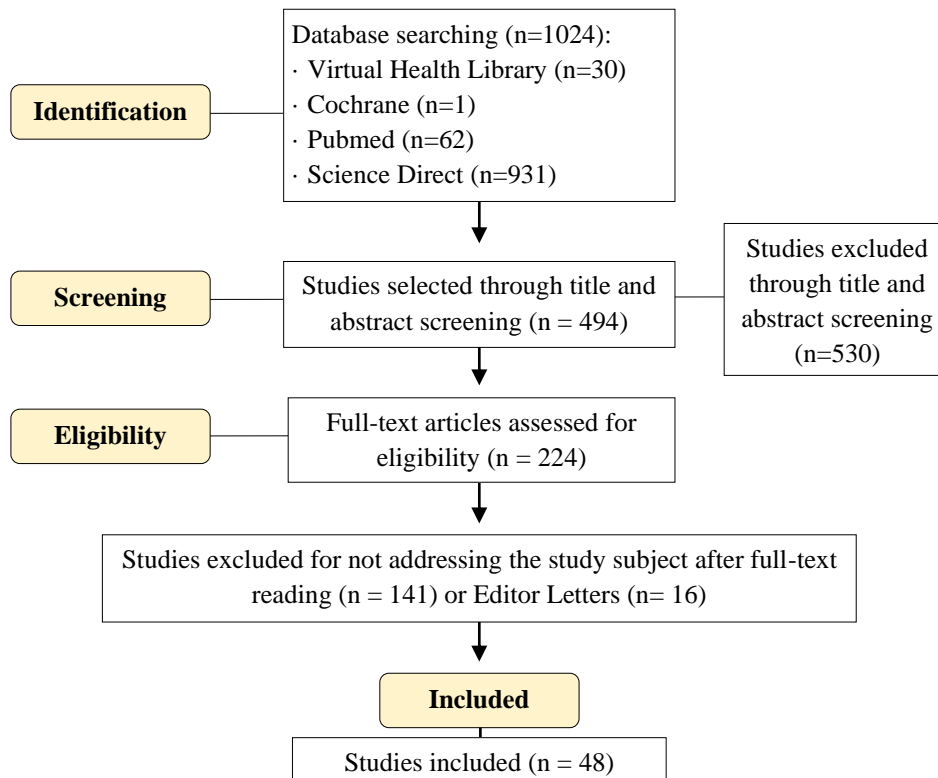
The following descriptors from the MeSH vocabulary were used in Pubmed, Science Direct, and Cochrane: “coronavirus”, “SARS”, and “neurologic symptoms”, using “MeSH Terms” as a query. In Science Direct, we limited the search to the year 2020. In the Virtual Health Library, the following descriptors from the Health Sciences Descriptors Vocabulary (DeCS in Portuguese) were used: “SARS Virus” and “Nervous System”, using “descriptor” as a query. No other filters were used to search for these articles, as the choice of descriptors based on their operational definitions was enough to make this search adequate.

The inclusion criteria were: (a) full-text studies addressing neuropsychiatric signs and symptoms related to SARS-CoV-2 infection, and (b) studies answering the research question of the integrative review. Duplicate articles were excluded as well as editorials, letters to the editor, and opinion articles. The bibliographic search took place from June to August 2020. Each database and the respective search engines were accessed in a single day, with a recording of the search retrieved from each database. The selection of studies was carried out in the subsequent days through reading of titles and abstracts. When necessary, full texts were accessed and read for assessment of the pre-established inclusion and exclusion criteria.

Two pairs of independent reviewers extracted information from the studies (1 pair for the Virtual Health Library, Pubmed, and Cochrane searches, and 1 pair for the Science Direct search). These pairs were also responsible for conducting the evaluation of selected studies based on the Joanna Briggs Institute (JBI) (Sousa et al., 2017). Data from the analyzed studies were extracted using an electronic form created in Microsoft Word 2013-2015 with the following variables: name of the database, title of the article, country of origin, study objective, study design, level of evidence, and results about the relationships between neuropsychiatric signs and symptoms and SARS-CoV-2 infection.

Figure 1 shows the PRISMA flowchart with a complete description of the studies included in the integrative review. At the end of the entire search and selection process, 48 articles were included.

Figure 1. PRISMA flowchart of included studies.



Source: Authors (2020).

The data analysis was done in a qualitative way, with a narrative approach. The researchers opted for this approach because the review included research with different methodological designs, resulting in a high heterogeneity of data and thus it would not be feasible to carry out a meta-analysis. The reading and synthesis of the selected studies allowed the identification of the following thematic categories that describe the results of the integrative review: (1) Neuropsychiatric signs and symptoms: prevalence, types, and relationship with sociodemographic and clinical characteristics; (2) Pathophysiological mechanisms of SARS-CoV-2 associated with CNS and PNS manifestations; (3) Neuroprotective mechanisms that decrease the occurrence of neuropsychiatric signs and symptoms; and (4) Neuropsychiatric signs and symptoms that occur and/or persist after COVID-19.

3. Results

3.1 Neuropsychiatric signs and symptoms: prevalence, types, and relationship with sociodemographic and clinical characteristics

Regarding the prevalence of neurological symptoms in people with COVID-19 infection, it was found that 36.4% had neurological symptoms, including smell and taste disorders. The findings also suggest that patients with the most severe form of the disease were more likely to manifest neurological symptoms, such as acute cerebrovascular diseases (5.7% vs. 0.8%), impaired level of consciousness (14.8% vs. 2.4%), and skeletal muscle injury (19.3% vs. 4.8%) compared to those with the mild form of the disease (Troyer et al., 2020; Rao & Jayabaskaran, 2020; Korálnik & Tyler, 2020; Msigwa et al., 2020; Singh et al., 2020; Pedicelli et al., 2020; Mao et al., 2020).

A second study with 58 patients hospitalized with severe acute respiratory syndrome caused by COVID-19 found that 69% of the patients had agitation, 67% had signs of corticospinal compromise, and 36% had dysexecutive syndrome, which is characterized by difficulty in concentration, attention, orientation, and in following commands (Helm et al., 2020). A study reported the first cases of myoclonus related to SARS-CoV-2 neuro invasion (Rábano-Suárez et al., 2020).

The Spanish Society of Neurology reports that ischemic stroke is the second more frequent neurological disorder in patients with COVID-19 (22.8%), followed by confusional state (28.3%) (Barrios-López, et al., 2020). There are many studies reporting other neurological signs and symptoms, including seizures (Msigwa et al., 2020; Pinna et al., 2020; Baig et al., 2020), encephalitis (Pinna et al., 2020; Baig et al., 2020; Román et al., 2020), meningoencephalitis (Carod-Artal, 2020; Dogan et al., 2020), acute hemorrhagic necrotizing encephalopathy (Román et al., 2020; Carod-Artal, 2020; Dogan et al., 2020), acute demyelination (Msigwa et al., 2020; Brun et al., 2020), delirium (Román et al., 2020; Hosseini et al., 2020; Beach et al., 2020; Afshar et al., 2020), unilateral neglect (Scullen et al., 2020), skeletal muscle injury (Rábano-Suárez et al., 2020; Scullen et al., 2020; Baig & Sanders et al., 2020; San-Juan et al., 2020), hearing loss (Zayet et al., 2020; Kilic et al., 2020), reversible bilateral visual loss (Kaya et al., 2020), Guillain Barré syndrome (Rábano-Suárez et al., 2020; Román et al., 2020; Carod-Artal et al., 2020; Freni et al., 2020; Farzi et al., 2020; Bigaut et al., 2020), and trigeminal neuralgia (Ramos et al., 2020).

Studies also cite psychosis as a neuropsychiatric symptom related with COVID-19 and, apparently, a potentially strong relationship between coronavirus infection and psychosis exist (Msigwa et al., 2020; Sher et al., 2020).

Regarding the sociodemographic characteristics associated with neurological/neuropsychiatric manifestations in people with SARS-CoV-2 infection, authors claim that elderly (Rao & Jayabaskaran, 2020; Carod-Artal et al., 2020; Ramos et al., 2020; Agyeman et al., 2020; Serrano-Castro et al., 2020; Avula et al., 2020) and women (Melley et al., 2020; Lee & Lee et al., 2020) are more likely to have such signs and symptoms. Some clinical variables can also increase the risk of neurological/neuropsychiatric complications in people with COVID-19, including the following: comorbidities such as diabetes mellitus, arterial hypertension, chronic kidney disease, cardiovascular disease, obesity, and chronic obstructive pulmonary disease (Rao & Jayabaskaran, 2020; Koralnik & Tyler, 2020; Scullen et al., 2020; Ramos et al., 2020; Avula et al., 2020; Zhang et al., 2020), pre-existing neurological diseases such as Parkinson's disease or dementia (Rejda & Grieb et al., 2020), multiple sclerosis (Safavi et al., 2020), use of immunosuppressive treatments for autoimmunity-mediated demyelinating diseases (Rejda & Grieb et al., 2020), smoking (Faried et al., 2020), and pre-existing psychiatric diseases (Panariello et al., 2020).

3.2 Pathophysiological mechanisms of SARS-CoV-2 associated with CNS and PNS manifestations

The following pathophysiological mechanisms are described in the literature: hematogenous invasion of the CNS (Carod-Artal et al., 2020; Brun et al., 2020; Ramos et al., 2020; Serrano-Castro et al., 2020; Das et al., 2020; Guiu et al., 2020), movement of the virus to the brain via the cribriform plate close to the olfactory bulb (Brun et al., 2020; Ramos et al., 2020; Zhang et al., 2020; Das et al., 2020; Guiu et al., 2020), trans-synaptic viral spread from the lung and lower respiratory airways to the brain (Carod-Artal et al., 2020; Scullen et al., 2020; Ramos et al., 2020; Zhang et al., 2020; Das et al., 2020), lymphatic pathway (Carod-Artal et al., 2020; Brun et al., 2020), immunological mechanisms (Li et al., 2020; Caamaño et al., 2020), hypoxia (Parry et al., 2020; Baig et al., 2020; Caamaño et al., 2020), and inflammatory factors (Zhang et al., 2020).

3.3 Neuroprotective mechanisms that decrease the occurrence of neuropsychiatric signs and symptoms

Authors describe that specific monoclonal antibodies that bind to the SARS-CoV-2 receptor and antibodies that block the action of inflammatory interleukins, such as tocilizumab, seem to offer a neuroprotective effect in people with COVID-19 (Carod-Artal et al., 2020). A follow-up study of people with severe cases of COVID-19 shows that the use of the anti-epileptic

medication levetiracetam via intravenous injection can prevent compromise of the Central Nervous System (Afshar et al., 2020).

Another study on the therapeutic use of botulinum toxin in people with COVID-19 shows the following benefits: (1) increased immune cell count such as platelet count (improvement of macrophage-mediated phagocytosis); (2) improved blood circulation and oxygen supply, which improves the survival rate of people with ischemic conditions, in particular, neuroprotection in ischemic brain; and (3) suppression of the angiotensin-converting enzyme 2 (ACE2) receptor expression (Sousa et al., 2017). It is important to highlight that there is a need for further investigation and development of clinical research on drugs that may offer neuroprotective effects in people with COVID-19. CNS and PNS compromise are concerning and should be considered as essential elements in the treatment of SARS-CoV-2 infection.

3.4 Neuropsychiatric signs and symptoms that occur and/or persist after COVID-19

Some observational studies, have shown that anosmia and hyposmia start in the acute phase of the disease and persist in up to 2 to 3 weeks (Rao & Jayabaskaran, 2020; Kosugi et al., 2020). Authors warn that the permanence of several neurological symptoms after SARS-CoV-2 infection can be prolonged, including cognitive deficits (Kandasamy, 2020; Baller et al., 2020), motor deficits, psychiatric symptoms (Kandasamy, 2020), cutaneous hyperesthesia (Kemp et al., 2020), and Guillain Barré syndrome (Carod-Artal et al., 2020).

4. Discussion

SARS-CoV-2 has the ability to selectively bind to ACE2 receptors, which are highly expressed in the epithelial cells of the respiratory and intestinal systems and also in the CNS, both in glial cells and neurons, which makes the CNS a potential target for the virus. The presence of the virus in the systemic circulation is proven and, consequently, in the brain. The slow movement of blood within the microcirculation may be one of the factors that can facilitate the interaction of the virus with the ACE2 receptor expressed in the brain capillary endothelium (Baig et al., 2020; Serrano-Castro et al., 2020).

Authors present a detailed summary of the physiological mechanisms that explain the CNS and PNS compromise related to the SARS-CoV-2 virus, as follows (Sousa et al., 2020): (a) hypercoagulability - coagulation dysfunction increasingly reported in severe cases of COVID-19, which can precipitate major bleeding, venous thrombosis, or intracranial hemorrhage; (b) vascular endothelial injury - resulting from tropism of the virus to endothelial cells that express ACE2. Endothelial damage induced by SARS-CoV-2 can predispose to cerebral vascular thrombosis in situ or can lead to the rupture of the blood-brain barrier; (c) hypoxia - acute hypoxemia can result in hypoxic ischemic encephalopathy. Prolonged hypoxia can induce demyelination or produce micro-hemorrhages in the white matter. Prolonged hypoxemia leads to oligodendroglial cell damage. Oligodendroglial cells form the myelin sheath on CNS axons, and their death causes demyelination of cerebral white matter; (d) neurotropism - SARS-CoV-2 S1 protein has an avid affinity for ACE2 receptors in humans, which are expressed in neurons; (e) immune-mediated injury - cranial nerve dysfunctions such as the Miller-Fisher syndrome and the cranial polyneuritis reported in COVID-19 are the result of an aberrant immune response to COVID-19 in some cases; (f) pro-inflammatory state - the infection has the potential to trigger ischemic stroke. The rupture of vulnerable atherosclerotic plaques in the presence of a severe pro-inflammatory state can lead to thromboembolic events in severe COVID-19; (g) dyselectrolytemia - hypokalemia and hyponatremia are commonly seen in patients with severe COVID-19, with a correlation with kidney damage. Hyponatremia causes diffuse cerebral edema, while rapid correction of hyponatremia is linked to demyelination.

Regarding the predominance of women with neurological symptoms, several authors explain that women were proportionally more affected by hyposmia or anosmia than men. Although more data are needed to determine whether sex is a predisposing factor for the development of anosmia, the predisposition of women to this symptom can be explained by sexual dimorphisms in the olfactory bulb (Rao & Jayabaskaran, 2020; Kosugi et al., 2020). In this context, it is important to highlight that elderly patients are more likely to develop severe forms of COVID-19, with neurological/neuropsychiatric manifestations and complications.

Prolonged hospitalizations in Intensive Care Units associated with severe pathological conditions, such as the cytokine storm, are related to the occurrence of persistent neurocognitive deficits up to 18 months after hospital discharge (Troyer et al., 2020). So the hospitalization itself combined with COVID-19 related complications and the invasion of the virus in the CNS and PNS increase the chances of neuropsychiatric sequelae.

Systemic inflammation triggered by the SARS-CoV-2 infection can further contribute to neuroinflammatory processes and increase susceptibility to neurological syndromes. CNS infections can thus promote the development of neurodegenerative diseases in individuals who are already at risk. Specifically, the impact of SARS-CoV-2 on the CNS can: (1) directly lead to neurological changes, (2) worsen pre-existing neurological conditions, and/or (3) increase susceptibility or aggravate the damage caused by other conditions (Felice et al., 2020).

It is worth noting that the SARS-CoV-2 infection is recently recognized and its long-term neurological consequences are still unknown, although there are indications that they do occur. Long-term monitoring of patients who survived COVID-19 is necessary to determine if there are any permanent neurological effects after the infection. Therefore, patients must be closely monitored, and future studies must consider late neurological complications including demyelinating and degenerative disorders in these patients (Abboud et al., 2020).

The studies included in this integrative review have lower levels of evidence. Therefore, the thematic categories that involve neuroprotective mechanisms and the persistence of neuropsychiatric signs and symptoms after COVID-19 must be further investigated, preferably by cohort studies and well-designed clinical trials.

This integrative review has the following implications: (a) it provides an in-depth and up-to-date synthesis of the knowledge produced by worldwide researchers about serious complications from the SARS-CoV-2 virus, such as neuropsychiatric signs and symptoms; (b) it can assist in the decision-making of health professionals when monitoring and treating patients with COVID-19; (c) it describes knowledge gaps and research questions that need to be investigated in further studies for the advancement of knowledge and improved practice in the area; (d) it can alert health professionals and managers about the need to implement monitoring services for people who have had COVID-19; and (e) in the context of this pandemic, studies involving the theme of SARS-CoV-2 infection are very important, regardless of the approaches used, because this is a new disease and the knowledge that has been produced and disseminated has reduced serious impacts caused by the virus.

The recommendation for health professionals is to monitor patients with COVID-19 during and after the disease for the neuropsychiatric signs and symptoms, especially elderly patients, people with comorbidities (including cardiovascular and pulmonary disorders, diabetes mellitus, and obesity), and patients with pre-existing neurological and psychiatric diseases. Such a situation can allow decision-making for the implementation of an early rehabilitation treatment, minimizing the sequels resulting from COVID-19.

This integrative review points out several questions that need to be investigated in future studies such as the existence of clinical, laboratory, or pharmacological neuroprotective factors that would decrease the chances of developing neuropsychiatric signs and symptoms; follow-up studies with people who had COVID-19, to ascertain the incidence of neuropsychiatric signs and symptoms at a later stage; and investigations on the recurrence of neuropsychiatric signs and symptoms or occurrence of new manifestations in patients who had had those in the early stage of the infection.

The limitations of this study are related to the number of studies listed, the few databases used, and the non-use of methods to assess the methodological quality of these studies. In addition, SARS-CoV-2 infection and its relationship with short, medium and long-term neuropsychiatric symptoms and symptoms are still under study, and its pathology (COVID-19) during and after infection (Post-COVID-19) is not yet fully clarified. It is also worth remembering that at the time, many studies with preliminary results were published, which may interfere with the quality of the reviews carried out on the subject.

5. Final Considerations

The studies included in this integrative review indicate that there is a pathophysiological relationship between SARS-CoV-2 infection and CNS and PNS compromise. Mechanisms underlying this relationship include the hematogenous pathway, the lymphatic pathway, immunological and inflammatory mechanisms, neuronal invasion in the cribriform plate close to the olfactory bulb (ethmoid bone), hypoxia, trans-synaptic transmission from the lung to the CNS, and through nerve cells present in the gastrointestinal tract and sympathetic afferents.

The chances of nervous system compromise increase in elderly patients, people with associated comorbidities such as obesity, diabetes mellitus, and chronic obstructive pulmonary disease, and in patients with pre-existing neurological/psychiatric diseases. The most cited neuropsychiatric signs and symptoms were headache, delirium, smell and taste disorders, and stroke. The evaluation and monitoring of patients with COVID-19 during and after the disease is important for the early detection and treatment of neuropsychiatric signs and symptoms.

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