Relationship between neuropsychiatric signs and symptoms and SARS-CoV-2 infection: a systematic review

Neuropsychiatric symptoms and COVID - 19

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ABSTRACT

Background: Infection caused by SARS-CoV-2 virus is a recent disease that is easily spread and has serious complications, such as neuropsychiatric signs and symptoms. Thus, studies are necessary on the clinical manifestations during and/or after the course of the disease.
Aims and objectives: To describe the relationship between neuropsychiatric signs and symptoms and SARS-CoV-2 infection.
Methods: Systematic review conducted in the Pubmed Portal, Brazilian Virtual Health Library, Cochrane, and Science Direct databases. The descriptors coronavirus, SARS, and neurologic symptoms were used in Pubmed, Cochrane, and Science Direct databases, while the descriptors SARS Virus and Nervous System were used in the Virtual Health Library database. A total of 1024 studies were found and 67 were selected to compose this systematic review. The studies were analyzed qualitatively with the narrative description divided into four thematic categories.
Results: There is a pathophysiological relationship between SARS-CoV-2 infection and manifestations involving the Central Nervous System and the Peripheral Nervous System through different pathways and mechanisms. The chances of Nervous System manifestations increase in elderly patients with associated morbidities, such as obesity, diabetes mellitus, chronic obstructive pulmonary disease and/or pre-existing neurological/psychiatric diseases. The most cited neuropsychiatric signs and symptoms were headache, delirium, smell and/or taste disorders, and stroke. The evaluation and monitoring of patients during and after COVID-19 infection is important for the early detection and treatment of neuropsychiatric signs and symptoms.
Conclusions: It is recommended that health professionals monitor patients with COVID-19 infection or who had recently had the disease for detecting neuropsychiatric signs and symptoms, especially elderly patients, people with comorbidities such as cardiovascular and pulmonary diseases, diabetes mellitus, and obesity, and patients with pre-existing neurological/psychiatric diseases. Decision-making for the implementation of an early rehabilitation treatment can be reinforced in this groups, minimizing the sequels resulting from COVID-19.
Key words: coronavirus, SARS; neurologic symptoms.

How did you gather the information you considered in your review?

Searching in various databases, reading, critical analysis and categorization of results this articles.

What is the 'take-home' message for the clinician?

The recommendation for clinican 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.

INTRODUCTION

In December 2019, in Wuhan, China, an epidemic of cases of atypical pneumonia caused by the new coronavirus emerged, similar to SARS-CoV and then called coronavirus 2 or 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, even exceeding the number of cases and deaths from SARS-CoV in 2003 (1).

With the erratic behavior and the rapid spread of the SARS-Cov-2 virus, the problem has become a worldwide public health emergency responsible for 39,944,882 confirmed cases and 1,111,998 deaths. The current epicenters of the disease are the United States of America, India, Brazil, and Russia (2).

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 (3-4) .

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, in order to explain and clarify other aspects comprising this pandemic.

Based on these facts, 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. This review provides a synthesis of the knowledge produced about neuropsychiatric manifestations and their relationship with the pandemic caused by SARS-CoV-2.

In addition, such synthesized knowledge can be used for decision-making by health professionals in the prevention, early detection, and treatment of COVID-19, as well as for the creation of multidisciplinary outpatient health services to accompany those with neuropsychiatric sequelae from COVID-19. The study can also assist in the elucidation of important issues that are still obscure.

In view of the aforementioned, the present study aims to describe the relationship between neuropsychiatric signs and symptoms and SARS-CoV-2 infection. The research

question was created using the PECOS (population, exposure, comparison, outcome, study design) format (Figure 1).

Figure 1: PECOS framework.

METHODS

Protocol

This research followed a protocol developed based on the PRISMA statement that provides guidelines for reporting systematic reviews, ensuring that the methodology and results are conducted and reported systematically. The systematic review was registered with PROSPERO under number CRD42020210880.

Eligibility criteria

Inclusion criteria

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 systematic review.

Exclusion criteria

Duplicate articles were excluded as well as editorials, letters to the editor, and opinion articles.

Sources of information

The following libraries and databases were selected for the bibliographic search: the Brazilian Virtual Health Library (BVS in Portuguese), which covers the LILACS, BDENF, WHO-IRIS, PAHO-IRIS, and SCIELO databases; Pubmed, which covers the Medical Literature Analysis and Retrieval System Online (Medline) database; Cochrane; and Science Direct.

Search strategy

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.

Figure 2 shows the PRISMA flowchart with a complete description of the selection process of the studies included in the systematic review.

Figure 2 - PRISMA flowchart of included studies.

Data collection process

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 carrying out the evaluation of the selected studies.

The evaluation of the selected studies was made based on levels of evidence (5). 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.

Data analysis

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 systematic 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.

RESULTS

A total of 67 studies were included in the systematic review. The levels of evidence (5) of the studies are shown in Table 1.

Table 1 - Levels of evidence of the included studies.

Most of the studies analyzed have evidence levels 5 and 6, because they are case studies, descriptive studies, and reviews. We emphasize that even with low levels of evidence, the studies allowed the identification and description of thematic categories that fit into the research question.

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, many studies (31, 39, 40, 42, 59, 67, 69, 72) refer to the work carried out by Mao et al. (73).

In this study (73), the researchers assessed 214 patients with COVID-19 and 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.

A second study (41) with 58 patients hospitalized with severe acute respiratory syndrome caused by COVID-19 at the University Hospital in Strasbourg 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.

A study (68) that analyzed a series of cases in Madrid reported the first cases of SARS-CoV-2 related myoclonus. According with the researchers, there are 2 possibilities that explain myoclonus in people with COVID-19, the first being related to an immunological mechanism during or after infection (post-infectious myoclonus) and the second is due to the neuro-invasive potential of the SARS-CoV-2 virus (68).

Regarding smell and taste disorders, a cohort study (9) of patients with COVID-19 in Germany showed that alterations in smell and taste were present in 41% of the patients. The findings also suggested that the incidence of hyposmia in the cohort was about 30%.

Anosmia and ageusia were reported in more than 80% COVID-19 cases as the first clinical presentation of the disease, or as the only neurological sign presented in mild cases (27). Furthermore, a sudden loss of smell and/or taste are sentinel symptoms that can be used as an alert to establish measures of social isolation to avoid the transmission of the disease (17,64).

Although researchers report lack of published studies on the incidence of stroke related to COVID-19 in young patients (22), 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%) (58,74).

In addition to the well-known COVID-19 infection-related neurological symptoms, there are many studies reporting other neurological signs and symptoms, including seizures (8, 13, 27, 59), encephalitis (8, 10-12) , meningoencephalitis (12, 20, 48), acute hemorrhagic necrotizing encephalopathy (10, 12, 20, 25), acute demyelination (46, 59), delirium (10, 19, 57, 62), unilateral negligence (45), skeletal muscle injury (11, 44, 45, 56, 68), hearing loss (7, 47), reversible bilateral visual loss (53), Guillain Barré syndrome (10, 12, 25, 63, 66, 68, 71), and trigeminal neuralgia (63).

Studies (18,26,51,59) also cite psychosis as a neuropsychiatric symptom related with COVID-19 and, apparently, a potentially strong relationship between coronavirus infection and psychosis exist. Currently, data on neuropsychiatric symptoms in people with COVID-19 are still limited due to the lack of long-term analyzes of the consequences of this pandemic.

A review (18) carried out on neuropsychiatric aspects of the COVID-19 pandemic shows that the neuropsychiatric sequelae are still unclear. However, there is growing concern about a wave of neuropsychiatric burden. Such neuropsychiatric manifestations include delirium, cognitive impairment, mood swings, insomnia, suicide, and psychosis. Existing evidence suggests that 0.9 to 4% of individuals infected with SARS-CoV-2 develop disorders of the psychotic spectrum. Psychosis can be secondary to viral diseases, treatments, increased psychosocial stress during the pandemic (18,26,30,51), and immune mechanisms (31).

Regarding the sociodemographic characteristics associated with neurological/neuropsychiatric manifestations in people with SARS-CoV-2 infection, authors claim that elderly (6, 11, 12, 30, 32, 39, 43, 60, 63) and women (20, 23, 29, 69-70) 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 (11, 23, 34, 35, 39, 40, 43, 42, 45, 60, 63), pre-existing neurological diseases such as Parkinson's disease or dementia (37, 65), multiple sclerosis (50), use of immunosuppressive treatments for autoimmunity-mediated deminielizing diseases (65), smoking (21), and pre-existing psychiatric diseases (54).

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 (12, 14, 15, 16, 32, 33, 40, 46, 63), movement of the virus to the brain via the cribriform plate close to the olfactory bulb (14, 16, 33, 34 40, 46, 63), trans-synaptic viral spread from the lung and lower respiratory airways to the brain (12, 14-16, 34, 45, 63), lymphatic pathway (12, 46), immunological mechanisms (11, 15, 16, 61), hypoxia (4, 11 , 13, 16, 61), and inflammatory factors (16, 34).

Neuroprotective mechanisms that decrease the occurrence of neuropsychiatric signs and symptoms

Authors (12) 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.

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 (62).

Another study (36) 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.

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.

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

Some observational studies (9, 17, 29, 30, 39, 52) have shown that anosmia and hyposmia start in the acute phase of the disease and persist in up to 2 to 3 weeks.

Authors warn that the permanence of several neurological symptoms after SARS-CoV-2 infection can be prolonged, including cognitive deficits (28, 36), motor deficits (36), psychiatric symptoms (18, 30, 36), cutaneous hyperesthesia (49), and Guillain Barré syndrome (12).

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 (13,32) .

Authors (4) present a detailed summary of the physiological mechanisms that explain the CNS and PNS compromise related to the SARS-CoV-2 virus, as follows: (a) hypercoagulabity - 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 (29, 69).

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. It is also noteworthy that the development of neuropsychiatric symptoms is not related only to the neurotropism of the SARS-CoV-2 virus, but also due to the impacts of social isolation (30).

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 (31,76). 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 (77).

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 (24).

IMPLICATIONS FOR PRACTICE

Limitations

The studies included in this systematic 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.

Gaps in knowledge

This systematic 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.

Future research

This systematic 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.

CONCLUSIONS

The studies included in this systematic 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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