Neurocovid, Causes and Consequences of a Differentiated Expression of COVID-19: A Literature Review

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Abstract

Introduction: COVID-19 mortality has been considerably reduced; however, diverse symptoms that persist in individuals who have been infected have highlighted the importance of a new line of care for the disease: the post-COVID-19 condition.

Objectives: This review aims to contribute to the planning of sound study designs and the collection of clinical data in future studies.

Methodology: This study is a narrative literature review, which used the DeCS/MeSH descriptors "Neurocovid", "Manifestations" and "Inflammation" to search the PubMed, ScienceDirect and VHL databases.

Results: When analyzing the auxiliary neurological tools that were used to elucidate the NeuroCOVID clinic, three articles reported the use of neuroimaging, Magnetic Resonance Imaging (MRI) and/or Computed Tomography (CT). Of these, only two showed findings and, in most cases, they were normal.

Conclusion: The study shows that certain patients who recover from COVID-19 may nevertheless have lasting neurological sequelae that may not have been considered in the acute course of the disease. Therefore, long-term monitoring of neurological deficits is fundamental in the clinical approach and may represent a better prognosis for individuals affected by the complications of neuroCOVID-19.

Keywords: Covid-19; Neurocovid; Neurological signs; Sars-COV2.

Introduction

The impact of the COVID-19 pandemic on health systems around the world has been considerable, given the more than 690 million cases diagnosed and the more than 6.8 million deaths recorded, making SARS-CoV-2 the leading cause of death worldwide today. The main clinical manifestation of SARS-CoV-2 is involvement of the respiratory tract, ranging from upper tract infections to severe pneumonia and death [1]. However, extrapulmonary manifestations have been constantly reported, revealing the virus's capacity for renal, gastrointestinal, cardiovascular and neurological involvement [2].

Since its discovery, several variants of the virus have been observed, including Alpha, Beta, Delta and Omicron, each with specificities regarding infection, mortality and the ability to spread and affect systems other than the respiratory system [3]. Currently, with the development of vaccines and their implementation in a significant part of the world's population, COVID-19 mortality has been considerably reduced; however, diverse symptoms that persist in individuals who have been infected have highlighted the importance of a new line of care for the disease: the post-COVID-19 condition.

Among the extrapulmonary manifestations, neurological involvement has been a constant concern during the course of the disease, given that one of the early manifestations is anosmia and dysgeusia [4]. The invasion of the nervous system by the virus has been the subject of studies, although one possible cause is the coexistence of ACE-2 receptors in both the respiratory tract and the nervous system. In the brain, the expression of these receptors occurs in excitatory and inhibitory neurons, as well as glial cells, such as astrocytes and oligodendrocytes, or invading endothelial cells. Although ACE-2 receptors are less present in the brain compared to the lung, there is a relevant presence in certain areas such as the olfactory bulb and piriform cortex, thus being fundamental in understanding the pathogenesis of neuro-COVID [5].

The most common forms of neuro-COVID include changes in taste and smell, dizziness, headache, vomiting, altered level of consciousness and seizures [5,6]; more serious manifestations include meningitis, Guillain-Barré syndrome, ischemic stroke and intracranial hemorrhage [7]. On the other hand, persistent post-covid manifestations include impaired sense of smell and taste, cognitive decline, headaches, difficulty concentrating, confusion, sleep disturbance and difficulty concentrating [8]. Despite the reports already recorded, there is a difficulty in fully understanding the neurological manifestations during and after coronavirus infection.

This is partly due to a number of factors such as the fact that some manifestations are non-specific, so symptoms such as headache and dizziness can occur due to systemic involvement or as a result of hospitalization and sedation; mild neurological disorders may not be reported in medical records in patients with a more severe condition; the studies do not include individuals who have not been hospitalized; finally,

complementary diagnostic tests, such as MRI, lumbar puncture and electromyography, were not widely available, especially during the critical phase of the pandemic [9,10].

In this sense, the central objective of this study is to analyze, through a robust literature review, information about the various neurological manifestations during and after SARS-Cov-2 infection in order to promote a better understanding of the prevalence of this important extrapulmonary manifestation. The specific objectives include: gathering a set of articles that address the proposed theme, organizing the data obtained in terms of the type of study, sample and clinical manifestation, and discussing the main findings by correlating the prevalence in the various studies analyzed.

Results

Methodology

This study is a narrative literature review, which used the DeCS/MeSH descriptors "Neurocovid", "Manifestations" and "Inflammation" to search the PubMed, ScienceDirect and VHL databases. The period was from 2020 to 2023.

In this way, 218 articles were found, according to the inclusion criteria, relevant aspects on the guiding question, such as the implications both for the individual health of patients who contract the disease, such as neurological and lasting affections and the repercussions for the state of health during the pandemic, as well as the main findings, treatments and prognoses of the pathology.

In the end, 100 articles were analyzed, of which 11 were selected to make up this review.
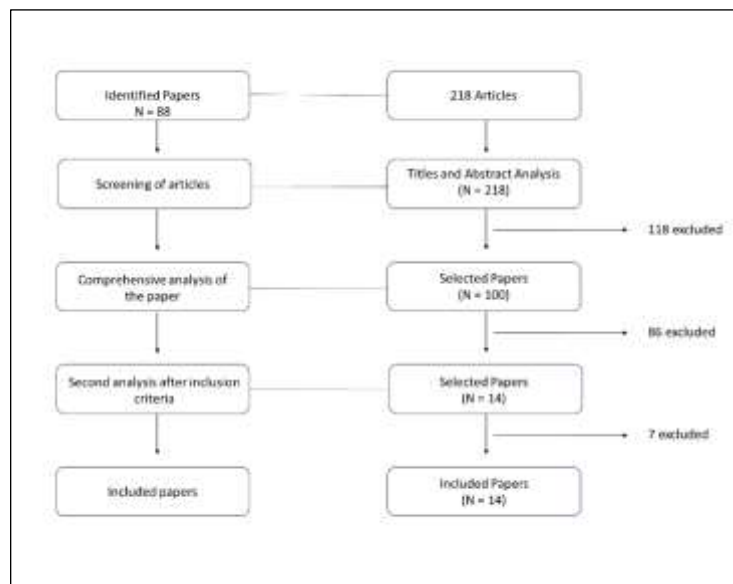

Figure 1: Flowchart of the article search and selection process.

After the first analysis, by reading the titles and abstracts and according to the inclusion

and exclusion criteria, 100 articles were selected. Of this total, after reading the

studies in full, 14 articles were selected to make up this review, of which, after a second analysis, five were excluded because they did not fit the selection criteria proposed by this study, culminating in seven eligible articles (Figure 1).

Of the studies excluded from the second analysis, two (28.6%) were correspondence articles, two (28.6%) were editorials, one (14.3%) was a commentary, one (14.3%) was an abstract, one (14.3%) was a draft article to be developed later (Table 1). To characterize the articles included, we used an instrument drawn up by the authors, containing information on the articles that were selected, such as authorship, year of publication, journal in which it was published, language, type of study and sample (Table 2). In addition, in order to extract and evaluate the data for later comparison between the studies, a table was created containing information on the objective and results found in each article, according to the authors (Table 3).

In this sense, when analyzing the seven articles eligible for this review, it was found that the publications ranged from 2020 to 2023, with a predominance (42.8%) referring to the year 2022. The samples were variable and involved patients with COVID-19, NeuroCOVID only and control groups, as well as presenting numerical variations in terms of patients, with a lower limit value equal to 30 and an upper limit value equal to 319. In terms of objectives, they all differed, although the majority (85.8%) described the neurological and/or neuropsychiatric manifestations resulting from COVID-19. Only one article showed the prognosis of patients, based on the role of neurotrophins and metalloproteinases in morbidity and mortality from COVID-19.

In addition, only one of the studies correlated specific changes in plasma and cerebrospinal fluid (CSF) with the pathological mechanisms underlying neurological sequelae (Tables 2 and 3).

Author and year of publication	Journal	Type of study
Ferrarese, C. et al., 2020	Neurological Sciences	Retrospective-prospective observational article project
Leal-Buitrago, A. et al., 2022	Journal of Clinical Neuroscience	Correspondence article
Helbok, R. et al., 2020	The Lancet	Correspondence article
Leonardi, M. et al., 2021	Journal of Clinical Neuroscience	Summary
Adlimoghaddam, A.; Albensi, B.; Eiser, A., 2022	Journal of Integrative and Complementary Medicine	Comment
Baig, A., 2022	CNS Neuroscience and Therapeutics	Editorial
Amanzio, M. et al., 2022	Frontiers	Editorial

Table 1: Characterization of the articles excluded in the second analysis (N=7), according to authorship, year of publication, journal, language, type of study, Brazil, 2023.

Author and year of publication	Journal	Type of study	Sample
Chaumont, H. et al., 2022	Revue Neurologique	Observational	60 patients with NeuroCOVID
Bhansali, S. et al., 2021	Journal of Clinical Neuroscience	Cross-sectional, descriptive, retrospectivo	162 patients with NeuroCOVID
García-Azorín, D. et al., 2021	Journal of Clinical Neuroscience	Observational, descriptive	233 patients with NeuroCOVID
Petrella, C. et al., 2023	Cells	Observational	30 patients with NeuroCOVID
Taruffi, L. et al., 2023	Neuropsychiatric Disease and Treatment	Observational, retrospective	103 patients with NeuroCOVID
Ariza, M. et al., 2022	Frontiers	Observational, retrospective	319 CPC patients and 109 controls
Etter, M. et al., 2022	Nature Communications	Prospective cross-sectional	40 NeuroCOVID patients and 50 controls, 25 with non-MS inflammatory disorders and 25 healthy individuals

Table 2: Characterization of the selected articles (N=7), according to authorship, year of publication, journal, language, type of study and sample, Brazil, 2023. Legend: CPC-post-COVID-19 condition; MS-Multiple Sclerosis.

Among the neurological and neuropsychiatric symptoms mentioned in the articles, the most prevalent were dysfunction of smell and taste, headache, encephalopathy and encephalitis, neuropsychiatric symptoms, mainly anxiety and depression, cognitive disorders, especially memory impairment, and stroke, as shown in Table 2. On the other hand, the other symptoms shown in Table 4 were manifested by a few patients in specific studies.

Furthermore, when analyzing the auxiliary neurological tools that were used to elucidate the NeuroCOVID clinic, three articles reported the use of neuroimaging, Magnetic Resonance Imaging (MRI) and/or Computed Tomography (CT).

Of these, only two showed findings and, in most cases, they were normal. CSF analysis was carried out in two studies. In both, abnormalities were observed in terms of increased protein concentration, although this was not present in all patients. Another finding that differed from the normal range for CSF was pleocytosis, shown in only one article.

Discussion

Since the COVID-19 pandemic, the neurotropism of the Sars-CoV-2 virus has been the subject of study for renowned neurologists, given that neurological symptoms are the most frequent extrapulmonary symptoms.

It is known that the spike protein and ACE receptors are the main mechanism of cell infection, however, the gateway of the virus to the nervous system is still under investigation, hypotheses such as the olfactory pathway, the vascular endothelium,

the migration of leukocytes in the bloodstream and infected synapses are analyzed, and the fact that the ACER receptor is also present in the blood-brain barrier further reinforces this hypothesis. The association with peripheral inflammation, neuroinflammation according to NeuroCOVID severity classes and COVID severity was investigated. The research in question identified alterations in the cerebrospinal fluid and plasma that point to the pathological mechanism related to the neurological sequelae of COVID-19.

A plasma cytokine storm combined with a non-inflammatory CSF profile was observed and class III patients had elevated levels of protein, glucose, and lactate in the CSF, correlating with severity.

The elevation of lactate in class III patients points to potential cerebral hypoxia and is correlated with the fact that patients in this class have had strokes or cerebral hemorrhages. Therefore, the main determinants of the severity of NeuroCOVID are peripherally induced cytokine disturbances, breakdown of the BBB with penetrating polyreactive autoantibodies, microglia reactivity and neuronal damage resulting in potential volumetric loss of gray matter, possibly explaining short- and long-term COVID-19-related neurological impairment.

Another study set out to investigate possible biomarkers in the serum of elderly men affected by COVID-19 at the beginning of the hospitalization period, such as NGF, BDNF, MMP-2, MMP-9 and NFL. Serum NGF values showed no significant differences between the patient groups (deceased, ICU, and ward) and controls. However, serum BDNF values were significantly higher in the control group compared to the COVID-19 groups. In addition, serum NFL values were significantly higher in deceased patients compared to the other groups.

When analyzing the frequency of neurological symptoms, anosmia is often associated with the acute phase of COVID due to a tropism of the olfactory pathways, being present in all studies, followed by headache, myalgia and psychiatric disorders. It is worth corroborating that in addition to neurological symptoms, studies show that patients' executive function, cognition and memory have been affected.

According to the study, 36% of patients developed neurological manifestations in the acute phase of COVID-19, most of which were mild, such as headache, myalgia, mental confusion, dizziness, anxiety, depressive symptoms, and cognitive deterioration.

In addition, it identified age as one of the predictors of residual neurological impairment after COVID-19, associating it with neurological manifestations, including CNS (83.3%), NNCC (11.7%) and PNS (8.3%). Among the neuropsychiatric manifestations were memory complaints (34%), anxiety (28%) and depression (16%). It also reports that 50% of the patients in the study remained with residual manifestations for a further 6 months after the acute phase of the disease, severely impacting on quality of life, in addition to the severity of the disease being strongly related to the development of anxiety disorders.

According to the study, which analyzed 162 patients with NeuroCOVID in a tertiary neurology center in Calcutta, when investigating the temporal association between neurological and respiratory characteristics, it was observed that 73.5% of the patients included in the study were diagnosed exclusively with NeuroCOVID, without febrile or respiratory manifestations. Of the patients who presented neurological symptoms, 44.4% presented an exacerbation of a previous neurological disease, while the majority (71%) presented a new neurological manifestation.

Among these manifestations, the involvement was of: CNS (56.2%), PNS (6.8%) and other non-specific (8%) In addition, it has been observed that stroke and encephalopathy are the most prevalent neurological parainfections in the acute phase of covid in the Indian population. in the American and Chinese population 42.5% and 36.4%, respectively, patients presented with NeuroCOVID without fever and signs of respiratory failure.

According to the descriptive observational study that analyzed 233 patients with NeuroCOVID according to the results of the NeuroCOVID Registry of the Spanish Society of Neurology, 27% of patients presented with stroke, having a major impact on quality of life and demonstrating a strong association of COVID with neurological manifestations.

In addition, patients had neuromuscular symptoms (23.6%), altered mental state (23.6%), anosmia (17.6%), headache (12.9%) and epileptic seizures (11.6%). Some of the patients (33%) had persistent neurological symptoms. The study in question brings a new perspective when analyzing demographic variables. Most of the patients were men and 13.3% were healthcare workers. The neurological manifestations were diverse and persisted in 33% of the patients, the main ones being anosmia, myalgia, and headache.

According to the study that analyzed 103 patients and the neurological manifestations post COVID-19, it was observed that part of the COVID patients (32%) had a neurological disease and others (16.5%) had a psychiatric condition.

The most frequent manifestations reported were fatigue (56%), olfactory/palate dysfunction (56%), headache (46%), cognitive disorders (45%), sleep disorders (29%), changes in sensitivity (28%), dizziness (7%) and tremor (7%). The neuropsychological assessment carried out on 30 patients revealed alterations in executive functions (20%), memory (37%), depression (30%) and anxiety (27%). Brain MRI was performed in 41 cases and revealed non-specific abnormalities in only 4 cases.

This study analyzed cognitive impairment in post-COVID patients and compared them with a control group by applying cognitive tests such as the MoCa and Dsst and phonetic fluency. It found that post-COVID patients had worse global cognitive function than the control group, such as deterioration in executive function, memory, attention, learning, processing speed, language, and long-term memory.

In general, the affected group showed neuropsychological symptoms compatible

with moderate executive dysfunction syndrome. The MoCA test assesses cognitive function while the Dsst assesses brain damage. Among the neuropsychiatric symptoms, the most commonly reported were cognitive complaints (38.6%), memory deficits (34.5%), depressive manifestations (31.7%) and anxiety (30.7%). The general symptoms most often described in the post-COVID condition were fatigue (65.5%), joint and body pain (43.9%) and headache (43.3%).

When addressing the causes of such manifestations, they may be related to the host's immune response; in the case of myalgia and headache, they are probably related to the release of cytokines and inflammatory agents. An important consideration is that the systemic consequences of the infection such as hypoxia, acute kidney injury, liver failure and hydroelectrolytic disturbance, as well as the drugs used in the treatment can act in the pathogenesis of neurological manifestations by altering the mental state and provoking seizures. Therefore, COVID should be included in the radiological and clinical differential diagnoses.

Furthermore, when analyzing the frequency of neurological manifestations in the studies, it was observed that all of them cited anosmia and only 1 study did not report headache, showing anosmia and headache as the main symptoms of NeuroCovid. It is important to note that neuropsychiatric symptoms, cognitive disorders, strokes, and encephalopathy were manifested by a significant number of patients, infringing on the magnitude of COVID and its manifestations, and are the subject of further studies.

Author and year of publication	Objective	Results
Chaumont, H. et al., 2022	Assess functional outcome and identify risk factors for neurological sequelae after COVID-19 associated with neurological manifestations.	Most patients (49%) had a negative impact on their quality of life after NeuroCOVID, with age being a predictor of residual impairment. The main neurological manifestations affected the CNS (83.3%), NNCC (11.7%) and PNS (8.3%). Among the neuropsychiatric manifestations, memory complaints (34%), anxiety (28%) and depression (16%) were described.
Bhansali, S. et al., 2021	To describe the spectrum of NeuroCOVID on admission to a tertiary neurology center in Kolkata and to verify the temporal association between neurological and respiratory characteristics in individual patients.	Most of the patients included in the study (73.5%) were diagnosed exclusively with NeuroCOVID, with no febrile or respiratory manifestations. Some patients (44.4%) had an exacerbation of a previous neurological disease, while the majority (71%) had a new neurological manifestation. Among these manifestations, the involvement was of: CNS (56.2%), PNS (6.8%) and other non-specific (8%).
García-Azorín, D. et al., 2021	Present the results of the NeuroCOVID Registry of the Spanish Society of Neurology and discuss the clinical implications for the management of NeuroCOVID	Among the 233 NeuroCOVID patients, the most commonly reported neurological manifestations were: Stroke (27%), neuromuscular symptoms (23.6%), altered mental state (23.6%), anosmia (17.6%), headache (12.9%) and epileptic seizures (11.6%). Some of the patients (33%) had persistent neurological symptoms. The majority of patients (91.2%) received treatment with chloroquine/hydroxychloroquine

		(89.0%), lopinavir/ritonavir (63.0%), corticosteroids (37.0%) and azithromycin (29.4%).
Petrella, C. et al., 2023	To investigate NGF, BDNF, MMP-2, MMP-9 and NFL in the serum of elderly men affected by COVID-19 at the beginning of the hospitalization period.	Serum NGF values showed no significant differences between the patient (deceased, ICU and ward) and control groups. Serum BDNF values were significantly higher in the control group compared to the COVID-19 groups. Serum NFL values were significantly higher in deceased patients compared to the other groups.
Taruffi, L. et al., 2023	Describe the neurological manifestations of patients with COVID-19.	Part of the COVID patients (32%) had a neurological illness and others (16.5%) had a psychiatric condition. The most frequent manifestations reported were fatigue (56%), olfactory/palate dysfunction (56%), headache (46%), cognitive disorders (45%), sleep disorders (29%), changes in sensitivity (28%), dizziness (7%) and tremor (7%). The neuropsychological assessment carried out on 30 patients revealed alterations in executive functions (20%), memory (37%), depression (30%) and anxiety (27%). Brain MRI was performed in 41 cases and revealed non-specific abnormalities in only 4 cases.
Ariza, M. et al., 2022	To describe cognitive dysfunctions in post-COVID patients and compare them with a control group. In addition, to compare objective performance in individuals with and without subjective cognitive complaints.	The most commonly described general symptoms in the post-COVID condition were: fatigue (65.5%), joint and body pain (43.9%) and headaches (43.3%). Among the neuropsychiatric symptoms, the most reported were: cognitive complaints (38.6%), memory deficits (34.5%), depressive manifestations (31.7%) and anxiety (30.7%).
Etter, M. et al., 2022	Characterize the immune mediators in the CSF and plasma of clinically well-characterized NeuroCOVID patients and correlate the findings with brain imaging data.	The main determinants of severe NeuroCOVID are: peripherally induced cytokine disturbances, BHE breakdown with penetrating polyreactive autoantibodies, microglia reactivity and neuronal damage resulting in potential gray matter volume loss, possibly explaining short- and long-term COVID-19-related neurological impairment. Plasma cytokine storm combined with a non-inflammatory CSF profile was observed and class III patients had elevated CSF protein and lactate levels, correlating with severity.

Table 3: Description of the objective and results of the selected articles, Brazil, 2023. Legend: NGF-Nerve Growth Factor; BDNF-Brain-Derived Neurotrophic Factor; MMP-Matrix Metalloproteinase; NFL-Neurofilament Light Chain; CNS-Central Nervous System; NNCC-Cranial Nerves; PNS-Peripheral Nervous System; CVA-Cerebral Vascular Accident; MRI-Magnetic Resonance Imaging; CSF-Cerebrospinal Fluid; BHE-Blood-Brain Barrier.

Analysis of the results allowed the neurological manifestations to be divided into five categories: central nervous system (CNS) involvement, peripheral nervous system (PNS) involvement, cranial nerve involvement, non-specific neurological manifestations, and neuropsychiatric manifestations (Table 4).

SNC	SNP	NNCC	MNI	MNPS
Encephalopathy; Encephalitis; STROKE; Cerebellar Ataxia; Meningitis; Meningoencephalitis; Epileptic seizure; Expansive Intracranial Lesions; Dementia Language disorders;	SBG; PDIC; Neuropathic pain; Neuromuscular disorders; Myasthenic Crisis; Myasthenia Gravis; Mononeuropathy or Polyneuropathy; Plexopathy; Radiculopathy; Polyradiculoneuropathy	Anosmia; Hyposmia or Parosmia; Ageusia; Hypogeusia or Parageusia; Bulbar palsy; Cranial neuropathy	Confusion Fatigue Dizziness; Headache; Myalgia; Myoclonus; Subdural hematoma; Parainfectious parkinsonism; Tremor; Aqueductal stenosis; Myopathy	Memory problems; Persistent cognitive dysfunction; Anxiety; Depression; Altered mental state; Bipolar disorder; Sleep disorder; Executive dysfunction; Obsessive-compulsive symptoms; Psychotic symptoms

Table 4: Breakdown of NeuroCOVID manifestations, by affected territory, Brazil. Legend: CNS-Central Nervous System; PNS-Peripheral Nervous System; NNCC-Cranial Nerves; MNI-Nonspecific Neurological Manifestations; MNPS-Neuropsychiatric Neurological Manifestations; CVA-Cerebral Vascular Accident; GBS-Guillain-Barre Syndrome; CIDP-Chronic Inflammatory Demyelinating Polyneuropathy.

Clinical manifestations	Studies that have described this symptom[*]	%
Anosmia or Ageusia [**]	1, 2, 3, 4, 5, 6, 7	100%
Headache	1, 2, 3, 5, 6, 7	85,7%
Encephalopathy or encephalitis	1, 2, 3, 5, 7	71, 4%
Neuropsychiatric symptoms [***]	1, 2, 5, 6	57,1%
Cognitive disorder	1, 2, 5, 6	57,1%
AVC	1, 2, 3, 7	57, 1%

Table 5: Frequency of the main manifestations of NeuroCOVID addressed by the included studies, Brazil, 2023. ([*]) The articles were coded in numbers, following the order shown in Table 2. ([**]) The following variations were also considered: hyposmia, hypogeusia, parosmia and dysgeusia. ([***]) Legend: Stroke - Cerebral Vascular Accident.

Conclusion

NeuroCOVID is a syndrome with a complex invasion mechanism, with the SPIKE protein and ACE receptors being fundamental for the virus to reach the nervous system, as well as promoting neuroinflammation at these sites, in view of the breakdown of the BBB and the modulation of the inflammatory profile of the microglia presented in the articles analyzed. Thus, the identification and quantification of pro-inflammatory cytokines in plasma and proteins, such as lactate, in the CSF can be used as a guide to the severity of neural involvement, for a possible worsening of the clinical picture and more serious manifestations such as stroke and cerebral hemorrhage, being useful for patient follow-up.

In addition, studies on serum biomarkers such as brain-derived neurotrophic factor (BDNF) and neurofilament light chain (NFL) may represent predictors of the effects of neuroCOVID. However, in order to prove this, future studies are needed that include a

more significant sample group and greater diversity in terms of the gender and age range of the individuals analyzed, because the papers analyzed have not evaluated specific treatments for neurological symptoms. The data gathered in this study shows that neuroCOVID encompasses a wide range of neurological and neuropsychiatric manifestations. Among these, the main clinical findings are anosmia, ageusia, headache, encephalopathy, encephalitis, cognitive disorders and stroke; these manifestations, being the most commonly described, should always be taken into account when managing the patient and designing long-term therapy, considering that symptoms such as headache and cognitive disorders persist even after the acute condition has resolved.

In this sense, prospective cohort studies are essential for understanding possible long-term neurological sequelae. In addition, neuroCOVID carries a risk of long-term neuropsychiatric disability, making it relevant to address these symptoms when designing therapy. Other findings, as elucidated in Table 4, are of great value to clinical knowledge as a possible consequence of Sars-CoV2 infection; however, as they are less well documented, studies that reaffirm these correlations are necessary for a better understanding of the prevalence of these neurological symptoms. In addition, there are research opportunities that cross-reference the clinical courses reported here with the patient's profile, with the aim of obtaining a possible relationship between demographic factors and comorbidities that may predispose individuals with COVID-19 to certain neurological manifestations. Thus, this review shows that reports of neurological manifestations associated with COVID-19 are on the rise in scientific circles. It is clear, therefore, that mental health, biopsychosocial and neurological data should be collected on patient admission and analyzed to help understand the characteristics and severity of these extrapulmonary manifestations. In this sense, health professionals should pay attention to differential diagnoses and consider the various neurological outcomes of neuroCOVID. Latent inflammation should also be considered, which may be asymptomatic in the initial course of the disease, but may become evident in the long term, and this correlation is still in need of more in-depth studies.

Finally, this review aims to contribute to the planning of sound study designs and the collection of clinical data in future studies. In addition, the study shows that certain patients who recover from COVID-19 may nevertheless have lasting neurological sequelae that may not have been considered in the acute course of the disease. Therefore, long-term monitoring of neurological deficits is fundamental in the clinical approach and may represent a better prognosis for individuals affected by the complications of neuroCOVID-19.

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