REVIEW ARTICLE

REVISTA ENFERMAGEM ATUAL IN DERME

UNDERSTANDING NEUROLOGICAL MANIFESTATIONS INDUCED BY INFECTIONS BY THE NEW CORONAVIRUS: AN INTEGRATIVE REVIEW

COMPREENSÃO DAS MANIFESTAÇÕES NEUROLÓGICAS INDUZIDAS POR INFECÇÕES PELO NOVO CORONAVÍRUS: UMA REVISÃO INTEGRATIVA

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ABSTRACT

Objective: To understand the clinical neurological manifestations of patients with Coronavirus of Severe Acute Respiratory Syndrome 2 (SARS-CoV-2)/Coronavirus Disease 19 (COVID-19). **Methods:** This integrative review was conducted in June 2020, based on the guiding question "What are the neurological manifestations presented by patients with SARS-CoV-2/COVID-19?", based on the PICO strategy. The combination of words "SARS-CoV-2" AND "COVID-19" AND "neurologic manifestations" was used in the search in the databases Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Library of Medicine (PubMed), Scopus, and Web of Science. **Results:** Of the six articles included, four were in PubMed, and all had been published in international journals. Among the manifestations observed, olfactory and gustatory disorders stood out. Other manifestations observed ranged from myalgia, headache, and dizziness to encephalitis and Guillain-Barré syndrome. **Conclusion:** Neurological manifestations are present in patients with SARS-CoV-2/COVID-19, including those not hospitalized, highlighting olfactory and taste disorders. These may be associated with early and severe COVID-19, and their recognition in infection is therefore essential. Despite the occurrence of these manifestations, it is still necessary to investigate the pathogenic mechanisms and progression of the disease in the context of the Central Nervous System (CNS) and Peripheral Nervous System (PNS).

Keywords: Neurological Manifestations; Coronavirus Infections; Nursing; Pandemics; Review.

RESUMO

Objetivo: Compreender as manifestações clínicas neurológicas apresentadas por pacientes com coronavírus da Síndrome Respiratória Aguda Grave 2 (SARS-CoV-2)/Doença Coronavírus 19 (COVID-19). **Métodos:** Trata-se de revisão integrativa, conduzida em junho de 2020, com base na pergunta norteadora "Quais as manifestações neurológicas apresentadas por pacientes com SARS-CoV-2/COVID-19?", elaborada a partir da estratégia PICO. A combinação de palavras "SARS-CoV-2" AND "COVID-19" AND "neurologic manifestations" foi utilizada na busca em bases de dados Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Library of Medicine (PubMed), Scopus e Web of Science. **Resultados:** Dos 6 artigos incluídos, 4 constavam na PubMed e todos tinham sido publicados em periódicos internacionais. Dentre as manifestações observadas, as disfunções olfativas e gustativas foram as que se destacaram. Outras manifestações observadas envolveram desde a mialgia, dor de cabeça e tontura à encefalite e Síndrome de Guillain-Barré. **Conclusão:** Manifestações neurológicas estão presentes em pacientes com SARS-CoV-2/COVID-19, incluindo aqueles não hospitalizados, destacando as disfunções olfativas e gustativas. Estas podem estar associadas a um quadro de COVID-19 precoce e severo, sendo, portanto, importante o seu reconhecimento na infecção. Apesar da ocorrência dessas manifestações, ainda se faz necessária a investigação dos mecanismos patogênicos e progressão da doença no contexto do Sistema Nervoso Central (SNC) e Periférico (SNP).

Palavras-chave: Manifestações Neurológicas; Infecções por Coronavírus; Enfermagem; Pandemia; Revisão.

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INTRODUCTION

Identified since the 1960s, coronaviruses are enveloped RNA viruses from the *Nidovirales* order, *Coronaviridae* family and *Coronavirinae* subfamily, whose appearance in electronic microscopy is similar to a crown (Latin – *corona*)[1]. Able to infect animals, including birds, and human beings, they cause respiratory, gastroenteric, hepatic, and neurological disturbances[2,3]. Seven coronavirus strains are currently recognized as human pathogens[4].

In 2002, humankind experienced an outbreak caused by the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), which has, as primary/definitive host, the bat[5]. Beginning in Guandong, in southern China, the infection spread to Southeast Asia, Europe, South Africa, and North America[6,7].

In epidemiological terms, in July 2003, the World Health Organization (WHO) recorded 8,437 cases of SARS, with 813 deaths[6]. Although no other outbreak of the disease has been reported since that year[8], there isn't adequate knowledge about the pathology of SARS-CoV, hindering treatment choices and the development of vaccines[5].

Ten years after SARS-CoV, a new coronavirus was identified, with the dromedary as definitive host and Jeddah, in Saudi Arabia, as the first site of the disease[9]. Since that first report, cases of the disease, named Middle East Respiratory Syndrome (MERS), have been notified throughout the Arabian Peninsula, Asia, Europe, Africa, and the United States[9].

Specifically, MERS is a condition triggered by MERS-CoV, whose manifestation varies from asymptomatic to severe pneumonia, SARS, multiple organ failure, and death[10]. According to the literature, MERS-CoV was considered an epidemic threat to public health due to the millions of pilgrims from 184 countries who move to Saudi Arabia[9]. MERS-CoV is still circulating[7], and, in January 2020, a total of 2,519 occurrences of the infection and 866 deaths had been reported, especially in the Arabian Peninsula[4].

Similarly to SARS-CoV, MERS-CoV initially infects the lower respiratory tract[11] and can be transmitted via contact with an infected person or contaminated surface and object. Its pathology is unclear, hindering treatment and the development of vaccines[5].

In December 2019, in Wuhan, China, began an outbreak caused by a new type of coronavirus, named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV). A few months later, SARS-CoV-2 spread across all five continents, leading the WHO, in March 2020, to declare an international public health emergency due to its high capacity for asymptomatic dissemination and transmission[12]. Currently, there is strong evidence that the virus originated from bats[13].

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According to WHO data[14], until April 25th, 2021, were reported 146,054,107 cases of Coronavirus Disease 19 (COVID-19), infection caused by SARS-CoV-2, and 3,092,410 deaths, with greater incidence in America. According to the WHO, the United States, India, and Brazil are among the most affected countries, with 31,656,636, 16,960,172 and 14,237,078 confirmed cases of the disease, respectively.

Regarding SARS-CoV-2, this virus, although it has many genetic characteristics similar to MERS-CoV, shows elevated homology with bat SARS and SARS-CoV[15-16]. Like SARS-CoV and MERS, it can be highly fatal, initially affecting the upper and lower respiratory tract[11]. Its transmission occurs via droplets from the nostrils or oral cavity of infected people, externalized while speaking, exhaling, coughing, or sneezing. The virus can be transmitted indirectly, through contact with contaminated objects[17] and through the placenta[18].

Concerning its mechanism of action, SARS-CoV-2 binds to the angiotensin converter enzyme 2 (ACE-2) (expressed in epithelial tissue of the respiratory tract, endothelium, kidney, pulmonary parenchyma and small bowel cells)[18–20], through its Spike protein (S), a phenomenon followed by endocytosis and activation of this protein by the transmembrane serine protease 2 (TMPRSS2) (enzyme bound to the cell membrane located in the vicinity of ACE-2)[21].

Proteolytic cleavage of protein S by TMPRSS2 can also occur directly, fostering the fusion between the viral membrane and plasmatic membrane, releasing RNA from the virus into the cytoplasm. The RNA in the cytoplasm or endosome will activate nucleic acid detection systems, such as Toll-like receptors, triggering the activation of nuclear factor – κβ (NF-κβ) and the production of inflammatory mediators[21].

In cases of SARS-CoV-2 infection, its symptoms have varied from mild to severe manifestations[11], having, as typical presentation, fever, cough, myalgia, fatigue, and pneumonia[22]. Mild symptoms range from fever, cough, and shortness of breath to headache, loss of smell and taste, and sore throat. Severe symptoms include pneumonia, SARS, and sepsis[11]. Epidemiological data indicate that 80% of the contaminated population has mild to moderate atypical pneumonia, 15% progresses to severe pneumonia, and 5% may develop SARS[23].

Regarding neurological symptoms and signs, due to the similarity between SARS-CoV-2 and other beta coronaviruses, this type of manifestation and possible complications are not expected[24]. However, reports of these manifestations have been increasingly frequent[25], seeming to occur in approximately 36% of patients[26]. These include headache, dizziness, cerebrovascular events, anosmia, ageusia, and encephalopathy[25,27]. Despite these occurrences, studies related to SARS-CoV-2

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infection of the Central Nervous System (CNS) and Peripheral Nervous System (PNS) are limited[26].

In this sense, the literature has suggested the action of immune dysregulation induced by SARS-CoV-2, marked by T-cell depletion and overproduction of cytokines, in the origin of neurological symptoms[25,28]. Although neuroinvasivity has not yet been confirmed, hematogenous and neuronal retrograde dissemination are suggested as access routes of the virus to the CNS[28].

Thus, regardless of the means used by SARS-CoV-2 in the induction of possible neurological signs and symptoms, it is necessary to raise awareness of this reality as an attempt to recognize, treat and manage potentially fatal neurological complications[27].

In this perspective, Nursing stands out for the relevant role it plays in combatting COVID-19, providing assistance at the different levels of health care for the individual, family, and community[27]. In addition, this professional category more easily establishes a bond with the patient and offers them 24-hour assistance[27], allowing the detection of the most diverse presentations of the disease, including within the CNS and PNS.

In view of the above, the study aimed to understand the neurological manifestations presented by patients with SARS-CoV-2/COVID-19.

METHODS

This is an integrative review, an Evidence-Based Practice (EBP) method that contributes to the deepening of knowledge on a given subject. This method enables gathering and synthesizing results of primary studies, in a systematic and orderly manner, facilitating the incorporation of evidence for decision making and indicating possible gaps to be clarified in new research in the field[29].

The conduction of this review followed six stages, namely: - identification of the theme and elaboration of the research question; - establishment of criteria for inclusion and exclusion of studies; - categorization of studies; - evaluation of the studies included in the integrative review; - interpretation of the results; - synthesis of the knowledge of the main results evidenced in the analysis of the included articles[29,30].

The guiding question was elaborated based on the PICO strategy, an acronym which means “patient, intervention, comparison and outcome”. Based on this strategy, seen as a relevant resource for the formulation of research questions and search for evidence in the literature[30,31], the review attributed to the letter “P” patient with SARS-CoV-2/COVID-19, “I” and “C” were not applied and “O” was associated with neurological manifestations. Thus, the following guiding question was obtained: What are the neurological manifestations presented by patients with SARS-CoV-2/COVID-19?

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The search for and analysis of the articles took place in June 2020, through consultation at the Journal Portal of the Coordination for the Improvement of Higher Education Personnel (CAPES)/Ministry of Education (MEC), in the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Library of Medicine (PubMed), Scopus, and Web of Science.

For the article search, we used the controlled descriptor "Neurologic manifestations", indexed in the Health Sciences descriptors (DeCS), and the keywords "SARS-CoV-2" and "COVID-19". These terms were combined as follows: "SARS-CoV-2" AND "COVID-19" AND "neurologic manifestations".

As inclusion criteria, we considered articles available in full, in Portuguese, English and Spanish, which answered the guiding question. The exclusion criteria adopted comprised: repeated publications, dissertations, case studies and articles that were not related to the objective of the review. Study selection followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method – PRISMA[32].

For the data collection and analysis from the selected articles, a tool was created based on the study by Ursi[33], with the following items: codification of articles, authors, title of publication, country of publication, journal, database, objective, type of study, level of evidence and results. These steps were performed by four Nursing undergraduate students from a Brazilian university of international nature, independently and in order to allow greater reliability in the evaluation of the selected studies.

The evidences of the articles were categorized, based on the quality or strength of the evidence, which can be characterized in the following levels: level I - systematic review or meta-analysis; level II - randomized controlled study; level III - controlled study without randomization; level IV - case-control study or cohort study; level V - systematic review of qualitative or descriptive studies; level VI - qualitative or descriptive study; level VII - opinion or consensus[34].

RESULTS

Through the application of the search strategy, 1,679 papers were found, of which 986 had been published in 2020. Of these, 481 were in English, Spanish, or Portuguese. After reading the title and abstract, 460 publications were excluded because they were not related to the objective of the review and 7 were excluded due to duplicity. Of the 14 articles read in full, 5 were excluded because they were case studies and dissertations and 3 were excluded for not answering the guiding question. Thus, the review consisted of 6 articles (Figure 1).

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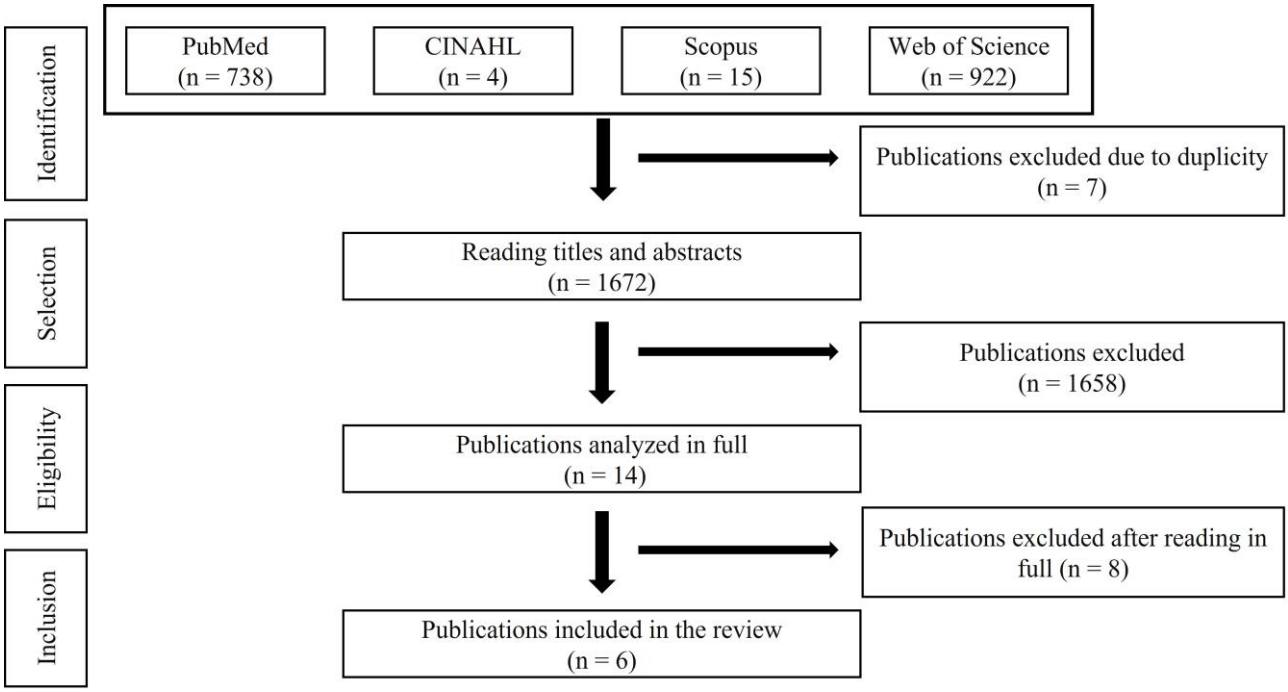
Figure 1 – Flowchart identifying the study selection process to make up the integrative review. Redenção - CE, Brazil, 2020



Source: The authors

Among the publications included, most were in the PubMed database (n = 4) and had been developed in Italy (n = 4). All articles were in English and had been published in international journals, especially in the journal European Archives of Oto-Rhino-Laryngology (n = 3) (Table 1).

Table 1 - Characterization of the publications included in the review, according to the number, database, title, country, and journal. Redenção - CE, Brazil, 2020.

N.	Database	Publication title	Publication country	Journal
1	PubMed	Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry	Spain	Neurology
2	PubMed	New onset of loss of smell or taste in household contacts of home-isolated SARS-CoV-2-positive subjects	Italy	European Archives of Oto-Rhino-Laryngology

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3	PubMed	Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real-life	Italy	European Archives of Oto-Rhino-Laryngology
4	PubMed	Subjective neurological symptoms frequently occur in patients with SARS-CoV-2 infection	Italy	Brain, Behavior, and Immunity
5	Web of Science	Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study	Italy, Belgium, and Spain	European Archives of Oto-Rhino-Laryngology
6	Web of Science	Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics	Switzerland	Otolaryngology–Head and Neck Surgery

Source: The authors

Regarding the objectives of the studies, they aimed to identify, quantify and characterize neurological manifestations related to SARS-CoV-2 infection, as well as to establish the recovery time and severity of these manifestations and associate them with classic symptoms of COVID-19. Regarding the type of study and level of evidence, most publications were descriptive studies (n = 4), and all had level VI of evidence (Table 2).

Table 2 - Characterization of the publications included in the review, according to the number, objective, type of study and evidence level. Redenção - CE, Brazil, 2020.

N.	Objective	Type of study	Evidence level
1	To determine the common neurological manifestations in hospitalized patients with SARS-CoV-2 and describe their main characteristics.	Observational and retrospective	VI

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2	To estimate the prevalence of impaired smell or taste in slightly symptomatic SARS-CoV-2 patients isolated at home.	Cross-sectional	VI
3	To investigate the recovery time for olfactory and gustatory dysfunctions in a cohort of patients with SARS-CoV-2 hospitalized at non-intensive care wards one month before the research.	Descriptive	VI
4	To identify and quantify the occurrence of subjective neurological symptoms in hospitalized patients with SARS-CoV-2 infection.	Observational and descriptive	VI
5	To investigate and characterize the occurrence of olfactory and gustatory dysfunctions in patients with SARS-CoV-2 infection confirmed by a laboratory.	Descriptive	VI
6	To characterize the prevalence, timing and severity of olfactory dysfunction reported by the patient, as well as other sinonasal symptoms and their association with classic symptoms of SARS-CoV-2, such as fever, cough, and shortness of breath.	Descriptive	VI

Source: The authors

Through detailed reading of the results presented by the articles, it was possible to identify neurological manifestations in patients with SARS-CoV-2, with the most reported being olfactory and gustatory dysfunctions. Other manifestations observed ranged from myalgia, headache, and dizziness to encephalitis and Guillain-Barré syndrome (Table 3).

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Table 3 - Characterization of the publications included in the review, according to the number and main results. Redenção - CE, Brazil, 2020.

N.	Main results
1	Out of 841 patients, 57.4% developed at least one neurological symptom. The most frequent symptoms were myalgia (17.2%), headache (14.1%), and dizziness (6.1%). Symptoms associated with cranial nerves were anosmia (4.9%) and dysgeusia (6.2%). Consciousness disorders were the most repeatedly observed neurological symptoms (19.6%). Other symptoms described were myopathy (1.3%), dysautonomia (2.5%), cerebrovascular diseases (1.7%), seizures (0.7%), movement disorders (0.7%), encephalitis (0.1%), Guillain-Barré syndrome (0.1%), and optic neuritis (0.1%).
2	Out of 296 interviewees who had home contact with patients infected with SARS-CoV-2, 74 reported loss of smell or taste. Among 121 submitted to serological test, 54 had a positive result for COVID-19 and 34 presented loss of smell and taste. Among the 175 who did not undergo the test, 67 had common symptoms of SARS-CoV-2 infection and 39 had loss of smell and taste.
3	Among 100 patients included in the study, 42 reported subjective chemosensory dysfunctions. Of these, 41 cited gustatory dysfunction, 29 olfactory and 28 both. All reported the occurrence of these symptoms in the first week or considered them as the first symptoms observed. The mean duration of olfactory and gustatory dysfunction was 18 and 16 days, respectively.
4	Of the 103 patients with confirmed SARS-CoV-2 infection included in the analysis, 94 reported at least one neurological symptom. Sleep impairment was the most frequent (49.51%), followed by dysgeusia (46.60%), headache (38.83%), and hyposmia (37.86%).
5	Among 417 patients, 85.6% and 88.0% reported the presence of olfactory and gustatory dysfunctions, respectively. There was a significant positive association between olfactory and gustatory dysfunctions. In 11.8% of cases, olfactory dysfunction appeared before other symptoms. The scores of the Questionnaire of Olfactory Disorders – Negative Statements were significantly lower in patients with anosmia compared to individuals with normosmia or hyposmia.

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6	The prevalence of olfactory dysfunction was 61.2% and its severity was significantly correlated with the severity of the loss of taste experienced by the patient. In 8.7% of the participants, olfactory dysfunction was experienced on the first day of SARS-CoV-2, becoming generalized on the third day of infection. Among patients with olfactory dysfunction, 95.2% had at least one of the following symptoms: fever, cough, or shortness of breath.

Source: The authors

DISCUSSION

This integrative review evidenced the neurological manifestations related to COVID-19, whose importance is grounded, in addition to the associated consequences, on the possibility of corresponding to the first signs of infection in so-called asymptomatic patients or patients with mild symptoms and occurring in individuals in the process of recovery from non-neurological manifestations a few weeks prior[35–38]. The knowledge of these manifestations by health professionals, especially nurses, may contribute to designing diagnostic and intervention strategies at different levels of disease severity, as well as evaluating the clinical consequences of infection[35].

After evaluating the number of studies included in this research, according to database, the highlight of PubMed emphasizes the fact that it is the largest database available since 1996, consisting of more than 26 million citations of Medline, life sciences journals, and online books. In addition, it displays access links to full texts in the citations of PubMed Central[39].

As for the journal of publication, the fact that all the articles included have been published in international journals can be justified based on the fact that COVID-19 did not begin in Brazil and became a global pandemic[40]. We can also propose, as possible reasons for that, the distribution range and the impact that a paper achieves when published in this type of journal.

In particular, for the largest number of productions included here that were published in the journal European Archives of Oto-Rhino-Laryngology, this finding can be explained if it is understood that it represents the Official Journal of the European Confederation of Otorhinolaryngology and Head and Neck Surgery, in addition to its agility in disseminating information related to basic sciences and diagnosis and treatment of head and neck diseases internationally[38].

It is also possible that this phenomenon occurred, considering that all the studies included in this review were

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developed in European countries, due to Europe having been the epicenter of SARS-CoV-2[41]. In this sense, it should be mentioned that the spread of the virus in Europe was marked by an atypical presentation of the disease, especially in patients with olfactory and gustatory dysfunction[42].

Concerning the country of publication, the emphasis on Italy can be based on the fact that it was the most affected European country at the beginning of the pandemic[14]. For the predominance of the English language among the articles of this research, this data can be understood considering that these journals publish their works in that language and because this is one of the strategies used for scientific internationalization[43].

Regarding the objectives, although the studies present different focuses, such as determining[44] (article n. 1), estimating the prevalence[42] (article n. 2), identifying[45] (article n. 4), characterizing[38] (article n. 5) and establishing the recovery time and severity of these manifestations and associating them to the classic symptoms of COVID-19[35] (article n. 6), we perceive the real need to understand the relationship between these manifestations and SARS-CoV-2 infection. Furthermore, it was noticeable that olfactory and gustatory dysfunction stood out among the studies' objectives[35,36,38,42].

Concerning the type of study, there was a predominance of descriptive studies. This result can be justified by the current and emerging nature of the disease, since descriptive studies aim to determine the distribution of health-related conditions, in order to describe a certain phenomenon based on its characteristics[46]. Despite its importance, this type of study does not aim to evaluate a possible relationship between the cause of the disease and its effect[47].

As for the evidence level, all studies were classified with low evidence level, signaling the need for further research with greater methodological rigor on neurological manifestations related to SARS-CoV-2 infection.

Through the analysis of the main results of the studies, it was observed that patients infected with SARS-CoV-2 presented, as more recurrent neurological manifestations, olfactory and gustatory dysfunction (articles n. 2-6). In this context, it is worth mentioning that olfactory dysfunction is a pathological alteration characterized by the partial or total inability to detect or distinguish volatile chemicals[48]. It is multifactorial and may be related to obstructive nasal and sinus diseases, upper respiratory tract infections, traumatic brain injury, aging, exposure to toxics and some medications, nasal or intracranial neoplasia, psychiatric pathologies, iatrogenic, and idiopathic or congenital causes[49].

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On gustatory dysfunction, it is characterized by loss or decrease in gustation, through the interaction between multicausative factors and sensory receptors of the oral cavity[49]. In addition to taste buds, gustatory dysfunction is directly related to chemical receptors, mechanoreceptors, thermoreceptors and nociceptors[50].

Regarding the mechanisms through which SARS-CoV-2 acts interfering in the neurological system of infected patients, two main routes of transmission are suggested: hematogenous dissemination and neuronal retrograde dissemination. The first is secondary to a viremia, which triggers Systemic Inflammatory Response Syndrome (SIRS). This fosters mechanisms of intracellular, paracellular and transcellular penetration through the blood-brain barrier. In the second, the invasion of the CNS occurs via transport of peripheral neurons invaded by the virus[4].

Specifically, for olfactory and gustatory dysfunction, the literature is unclear regarding pathophysiological mechanisms. According to Meini et al.[36] (article n. 3), SARS-CoV-2 infects host cells, including non-neuronal cells of the olfactory epithelium and oral mucosa (including the tongue), by binding to ACE-2, increasing des-Arg9-bradykinin levels and inducing inflammatory process. For gustatory dysfunction, bradykinin can trigger it through an inflammatory neurogenic mechanism or through excessive direct activity in the CNS[51].

It is also speculated that the infection of support cells and regenerative stem cells of olfactory neurons inhibits the function of the latter, triggering anosmia. Another hypothesis would be infection of the CNS by coronavirus, via cribriform plate, causing an inflammatory response capable of reducing sensitivity to smell[52].

For dysgeusia, it is speculated that high levels of pro-inflammatory cytokines, such as tumor necrosis factor – α (TNF-α), interferon – γ (INF-γ) and interleukin – 6 (IL-6), induced by COVID-19, may inhibit the proliferation of stem cells and decrease the half-life of mature cells of taste buds[52].

Thus, olfactory and gustatory dysfunction can be considered a marker of SARS-CoV-2 infection, especially in situations where the test capacity is limited[35].

In addition to these manifestations, the included studies revealed that patients infected with SARS-CoV-2 could present recurrent headache (articles n. 1 and 4), sleep impairment (article n. 4), myalgia and dizziness (article n. 1). As for headache, this symptom may be related to increased permeability of the blood-brain barrier due to cytokine production, triggering a neuronal disorder of inflammatory nature[44,53]. It could also result from direct invasion of the nerve endings of the trigeminal nerve in the nasal cavity by the virus, resulting in dysregulation of ACE-2 and angiotensin II[54].

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Regarding myalgia, this can be caused by the intense inflammatory response induced by SARS-CoV-2, which increases the levels of cytokines, including IL-6, whose positive regulation causes muscle and joint pain[55]. Another hypothesis associated with myalgia is based on the elevation of lactate dehydrogenase, due to the damage caused by the virus in muscle tissue, and lactate and decreased cytoplasmic pH and oxygen levels[56]. For dizziness, the literature points out, as possible mechanisms, direct invasion of the nervous system, hypoxia, hypercoagulopathy and immune-mediated insults[57].

Among other neurological manifestations presented in the articles, dysautonomia, conceptualized as the failure or hyperactivity of the Autonomic Nervous System (ANS)[58], when associated with hemodynamic instability in patients severely affected by COVID-19, may result from afferent baroreflex insufficiency secondary to SARS-CoV-2 infection and invasion of the nucleus of the solitary tract[58].

On cerebrovascular diseases, ischemic cerebrovascular accident, although the mechanisms involved are not yet clear, has been associated with a state of hypercoagulability[59]. As for intracranial hemorrhage, this has been related to the elevation of blood pressure as a consequence of the binding of SARS-CoV-2 to ACE-2[53].

As for convulsion, it can result from hypoxia, metabolic disorders, organ failure, and brain damage[60]. On encephalitis, characterized by inflammatory lesions in the brain[61], although its mechanism is not clear, it is suggested that it originates from an inflammatory response to SARS-CoV-2, capable of raising the levels of interleukins and ACE in the cerebrospinal fluid[62].

Concerning optic neuritis, it can occur if we consider that SARS-CoV-2 can be transported by the optic nerve[63]. As for Guillain-Barré Syndrome, considered as an autoimmune process that affects peripheral nerves and induces a demyelinating neuropathy[64], Morsy's hypothesis[65] suggests that the NCAM protein (neuronal cell adhesion molecule) is responsible for the development of the syndrome in patients with SARS-CoV-2, in the presence of HLA-A*68 and HLA-DQA1/HLA-DQB1.

Regarding myopathy, observed in patients with the severe form of COVID-19, its development has been attributed to the injury of peripheral nerves and striated muscle by the virus, as well as the presence of vascular events, both thrombotic and ischemic[66].

Concerning movement disorders, when sitting (twisted movements of the lower limb), walking (ataxic gait) or at rest (spasmodic movements in supine position), they may express an involvement of the CNS and PNS. As for sleep impairment, it may be associated with hospitalization, a phenomenon capable of triggering insomnia symptoms[67-68].

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REVISTA ENFERMAGEM ATUAL IN DERME

Regarding the limitations of the study, we can mention the small number of publications included in this review, despite a comprehensive search in four databases of international relevance. This phenomenon suggests the need to conduct more research on the theme addressed.

CONCLUSIONS

It can be concluded that neurological manifestations are present in patients with SARS-CoV-2/COVID-19, including those who are not hospitalized, with emphasis on olfactory and gustatory dysfunctions. These may be associated with early and severe COVID-19 conditions, and therefore their recognition in infection is important.

In addition to these dysfunctions, other neurological signs and symptoms, such as myalgia, headache, dizziness, and cerebrovascular diseases, are observed in patients with COVID-19. Regardless of this form of disease presentation, it should be considered, since it is capable of compromising the well-being and life of human beings.

Despite the occurrence of neurological manifestations induced by SARS-CoV-2, it is still necessary to investigate the pathogenic mechanisms and progression of the disease in the context of the CNS and PNS.

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