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REVIEW ARTICLE

Neurological manifestations in patients with COVID-19

Manifestaciones neurológicas en pacientes con la COVID-19

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ABSTRACT

Introduction: COVID-19 pandemic represents a challenge for healthcare systems, due to the impact on different systems, such as respiratory, cardiovascular and nervous systems.
Objective: to describe the neurological manifestations in patients with COVID-19.
Methods: a search for information was carried out in the PubMed/Medline, SciELO, EBSCO, Lilacs and Scopus databases. A search strategy was applied by combining terms and using Boolean operators. Thirty references were chosen.
Results: olfactory nerves and invasion of peripheral nerve terminals are suggested as routes of entry; the presence of severe neural symptoms associated with lesions of other organs and cytokine storm is also described. Headache was the most common neurological manifestation in patients with COVID-19, and rhabdomyolysis, acute hemorrhagic necrotizing encephalopathy, Guillain Barré syndrome, meningitis and encephalitis are rare neurological entities. In Guillain Barré syndrome, the literature suggests both a post infectious and para-infectious pattern.
Conclusions: COVID-19 is associated with different neurological manifestations, including headache, dizziness, vertigo, vomiting, and alterations of consciousness, stroke and others not so frequent. These symptoms as a whole should be evaluated by healthcare personnel, with a view to their rapid detection and management, in order to guarantee the disappearance of sequelae that reduce the quality of life of patients, as well as to reduce the associated mortality records.

Keywords: COVID-19; SARS-CoV-2; Nervous System Diseases.

RESUMEN

Introducción: la pandemia por la COVID-19 representa un reto para los sistemas de salud, debido a la repercusión en diferentes sistemas, como el respiratorio, cardiovascular y sistema nervioso.
Objetivo: describir las manifestaciones neurológicas en pacientes con la COVID-19
Método: se realizó una búsqueda de información en las bases de datos PubMed/Medline, SciELo, EBSCO, Lilacs y Scopus. Se empleó una estrategia de búsqueda mediante la combinación de términos y uso de operadores booleanos. Se seleccionaron 30 referencias.
Resultado: se sugieren como rutas de entrada los nervios olfatorios y la invasión en terminales nerviosas periféricas; de igual forma se describe la presencia de síntomas neurales severos asociados con lesiones de otros órganos y la tormenta de citoquinas. La cefalea constituyó la manifestación neurológica más común en los pacientes con la COVID-19, y la rabdomiólisis, la encefalopatía necrotizante hemorrágica aguda, síndrome de Guillain Barré, la meningitis y encefalitis constituyen entidades neurológicas de rara

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presentación. En el síndrome de Guillain Barré, la literatura sugiere un paradigma tanto postinfeccioso como parainfeccioso.
Conclusiones: La COVID-19 se asocia a diferentes manifestaciones neurológicas, entre ellas la cefalea, el mareo, el vértigo, los vómitos, las alteraciones de la consciencia, el ictus y otros no tan frecuentes. Estos síntomas en conjunto deben ser valorados por parte del personal sanitario, con vistas a su rápida detección y manejo, en post de garantizar la desaparición de secuelas derivadas y que reducen la calidad de vida del paciente, así como para disminuir las cifras de mortalidad asociadas.

Palabras clave: COVID-19; SARS-CoV-2; Enfermedades del Sistema Nervioso.

INTRODUCTION

Epidemics due to unknown emerging diseases test not only the technical and human capacity of healthcare professionals who directly care for the sick person, but also the integrity of health care systems and society in general. For an adequate understanding of these entities, a broad-range approach is needed that integrates the particularities that, otherwise, can only give a partial vision of the issue. These diseases generate an accumulation of questions to the scientific community, which need a rapid solution.[1]

On December 31, 2019, the Wuhan Municipal Health and Sanitation Commission (Hubei Province, China) reported 27 cases of pneumonia of unknown etiology with common exposure to a wholesale seafood, fish and live animal market in Wuhan City, including seven severe cases. On January 7, 2020, Chinese authorities identified as the causative agent of the outbreak a new type of virus of the *Coronaviridae* family that was later named *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2), causing *Coronavirus Disease 2019* (COVID-19); whose genetic sequence was shared by the Chinese authorities with the international scientific community on January 12 of the same year.[2]

Cases of COVID-19 were quickly reported in other countries in Asia, Europe and progressively in other regions of the world. On February 27, the first case in South America was confirmed in Brazil and two days later, the first case was also reported from Ecuador.[3] It was classified by the World Health Organization (WHO), on January 30, 2020, as a public health emergency of international concern; on March 11, 2020, COVID-19 was considered as a pandemic.[4,5]

Until February 7, 2021, 190 countries and 29 territories were reported with positive cases of COVID-19, with 106 677 368 confirmed positive cases and 2 326 819 deaths for a case fatality of 2,18 %. Of the total number of cases, 47 996 818 were from the Americas region (44,99 %).[6] On March 11, 2020, the first case of COVID-19 was confirmed in Cuba.[7] From that time to date, 33 484 confirmed patients have been registered, including 240 deaths.[8]

The COVID-19 pandemic represents an unprecedented international challenge given the daily increase in cases and deaths. This demands a rapid pace of scientific discovery from the clinical data generated, which will ultimately condition better modes of action in dealing with COVID-19.[8]

Huang et al.[9] identified that about 8 % of patients with COVID-19 reported the presence of headache; Cheng et al.[10] in a study of 99 patients reported that 8 % had headache, 9 % had altered consciousness and 11 % had myalgia. Mao et al. [11] published in JAMA Neurology in its April issue, the first report with a neurological approach.

The medical literature shows the existence of neurological symptoms in patients with COVID-19, which were directly related to the severity of the clinical picture, including: dizziness, headache, muscle damage, altered consciousness, hypogeusia, hyposmia, acute cerebrovascular disease, neuralgia, altered visual acuity, ataxia, and epileptic seizures.[3,12,13] This suggests that SARS-CoV-2 infection is associated with neurological involvement, with the central nervous system (CNS), and in particular the brain, being among the most affected structures.

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The study of the neurological signs and symptoms associated with COVID-19 allows a better understanding of this entity and therefore, a successful way to face it up. The timely recognition of these signs and symptoms, since they may occur in the absence of respiratory or gastrointestinal symptoms, is a positive factor in the early detection and isolation.[3]

Given the current importance of this topic, the lack of depth of the research carried out in the Cuban context and the need for neurologists and health care professionals in general to know about it, the present review was carried out with the aim of describing the neurological signs and symptoms in patients with COVID-19.

METHODS

A search for information was carried out in the PubMed/Medline, SciELO, EBSCO, Lilacs and Scopus databases.

The terms coronavirus disease 2019, Coronavirus Disease 2019, COVID-19, SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2, *sistema nervioso*, nervous system, *manifestaciones neurológicas* and neurological manifestations were used. To create the search strategy, the Boolean operators AND-OR were used, and the appearance of the terms in the title and abstract fields was conditioned. Articles in Spanish and English were chosen. The search resulted in the selection of 30 articles after reading them, which served as the basis for the present narrative review.

DEVELOPMENT

Coronaviruses are single-stranded RNA viruses; the term is due to the peculiar corona-like appearance of the virus envelope, which is visible by electron microscopy. Specific animal coronaviruses have been described affecting cattle, swine and poultry, as well as cats, dogs, camels and bats. At least seven types of coronaviruses are currently known to be capable of infecting humans, but probably all lineages are still far from being known. This is due to the remarkable genetic diversity and high capacity of coronaviruses to recombine, hence the emergence in recent years of variants capable of infecting humans.[13, 14]

SARS-Cov-2 virus is transmitted between humans by inhalation of the named Flügge droplets, produced by coughing and sneezing, as well as by direct contact with hands or fomites contaminated with these secretions followed by contact with the mucous membranes of the mouth, nose or eyes.[4,13] Infected droplets spread 1-2 meters, the virus remains on viable surfaces for up to 9 days under favorable atmospheric conditions, but is destroyed in less than a minute with common disinfectants such as sodium hypochlorite, alcohol solution or hydrogen peroxide.[14] This transmission by respiratory route has allowed the rapid and extensive spread of COVID-19 in the world, which in turn is the starting point for prevention measures against this emerging disease. Likewise, other routes have been defined, such as the oral fecal route[13,15] and the transplacental route[2,13].

Symptoms generally begin 2 to 7 days after exposure, although in some individuals it may take up to 14 days for symptoms to appear.[14,15] COVID-19 has a wide variability in symptoms, initial appearance of cases, and severity of disease. It has been reported that 80 % of those infected present with mild disease, 15 % with severe disease and 5 % with critical illness.[3,15] It is important to note that many of those infected may be asymptomatic,[4] which presents a problem for diagnosis, treatment, follow-up, as well as for stopping transmission of the disease.

The asymptomatic form and mild presentations are more common in children, adolescents and young adults, while severe forms are seen more in those over 65 years of age and in people with chronic conditions such as diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular or cerebrovascular disease, hypertension, among others.[15]

Although the main signs and symptoms are on the respiratory tract, there are other presentations such as gastrointestinal, cutaneous, renal, hematopoietic and cardiac. However, as the number of infections

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increases, it would be possible to observe other less common presentations, including those that could affect the nervous system.[3]

Several routes by which coronaviruses could enter the CNS have been demonstrated in animals. Among them, entry through the olfactory nerves has been observed, invading areas such as the brainstem and thalamus. Another route is invasion into peripheral nerve terminals and then gaining access to the CNS through a synaptic pathway from the respiratory system, once it has interacted with the Angiotensin Converting Enzyme 2 (ACE 2) receptor. Viral antigens have been detected in the brainstem, particularly in regions including the tractus solitarius and nucleus ambiguus. The nucleus tractus solitarius receives sensory information from pulmonary mechanoreceptors and chemoreceptors and respiratory tract; while efferent fibers from the nucleus ambiguus and nucleus tractus solitarius provide innervation to glands, airway smooth muscle and blood vessels. Such neuroanatomical interconnections could indicate that death in infected animals or even humans may be due to dysfunction of cardiorespiratory centers in the brainstem, suggesting that respiratory dysfunction in COVID-19 may have a neurogenic component.[15]

The presence of reported severe neural symptoms has been reported to be associated with lesions of other organs thus reinforcing the lethality of COVID-19. Autopsy studies performed on SARS-CoV-2 patients who evident neurological symptoms showed widespread lesions in the brain, mainly reflecting ischemic hypoxia lesions. Paradoxically, viral RNA was discovered at a lower frequency in brain tissue and cerebrospinal fluid (CSF), hence there is still much uncertainty regarding this new coronavirus.[15]

The direct action of SARS-CoV-2 on the CNS is not the only way in which this system becomes damaged by COVID-19; cytokine storm also seems to play an important role in this regard.[14] A case has recently been described of an adult woman diagnosed with COVID-19 who, after a few days of fever, cough and altered mental status, developed acute necrotizing hemorrhagic encephalopathy, a rare entity associated with intracranial cytokine storm and blood-brain barrier rupture, although without direct viral invasion.[16,17]

Drawing on previous evidence, it is known that chronic neuro-inflammation associated with elevated levels of cytokines/chemokines have been associated with the pathophysiology of some neurodegenerative diseases (NDDs) such as Parkinson's disease, Alzheimer's disease, Huntington's disease or amyotrophic lateral sclerosis. On many occasions, the immune mechanisms triggering the cytokine storm, typical of severe SARS syndromes, play a relevant role in the onset of many NDDs, as well as in their progression.[14,17]

A study by Xuy et al.[18] reported the presence of neurological alterations in 36.8% of patients. This study divided the neurological alterations into three categories: a- central nervous system symptoms (headache, dizziness, vertigo and vomiting, altered consciousness, ataxia, stroke, epilepsy, acute disseminated encephalomyelitis (ADEM), meningitis, and encephalitis), b - peripheral nervous system involvement (hypogeusia, hyposmia, visual symptoms, neuralgias), and c- musculoskeletal symptoms (Guillain-Barré syndrome). Additionally, neurological symptoms were more frequent in patients with severe disease compared to those with mild symptoms and have been reported in all age groups.

Central Nervous System Alterations

Headache has been the most common neurological symptom reported by COVID-19 patients. Between 8 % and 34 % of patients in several studies in China reported this symptom,[9, 18] with the intensity of the headache being generally mild, even though the clinical details are incomplete. These studies do not mention whether the patients had a previous history of primary headache (migraine) or meningeal signs.[19]

In the series of Guan et al.[20] 15 % of patients reported myalgias, 13,7 % had elevated creatine kinase levels (19 % in severe cases), and two cases of rhabdomyolysis (0,2 %) were reported in patients with non-severe COVID-19. Rhabdomyolysis, increased creatine kinase and multiple organ failure have also been reported as a late complication of COVID-19.[11]

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In addition to headache, vomiting and nausea associated with vertigo have been recurrent symptoms in patients with COVID-19, reported in 7 % and 9,4 %, respectively.[21] This symptom is not specific, which increases the diagnostic difficulty when the patient seeks medical attention, which is why in addition to routine protocols, neurologists should inquire about the medical and epidemiological history of patients, insisting on details under the current circumstances, especially in those who present febrile symptoms and/or contact with suspected or confirmed cases of COVID-19. For atypical cases, blood tests, reverse transcriptase polymerase chain reaction (RT-PCR) and chest CT scans should be performed.

Elderly patients at vascular risk appear to be at higher risk for cerebrovascular complications when they develop COVID-19 than younger persons without comorbidities.[21] In the series of cases of COVID-19 with neurological signs and symptoms of the Spanish Society of Neurology (SSN),[13] it was reported that 20 of 92 patients had ischemic stroke, although they did not describe the characteristics of these patients, they did consider ischemic stroke to be the second most frequent neurological sign with 22,8 %. These publications show that the concurrence of ischemic stroke and COVID-19 is not so infrequent.

Li et al.[21] conducted a retrospective study in a hospital in Wuhan showed that in 221 patients with COVID-19, 5,9 % had strokes, of which 11 (5 %) were ischemic, 0,5 % were cerebral thrombosis of the venous sinuses and 0.5% were cerebral hemorrhage. The risk factors for stroke were: advanced age, having severe forms of COVID-19, having a previous history of high blood pressure, diabetes mellitus, smoking or cerebrovascular disease, or having a marked inflammatory and procoagulant response.

The series of Mao et al.[11] describes 5 stroke patients (80 % ischemic), who had severe forms of COVID-19, with increased D-dimer levels, thrombocytopenia and multiple organ involvement. Regarding the pathophysiopathogenesis it is known that SARS-CoV-2 binds to ACE 2 receptors on endothelial cells, which can lead to increased blood pressure. Increased blood pressure together with the presence of thrombocytopenia and coagulation disorders is a factor that may contribute to the increased risk of both ischemic and hemorrhagic stroke in patients with COVID-19. Cytokine storm syndrome may be another risk factor for cerebrovascular disease.[22]

A case series of 13 patients with COVID-19 and stroke identified that 11 were ischemic.[19] An increased likelihood of cardiovascular risk factors and severe SARS-CoV-2 infection may be present in these patients.[22]

Other neurological entities that have been reported include possible central hypoventilation syndrome [21] in a 24-year-old female patient,[21] rhabdomyolysis in a 60-year-old man,[23] acute hemorrhagic necrotizing encephalopathy,[16] ; Guillain Barré syndrome (GBS) during COVID-19,[24] and the first case of meningitis and encephalitis associated with SARS-CoV-2 infection.[25]

Encephalitis should be included in the differential diagnosis along with other neurotropic viruses, such as the herpes simplex family, varicella zoster virus or West Nile virus, among others. Thus, patients with fever, headache, epileptic seizures, behavioral disorders and altered level of consciousness, should be appropriately studied in case of suspicion. However, except for an isolated communication reported in the medical literature, there is no evidence of encephalitis or meningitis due to SARS-CoV-2, or at least it does not seem to be a frequent direct complication of this virus. Data are recorded from CSF analysis and post-mortem brain samples, where all samples taken were negative by RT-PCR for COVID-19 virus.[21]

Moriguchi et al.[25] reported the first case of COVID-19-associated meningitis and encephalitis in a 24-year-old Japanese patient. The patient presented with loss of consciousness followed by seizures on the ninth day of a febrile illness. The patient presented with nuchal rigidity and lumbar puncture showed pressurized CSF (>320 mm H20) and mild pleocytosis of 12 mononuclear cells/µL. RT-PCR for SARS-CoV-2 was negative in the nasopharyngeal specimen, but positive in the CSF.

A letter to the editor published by Helms et al.[26] in The New England Journal of Medicine discussed the neurologic symptoms and signs present in a series of 58 patients admitted to an intensive care unit for acute respiratory distress syndrome due to COVID-19. Neurological symptoms or signs were observed in

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84 %, 65 % of patients had confusion, 69 % had agitation, 67 % had corticospinal tract signs and 36 % had dysjective syndrome. Cranial MRI showed leptomeningeal enhancement (8/13), perfusion alterations (11/11) and ischemic stroke (3/13). CSF was analyzed in 7 patients, with negative RT-PCR for SARS-CoV-2 in all cases.

Encephalopathy, a transient brain dysfunction syndrome manifesting as acute or sub-acute impairment of the level of consciousness, has occurred in patients with COVID-19. It constitutes a risk for an altered mental state associated with COVID-19, and is greater in persons of advanced age or with previous cognitive impairment, as well as in those with cardiovascular risk factors and/or previous comorbidities, hypoxia being the main factor responsible in such cases. It may also be due to toxic or metabolic causes or to the effect of some drugs.[27] There is a record of a case with COVID-19 which presented an encephalopathy picture, unable to follow verbal commands; the electroencephalogram showed diffuse slow waves in the bilateral temporal region. Pathological findings were cerebral edema in the absence of CSF swelling.[28]

Peripheral Nervous System Alterations

Anosmia and, secondarily, taste disorders appear to be common in persons with COVID-19, even in the absence of nasal symptoms; these may appear suddenly.[20] Anosmia or hyposmia are early markers of SARS-CoV-2 infection. This phenomenon may be caused by different factors, including cytokine storm or direct damage of olfactory receptor neurons located in the olfactory epithelium. The latter possibility is particularly likely due to the fact that cells located in the olfactory epithelium express both protein receptors required for SARS-CoV-2 infection in humans: ECA 2 and transmembrane serine protease 2 (TMPRSS2).[26]

The prevalence of olfactory and gustatory dysfunction has been analyzed in a registry of 417 patients with COVID-19 in 12 European hospitals. [28] Patients answered taste and smell disturbance questionnaires based on the nutritional and health examination survey and the short version of the olfactory disorders questionnaire. Olfactory and taste disorders were described by 85,6 % and 88 % of the patients respectively; olfactory dysfunction was the initial symptom (12 %), 18 % of the patients had no rhinorrhea or nasal obstruction, but 80 % had anosmia or hyposmia. It should be mentioned that anosmia is not specific to this infection.

In the 2003 SARS-CoV epidemic, a 27-year-old patient was described who developed anosmia 3 weeks after the onset of symptoms, with a normal brain MRI, which was interpreted as an isolated olfactory neuropathy. In the current SARS-CoV-2 pandemic, Mao et al.[11] described anosmia in 5,1 % of patients, and ageusia in 5,6 %.

In view of these findings and the experience of countries such as South Korea, China and Italy, where it is mentioned that up to one third of patients may present anosmia, an alert has been issued in cases of acute anosmia and it has been considered as one of the symptoms of COVID-19 infection, recommending isolation for 2 weeks. [26] The authors consider that anosmia or hyposmia and, secondarily, taste disorders are indeed primary symptoms associated with SARS-CoV-2 infection, so their early identification is of vital importance for the reduction of COVID-19 infections by establishing an early diagnosis.

GBS is a post-infectious inflammatory disease that has been associated with influenza, cytomegalovirus or Epstein Barr viral infections, and recently with new emerging viruses, such as Zika, Dengue or Chikungunya and SARS-CoV-2. Cases have also been reported in relation to other coronaviruses, such as Middle East Respiratory Syndrome (MERS).[21, 27]

A few isolated cases and small series of GBS or variants in COVID-19 positive patients have been published. Zhao et al. [24] reported a 61-year-old patient from Wuhan, with no general symptoms, but with positive nasopharyngeal RT-PCR. CSF showed albuminocytologic dissociation and RT-PCR was not performed on the CSF. The patient had GBS, but the causal relationship was not established and the authors argued for a para-infectious rather than post-infectious profile.

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Sedaghat et al. [29] reported an Iranian male patient, 65 years of age. Two weeks prior to hospitalization, he presented with cough and fever; RT-PCR on nasopharyngeal swab was positive, and thoracic computed tomography was characteristic. The neurophysiologic pattern was axonal and CSF study was not performed because the patient did not give consent. The authors stated that it is not known exactly whether antibodies against specific gangliosides are produced in COVID-19.

Another case[30] reported by the SEN corresponds to a 54-year-old patient with a history of hypertension, dyslipidemia, obesity, obstructive sleep apnea syndrome, hepatorenal polycystic kidney disease with stage 3b chronic renal failure and anterior cervical arthrodesis due to disc herniation. She came to the emergency department for 4 days of evolution of paresthesia initially in the fingertips of the hands and later of the feet, associated with progressive distal weakness. Lumbar puncture showed albuminocytologic dissociation, and with the clinical diagnosis of GBS with sensory-motor involvement, treatment with immunoglobulins (IVIG) was started. The patient showed progressive improvement until complete resolution of weakness after 10 days. Due to the epidemiological context, SARS-CoV-2 was considered as a possible trigger for GBS, and a PCR-RT was performed on nasopharyngeal swab, which was negative, but was positive after several days.

Since the beginning of the pandemic, several cases of GBS associated with COVID-19 have been described, but the pathogenic mechanism is still unknown. In most cases the viral picture presents prior to the neurological picture following the post-infectious paradigm;[30,19] however, in other cases it presents in an overlapping manner, suggesting the possibility of a para-infectious mechanism.[27]

In the current epidemiological context, the authors consider that it is necessary to maintain a high suspicion of SARS-CoV-2 infection in all cases of GBS, since systemic symptoms may be even more determinant than neurological symptoms in the prognosis of these patients. It is of great importance that in the current context of COVID-19 pandemic, neurologists and health care professionals in general pay close attention to all these issues and have a high index of suspicion, due to the fluency with which new information is reported in this regard.

CONCLUSIONS

COVID-19 is associated with different neurological signs and symptoms, including headache, dizziness, vertigo, vomiting, and alterations of consciousness, stroke and other not so frequent symptoms and sings, which should be evaluated by the healthcare personnel to their timely detection and management, to guarantee the attenuation of sequelae that reduce the quality of life of patients, as well as to reduce the associated mortality rates.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTION

All of the authors participated in the conceptualization, writing, revision of the draft and the writing-revision and edition of the original.

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