Afecciones, manifestaciones y repercusiones neurológicas del COVID-19.

COVID-19 conditions, manifestations, and neurological repercussions

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Abstract

Introduction: Severe Acute Respiratory Syndrome (SARS-CoV-2) is the pathological entity responsible for the current pandemic that not only generates a distinctive respiratory pattern but has also been associated with multiple mechanisms of central nervous system (CNS) invasion.

Objective: To determine the neurological conditions, manifestations and repercussions that can be caused by SARS-CoV-2 infection.

Methods: Review of the scientific literature of patients with SARS-CoV-2 infection, in whom the development of conditions, manifestations and neurological repercussions, selected outcome in the studies, presence of micro and macroscopic conditions of the CNS and peripheral (PNS) were evaluated.

Results: 40 articles were included where the family and structure of SARS-CoV-2, pathophysiological mechanisms, neurological clinical manifestations, and possible repercussions at the central nervous system level were analyzed.

Conclusions: SARS-CoV-2 is a pathological entity that is associated with

different mechanisms of neurological intervention, through direct infection to the CNS, secondary to a parainfectious and postinfectious process, related to cytokine storm syndrome, endothelial damage, thrombotic disorders, in addition to secondary to hypoxia, hypoxemia and multiple organ failure.

Keywords: SARS-CoV-2; infection; nervous system; pathophysiology; pandemic.

Resumen

Introducción: El Síndrome Respiratorio Agudo Severo (SARS-CoV-2) es la entidad patológica responsable de la actual pandemia que no solo genera un cuadro respiratorio distintivo sino que también se ha asociado con múltiples mecanismos de invasión al sistema nervioso central (SNC).

Objetivo: Determinar las afecciones, manifestaciones y repercusiones neurológicas que puede generar la infección por SARS-CoV-2.

Métodos: Revisión de la literatura científica de pacientes con infección por SARS-CoV-2, en quienes se evaluó desarrollo de afecciones, manifestaciones y repercusiones neurológicas, desenlace seleccionado en los estudios, presencia de afecciones micro y macroscópicas del SNC y periférico (SNP).

Resultados: Se estudiaron 40 artículos que analizaban la familia y estructura del SARS-CoV-2, mecanismos fisiopatológicos, manifestaciones clínicas neurológicas y las posibles repercusiones a nivel sistema nervioso central.

Conclusiones: El SARS-CoV-2 es una entidad patológica que se asocia a distintos mecanismos de intervención neurológica, por medio de infección directa al SNC, secundario a un proceso parainfeccioso y postinfeccioso, relacionado con el síndrome de tormenta de citoquinas, daño endotelial, trastornos trombóticos, adicionalmente de secundario a hipoxia, hipoxemia y fallo multiorgánico.

Palabras clave: SARS-CoV-2, infección, sistema nervioso, fisiopatología, pandemia.

Introduction

Covid-19, acronym of Coronavirus Disease 2019, emerged in Wuhan, China (1); it is a microorganism that by its genome sequencing and phylogenic analysis belongs to the betacoronavirus group, in the same subgenus as the Severe Acute Respiratory Syndrome (SARS) virus. The structure of the receptor-binding gene region is very similar to SARS coronavirus, it has been shown to use the same receptor, angiotensin-converting enzyme 2 (ACE2), for cellular entry (2). The Coronavirus Study Group of the Interna-

tional Committee on Taxonomy of Viruses has proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3, 4).

The outbreak of the virus began in the Asian continent in the province of Wuhan, where initially pneumonia cases began to be reported at the end of December 2019, finally, on March 11, 2020, the WHO declared the pandemic (4). 1'133,758 confirmed cases and 62,784 deaths have been reported, where the most affected continent is Europe with 621,407 confirmed cases and 46,416 deaths (5), data reported up to April 5, 2020.

Some Coronaviruses (SARS-CoV-2) were originally found to be zoonotic infections, limited only to their natural animal hosts, it has crossed the animal-human species barrier and progressed to establish zoonotic disease in humans (6, 7). As the outbreak progressed, person-to-person spread became the main mode of transmission on a continuous basis, in people with close contact (up to 6 feet or 2 meters as a maximum distance), through Flügge droplets, similar to the spread of influenza, such droplets can infect another person if it comes in direct contact with mucous membranes or infected surfaces (8).

The virus affects people of all ages; however, older and middle-aged adults are most commonly affected (9). Symptomatic infection in children is uncommon, and when it occurs it is usually mild, although severe cases have been reported (10).

Associations with different comorbidities have been found as risk factors for severe disease, including cardiovascular disease, diabetes mellitus (DM), arterial hypertension (AHT), chronic pulmonary disease, asthma, cancer, chronic kidney disease (CKD) (11), immunosuppression states, severe obesity (body mass index (BMI) ≥40) and liver disease (9). Additionally, patients with lymphopenia or elevated liver enzymes, lactate dehydrogenase (LDH), inflammatory markers (C-reactive protein [CRP], ferritin, D-dimer), troponin, creatine phosphokinase (CPK) and prolonged clotting times are at increased risk of presenting a severe respiratory syndrome (11).

Infected patients may present clinical manifestations such as fever, fatigue, and respiratory symptoms (dry cough, dyspnea or respiratory distress), some present pain, nasal congestion, rhinorrhea, odynophagia or diarrhea, in severe cases, it can cause pneumonia, severe acute respiratory syndrome and renal failure that can lead to the death (12).

It should be noted that the microorganism not only affects the respira-

tory system, but can also invade other organs (13), including the brain, facilitating the appearance of pathologies or neurological symptoms that could lead to the death of the patient, which is why it was decided to conduct this review in order to determine the conditions, manifestations and neurological repercussions that can be generated by SARS-CoV-2 infection.

Methodology

1. Type of study and population: A review of the scientific literature of patients with SARS-CoV-2 infection, in whom the development of neurological conditions, repercussions and symptomatology were evaluated.

2. Definition of the outcome: The outcome selected in the studies was the presence of alterations of the central nervous system (CNS) and peripheral nervous system (PNS), with the consequent clinical manifestations, evolution and repercussions or consequences that may be generated, based on the respective clinical and paraclinical findings.

3. Search strategy: A literature search was conducted between March 04 and May 01, 2020, in the following databases: Pubmed/Medline, Science Direct, Scopus, Embase, Direme, Redalyc and Scielo. The words used to perform the search were: (manifestations OR illness or repercussions) and (neurological OR neurology OR brain OR nervous system) and (coronavirus OR COVID-19 OR SARS-CoV-2).

4. Inclusion criteria: Systematic reviews, meta-analyses, cohort studies, cross-sectional studies, and relevant case reports. Articles that evaluate one or more of the described outcomes.

5. Exclusion criteria: Research other than those mentioned in the inclusion criteria. Articles that do not evaluate the described outcomes.

6. Restrictions used in the search: The literature search was limited to human effects, publications within the last year, and a language restriction was applied to English and Spanish.

7. Data extraction: Data extraction was performed by three (3) researchers belonging to the project, who as a search strategy carried out the identification and detection of the literature to be studied. Then, the articles were selected according to the title in order to choose those that were in line with the proposed objective. Subsequently, the abstracts of the selected research were evaluated and, finally, the complete articles were reviewed to be chosen and included in the present study. Once the research was selected, the specific characteristics of each one was extracted.

Results

For this literature review, 40 articles were selected that analyzed the family and structure of SARS-CoV-2, pathophysiological mechanisms, clinical neurological manifestations, and possible repercussions at the central nervous system level. The main findings are described in the discussion.

Discussion

a. Coronavirus family

Phylogenetic analyses of coronavirus genomes have identified Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) as a member of the family Coronaviridae, subfamily Orthocoronavirinae, genus Betacoronavirus (includes SARS-CoV, MERS-CoV) and subgenus sarbecovirus (14 - 16).

They have been called coronaviruses because of the crown of spikes observed around the virus in electron microscopy images; these spikes correspond to spike (S) glycoproteins, distributed throughout the viral surface (16).

SARS-CoV-2 is the seventh coronavirus known to infect humans; these include SARS-CoV, MERS-CoV and SARS-CoV-2, which can cause severe disease, while others such as HKU1, NL63, OC43 and 229E are associated with mild symptomatology (16 -18).

The bat coronavirus RaTG13 appears to be the closest relative of SARS-CoV-2, sharing more than 93.1% of the sequence in the spike-in protein (S) gene, whereas SARS-CoV and other SARSr-CoV share less than 80% sequence identity with SARS-CoV-2 (14, 15).

b. SAR-CoV2 structure

The virus is enveloped and contains single-stranded, unsegmented, positive-sense RNA. Two thirds of the viral RNA is located mainly in the open reading frame 1a/1b, and 16 unstructured proteins are encoded, which interfere with the innate immune response of the host. While the remaining part of the virus genome encodes four structural and essential proteins, among these the spike glycoprotein (S), responsible for the binding and fusion of the virus to cell membranes, as it binds to the host angiotensin-converting enzyme receptor 2 (ACE2), including its subunits S1, responsible for binding to the host cell receptor and the S2 subunit, responsible for the fusion of the virus with cell membranes; the membrane protein (M), which allows transmembrane transport of nutrients, release of the viral particle and eventual formation of its envelope; in addition, the nucleocapsid proteins (N) and envelope proteins (E) (16, 17).

Two notable genomic features have been established in SARS-CoV-2. The first of these is the optimization of spike (S) protein binding to the human ACE2 receptor. This explains the efficient transmission of human-to-human, as in SARS-CoV (16, 17, 19, 20).

The second genomic feature is the presence of a polybasic cleavage site at the junction of S1 and S2 (the two subunits of the spike (S) protein), through the insertion of 12 nucleotides, which led to the predicted acquisition of three glycans, allowing effective cleavage by furin and other proteases, influencing the determination of viral infectivity and host range (14, 16, 17, 20).

The receptor binding domain (RBD) in the spike protein is the most variable part of the coronavirus genome and six RBD amino acids have been shown to be critical for binding to ECA2 receptors (20).

Mutations in the receptor-binding domain of SARS-CoV-2. The receptor binding domain (RBD) in the spike protein is the most variable part of the coronavirus genome. Six RBD amino acids have been shown to be critical for binding to ACE2 receptors, and SARS-CoV-2 appears to have an RBD that binds with high affinity to human ACE2 (20).

c. Receptors and their association in the pathophysiological process of the CNS

Two key receptors for SARS-CoV-2 entry into the cell, ACE2 and transmembrane type II serine protease serine (TMPRSS2), have been identified across multiple tissues, including brain tissue (15, 21, 22). The only type of brain cell where both genes have been found to be expressed is the oligodendrocyte, so it could be expected that SARS-CoV-2 encephalitis is a predominantly white matter disease (21).

The spike S proteins of the virus uses its two subunits, the S1 and S2 subunit, to bind to the ECA-2 receptor of the target cell, the resulting complex is proteolytically processed by TMPRSS2 which increases cellular uptake of the coronavirus as it cleaves the ECA-2 receptor, allowing the spike S protein to become activated. Once the ECA-2 receptor is cleaved and the spike S protein activated, viral entry into the host cell is facilitated (15, 16, 22, 23).

Viral genomic RNA is released into the cytoplasm to allow the formation of polyproteins (pp) 1a and 1ab, the transcription of subgenomic RNAs and replication of the viral genome. Once the viral particles are structured, they are released from the cell and proceed to infect new ones, leading to a repetitive cycle that culminates in the recovery or death of the patient (16).

Entry of SARS-CoV-2 to reach the brain is achieved through the cribriform plaque, as ACE2 and TMPRSS2 have been detected in the nasal epithelium or via systemic circulatory spread following pulmonary infection (19, 22, 24). This possible neural pathway through the olfactory nerve should be considered, especially in patients with COVID-19 who in early phase present anosmia or ageusia (16, 25).

SARS-CoV-2 binds to any body cell that expresses ECA2 and TMPRSS on its surface, such as brain tissue, causing a systemic inflammatory response. This is initiated by a cytokine storm consisting of the release of large amounts of pro-inflammatory cytokines (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10) (16, 26, 27).

That is, it causes a violent attack of the immune system, causing multiple organ failure and death in severe cases of SARS-CoV-2 infection (16). Recently, a case was reported of a patient with acute necrotizing encephalopathy identified through imaging, diagnosed with COVID-19, a condition probably related to this cytokine storm that occurs within the CNS (15) (19).

Nerve diffusion is possible due to the polarization of neurons, a feature that gives them the capacity to receive and transfer information. This transport can be retrograde or anterograde and is facilitated by proteins called dynein and kinesin, which can be targets of viruses. Once the virus enters the CNS, it can generate alterations in neurons, as it has been identified in autopsies of SARS victims, neuronal histopathological changes at the level of the cortex and hypothalamus (19).

The olfactory pathway begins in the bipolar cells of the olfactory epithelium, from there its axons and dendrites extend to the olfactory bulb, making synapses with the cells of this structure. Subsequently, the cranial pair divides into two branches and goes to the olfactory nucleus located in the piriform cortex and to the dorsal nucleus of the raphe, the latter located in the brainstem; a nervous route that has been used by some coronaviruses in rodent models exposed to nasal inoculation (19).

Of this possible propagation mechanism, the presence of the virus in areas of the brainstem stands out, since this structure contains nuclei that regulate the respiratory rhythm. On the other hand, there is also the presence of ACE2 receptors in the cerebral vascular endothelium which, when invaded by the virus, reduces its functionality causing elevation of cerebral blood pressure and consequently, the rupture of blood vessels (19).

This suggests that respiratory distress is the result not only of inflammatory lung structural damage, but also due to the damage caused by the virus in the respiratory centers of the brain, making it difficult to patient management (19).

d. Neurological repercussions

Due to the fact that SARS-CoV-2 patients suffer severe hypoxia, this causes CNS damage, increases anaerobic metabolism in brain mitochondria; the accumulation of lactic acid can cause cerebral vasodilatation, neuronal and interstitial edema, cerebral blood flow obstruction and even headache due to ischemia and congestion; if this worsens abruptly in association with intracranial hypertension, brain function deteriorates, drowsiness, bulbar conjunctival edema and may even progress to coma (28, 29).

Autopsy reports have revealed the presence of edema in brain tissue, along with partial neuronal degeneration and meningeal vasodilatation in deceased patients (30).

Critically ill patients show elevated D-dimer levels and thrombocytopenia, which may be facilitated by the pathophysiology of the cytokine storm and this, in turn, generates a prothrombotic state, whereby it may facilitate acute cerebrovascular events (31, 32).

Several authors have suggested that respiratory failure, the main cause of death in patients with severe SARS-CoV-2, may have a central component and be due, in part, to a primary lesion of the respiratory center neurons in the brainstem (33, 34).

e. Neurological clinical manifestations

The entire pathophysiological process and alterations that occur in patients with SARS-CoV-2 infection can lead to systemic clinical manifestations (35). Patients with severe respiratory disease are more likely to develop neurological symptoms than patients with mild or moderate disease (36). Among those that may occur are those shown in Table 1.

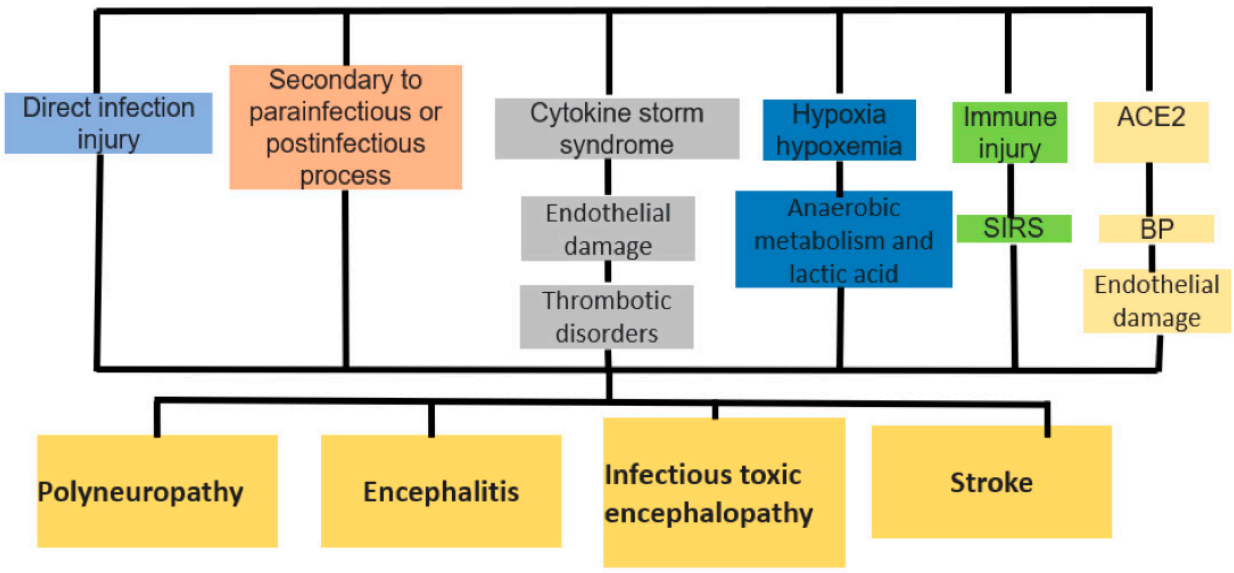
Table 1. Neurological manifestations of SARS-CoV-2

Author	Number of patients	Clinical manifestations
L. Mao, et al (37)	214 patients	Headache (25%); vertigo (17%); confusion (8%); ischemic CVA (3%); ataxia (0.5%); seizures (0.5%)
Y. Li, et al (38)	221 patients	Ischemic CVA (5%); cerebral venous thrombosis (0.5%); intracranial hemorrhage (0.5%)
Abdelnour L, et al (39)	1 patient	Lower limb strength decrease, hyporeflexia, ataxia and confusion.
Alberti P, et al (40)	1 patient	Guillain Barré Syndrome
Chen T, et al (41)	113 patients	Headache (11%); vertigo (8%)
Giacomelli A, et al (42)	59 patients	Anosmia y ageusia (34%)
Gilani S, et al (43)	8 patients	Anosmia (100%); ageusia (25%)
Kaya Y, et al (44)	1 patients	Confusion and visual agnosia
Lechien J, et al (45).	417 patients	Headache (45%); anosmia (86%); ageusia (89%)
Li Y, et al (38)	221 patients	CVA (6%)
Lodigiani C, et al (47).	338 patients	CVA (2.5%)
McAbee G, et al (48)	1 patient	Encephalitis and status epilepticus
Wang D, et al (32).	138 patients	vertigo (9%); headache (7%)
Wang Z, et al (50).	69 pacientes	Headache (14%) and vertigo (7%)
Enguita M, et al (51)	1 patient	Guillain Barré Syndrome
C. Huang, et al (52).	41 patients	Headache 8%
Pérez A, et al (53)	1 patient	Diplopía

Based on the data above, Figure 1 shows the possible repercussions at the level of the central nervous system and their clinical manifestations.

«Autopsy reports have revealed the presence of edema in brain tissue, along with partial neuronal degeneration and meningeal vasodilatation in deceased patients.

Figure 1. Possible mechanisms of neurological involvement.



Limitations: This manuscript has several limitations, among which the following are noteworthy: a) it is a review of a subject where heterogeneous population groups and studies are found; b) the sample sizes and follow-up times to patients were variable, so it is not possible to evaluate the temporality of exposure.

Conclusions

SARS-CoV-2 is a pathological entity that is associated with different mechanisms of neurological intervention, through direct infection to the CNS, secondary to a parainfectious and post-infectious process, related to cytokine storm syndrome, endothelial damage, thrombotic disorders and is secondary to hypoxia, hypoxemia and multiorgan failure.

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