Research, Society and Development, v. 9, n. 12, e4291210724, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i12.10724

COVID-19 neurological manifestations: a narrative review on the mechanisms, pathogenesis, and clinical management

Manifestações neurológicas da COVID-19: uma revisão narrativa nos mecanismos, patogênese e manejo clínico

Manifestaciones neurológicas de COVID-19: una revisión narrativa sobre los mecanismos, patogénesis y manejo clínico

Received: 11/29/2020 | Reviewed: 12/04/2020 | Accept: 12/08/2020 | Published: 12/13/2020

Letícia Nunes Campos
ORCID: https://orcid.org/0000-0002-8064-5698
Universidade de Pernambuco, Brasil
E-mail: leticia.campos@upe.br
Ana Clara Santos Costa
ORCID: https://orcid.org/0000-0003-4695-323X
Universidade de Pernambuco, Brasil
E-mail: anasantosc97@gmail.com
Débora Dantas Nucci Cerqueira
ORCID: https://orcid.org/0000-0003-4392-3991
Universidade de Pernambuco, Brasil
E-mail: deboradnucci@gmail.com
Gabriele Rodrigues Rangel
ORCID: https://orcid.org/0000-0002-7844-7457
Universidade de Pernambuco, Brasil
E-mail: gabrielle_rr@hotmail.com
Isabela Cristina de Farias Andrade
ORCID: https://orcid.org/0000-0001-7559-4075
Universidade de Pernambuco, Brasil
E-mail: isabela.andrade@upe.br
Stella Costa Batista de Souza
ORCID: https://orcid.org/0000-0002-0369-6563
Universidade de Pernambuco, Brasil
E-mail: stella94dv@hotmail.com

Julio Cesar Dias de Melo Silva
ORCID: https://orcid.org/0000-0002-8448-7498
Universidade Federal Rural de Pernambuco, Brasil
E-mail: julio.cesardias@outlook.com
Brayan Marques da Costa
ORCID: https://orcid.org/0000-0002-5341-6208
Universidade de Pernambuco, Brasil
E-mail: brayanmd.costa96@gmail.com
Sura Wanessa Santos Rocha
ORCID: https://orcid.org/0000-0003-2312-085X
Universidade de Pernambuco, Brasil
E-mail: sura.rocha@upe.br

Abstract

Coronaviruses are a large viral family, whose infections are recognized since 1960, varying from the common cold to more critical respiratory conditions. Regarding coronavirus 2019 (COVID-19), a wide spectrum of neurological manifestations among infected patients were reported, raising concerns whether Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) had tropism for the central nervous system. To clarify these questions, this bibliographic review was carried out by searching for articles based on national and international data during the period from December 2019 to June 2020. Thus, this review summarizes the current evidence on the transmission routes, focusing on the olfactory bulb and the hematogenic pathways, as well as the direct and indirect pathological mechanisms through which SARS-CoV-2 causes neurological damage. Moreover, clinical, laboratorial, and therapeutic aspects to manage patients with COVID-19 related neurological symptoms are outlined. Finally, development of treatments tackling specific structures and pathways related to viral entry and cardiovascular regulation on the brain are expected, in addition to monitoring of patients affected by the COVID-19 to assess long-term consequences on the nervous system.

Keywords: Central nervous system viral diseases; Encephalitis; SARS virus; Viral tropism.

Resumo

Os coronavírus são uma grande família viral, cujas infecções são reconhecidas desde 1960, variando desde o resfriado comum até condições respiratórias mais críticas. Em relação à

doença causada pelo novo coronavírus (COVID-19), um amplo espectro de manifestações neurológicas entre os pacientes infectados foi relatado, levantando questões se o coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2) tinha tropismo pelo sistema nervoso central. Para esclarecer tais questões, esta revisão bibliográfica foi realizada por meio da busca de artigos baseados em dados nacionais e internacionais durante o período de dezembro de 2019 a junho de 2020. Assim, esta revisão resume as evidências atuais sobre as vias de transmissão, focando no bulbo olfatório e na via hematogênica, bem como nos mecanismos patológicos diretos e indiretos pelos quais o SARS-CoV-2 causa danos neurológicos. Além disso, os aspectos clínicos, laboratoriais e terapêuticos para manejar pacientes com sintomas neurológicos relacionados a COVID-19 são descritos. Por fim, espera-se o desenvolvimento de tratamentos que abordem estruturas e vias específicas relacionadas à entrada viral e à regulação cardiovascular no cérebro, em conjunto ao monitoramento dos pacientes afetados pelo COVID-19 para avaliar as consequências de longo prazo no sistema nervoso.

Palavras-chave: Encefalite; Viroses do sistema nervoso central; Tropismo viral; Vírus da SARS.

Resumen

Los coronavirus son una gran familia viral, cuyas infecciones son conocidas desde 1960, y varían desde el resfriado común hasta afecciones respiratorias más críticas. Con respecto a la enfermedad del coronavirus 2019 (COVID-19), se mostró un amplio espectro de manifestaciones neurológicas entre los pacientes infectados, lo que generó inquietudes sobre si el virus del síndrome respiratorio agudo severo tipo-2 (SARS-CoV-2) tenía tropismo por el sistema nervioso central. Para aclarar tales interrogantes, esa revisión bibliográfica fue realizada a través de la búsqueda de artículos en base a datos nacionales e internacionales durante el periodo de Diciembre de 2019 a Junio de 2020. Así, esta revisión resumen la evidencia actual sobre las vías de transmisión, centrándose en el bulbo olfatorio y las vías hematogénicas, así como los mecanismos patológicos directos e indirectos a través de los cuales el SARS-CoV-2 causa daño neurológico. Además, se describen aspectos clínicos, de laboratorio y terapéuticos para el manejo de pacientes con síntomas neurológicos compatibles con COVID-19. Por último, se espera el desarrollo de tratamientos que aborden estructuras y vías específicas relacionadas con la entrada viral y la regulación cardiovascular cerebral, además del seguimiento de los pacientes afectados por la COVID-19 para evaluar las consecuencias a largo plazo sobre el sistema nervioso.

Palabras clave: Encefalitis; Enfermedades virales del sistema nervioso central; Tropismo viral; Virus del SARS.

1. Introduction

In late December 2019 in Wuhan, China, several patients were admitted in hospitals with an incomprehensible pneumonia, whose causative agent was later identified as belonging to the Coronavirus family and named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19) (Kim et al., 2020).

Coronaviruses are a large viral family whose infections in humans are acknowledged since 1960, varying from common cold to severe acute respiratory syndrome (Graham et al., 2013; The WHO MERS-CoV Research Group, 2013). Coronaviruses are enveloped positive-sense single-stranded RNA virus, classified as a family in the order *Nidovirales* and divided into four genera: alpha, beta, gamma, and delta (Mattos et al., 2020; Nadeem et al., 2020; Yan et al., 2020).

Seven main types of Human Coronavirus are known to exist, in which HCoV-OC43, HCoV-HKU1, HCoV-229E and HCoV-NL63 account for 5 to 10% of mild acute respiratory disorders (Ye et al., 2020). Conversely, three beta coronaviruses may lead to severe respiratory syndromes: Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and, more recently, SARS-CoV-2 (Ye et al., 2020).

Primarily, most patients with COVID-19 had mild to moderate clinical manifestations, including fever, sore throat, dry cough, myalgia, and fatigue (Guan et al., 2020; Zhou et al., 2020). However, with the pandemic evolvement, a wide spectrum of neurological syndromes among patients infected with SARS-CoV-2 are reported, ranging from mild ones, such as taste and smell impairment, dizziness, headache, ataxia, seizures, skeletal muscle injury, and acute cerebrovascular disease to more severe cases with development of Guillain-Barré syndrome and coma (Hoch et al., 2020; Mao et al., 2020; Zhao et al., 2020).

Of the 841 subjects included for the ALBACOVID registry, 57.4% patients presented some form of neurological symptom (Romero-Sánchez et al., 2020). In other samples, 36.4% of subjects had manifestations in the nervous systems, with higher predominance on central nervous system (CNS) (24,8%) than peripherally (8,9%) (Mao et al., 2020). Additionally,

encephalopathy, agitation and corticospinal symptoms were found in patients with SARS-CoV-2 (Helms et al., 2020).

After confirming that SARS-CoV-2 was the etiological agent of meningitis cases, in which viral RNA was not detected in the nasopharyngeal swab but in the cerebrospinal fluid (CSF), this warns that COVID-19 transmission route is not limited to lower respiratory tract and that neurological symptoms can be the only clinical findings during disease onset (Moriguchi et al., 2020). Taking this into account, comprehension on SARS-CoV-2 neurotropism is indispensable to make evidence-based recommendations and provide the greatest benefit for the patients.

Therefore, the objective of this narrative review is to summarize the state of art regarding the transmission routes and pathological mechanisms by which neurological damage can occur in COVID-19, highlighting interventions to manage individuals with neurological symptoms caused by SARS-CoV-2.

2. Methodology

This study corresponds to a narrative bibliographic review, qualitative, with exploratory characteristic as recommended by Pereira *et al.* (2018), whose aim is to describe and discuss useful information regarding a subject, under a theoretical and contextual perspective. Usually, narrative reviews are used as a teaching tool to introduce a topic to a broader audience. Furthermore, narrative reviews consist of critical analysis of books and journal articles, in both printed and electronic forms (Rother, 2007).

This bibliography review was carried out by searching for articles in databases including: National Library of Medicine (PUBMED), Scientific Electronic Library Online (SciELO), Google Scholar and national and international Hospitals Clinical Protocols. Articles from December 2019 to June 2020 were used, which included the keywords: COVID-19 and nervous system, SARS-CoV-2 infection, neurological symptoms, and treatment

3. Results and Discussion

3.1 Major Routes of CNS Infection and Pathological Mechanisms

Regarding SARS-CoV-2 mechanisms to neuroinvasion, the olfactory bulb via trans synaptic transmission route should be considered (Steardo et al., 2020). Through this pathway, which is well documented for beta coronaviruses, the virus enters the hosting organism by peripheral nerves, sensory or motor ones, and gains access to the CNS by anterograde or retrograde transport (Y. C. Li et al., 2012; Matsuda et al., 2004; Wu, Xu, Chen, Duan, Hashimoto, & Yang, 2020). For this pathway, angiotensin-converting enzyme 2 (ACE2) receptor plays a crucial role. ACE2, whose gene is located on chromosome Xp22, is an enzyme responsible for converting, respectively, Angiotensin I into Angiotensin 1-9, and Angiotensin II into Angiotensin 1-7 (Gheblawi et al., 2020).

ACE2 has two domains: the N-terminus, a carboxypeptidase homologous to ACE, which metabolizes Angiotensin II into Angiotensin 1-7, and other peptides, like apelin (Alenina & Bader, 2019; Gheblawi et al., 2020); and the C-terminus, homologous to collectrin, that traffic amino acids transporters to the cell surface, such as neutral amino acid transporter, in order to regulate seric amino acids levels (Alenina & Bader, 2019; Gheblawi et al., 2020).

ACE2 receptor is present in distinct brain regions, expressed at cytoplasmic level in neuronal cells, though in a lower degree in comparison to the lungs, airways epithelial cells, cardiovascular system, adipose tissue, gastrointestinal system, and kidney (Alenina & Bader, 2019; Doobay et al., 2007; Gheblawi et al., 2020; Harmer et al., 2002; Nakagawa & Sigmund, 2017). By taking advantage of the ACE2 receptor, SARS-CoV-2 invades host cells, like SARS-CoV.

Firstly, SARS-CoV-2 spike protein binds onto target cells through the receptor-binding domain (RBD), from spike subunit 1, to ACE2 (Tortoric & Veesler, 2020). This process also requires furin-like cleavage site and transmembrane serine protease 2 (TMPRSS2) (Zhang et al., 2020). In sequence, SARS-CoV-2 is exposed to endosomal proteases, causing the union of Heptad Repeat 1 and 2 regions from spike subunit, which leads to membrane fusion and the virus' release into the cell cytoplasm (Tay et al., 2020). Afterwards, the viral genome is liberated in the cytoplasm and begins to replicate, translating two polyproteins and structural proteins (X. Li et al., 2020).

Owing that SARS-CoV and MERS-CoV were encountered in the neurons from infected patients, and both SARS-CoV and SARS-CoV-2 share similar mechanisms to invade cells, the CNS infection must be considered (Guan et al., 2020; Lu et al., 2020; Tortoric & Veesler, 2020; J. Xu et al., 2005; Yamashita et al., 2005). In animal experimental models, SARS-CoV intranasal inoculation in human ACE2 transgenic mice caused a significant spread of the virus by subcortical and cortical regions (Gu et al., 2005). Albeit the whole brain was invaded, SARS-CoV had a notorious tropism for the brainstem and hypothalamus (Gu et al., 2005). In parallel, a mouse strain K18-hACE2 model demonstrated that SARS-CoV strongly infected the brainstem nuclei (McCray et al., 2007). Moreover, olfactory bulb ablation in mice prevented mouse hepatitis virus, a beta coronavirus, from spreading, upon nasal infection (Bohmwald et al., 2018).

The brainstem includes both solitary tract nucleus and nucleus ambiguus, responsible for respiratory autonomic regulation, as well as the pre-Bötzinger complex, a neuronal network which serves as primary respiratory oscillator (Gandhi et al., 2020; Ogier et al., 2020). Hence, the olfactory bulb via offers a reasonable explanation for those patients with COVID-19 who presented respiratory insufficiency, despite the absence of breathing symptoms during disease onset (Mao et al., 2020).

Besides, incompatibility between respiratory failure and neuronal pathway is corroborated by a second via, in which SARS-CoV-2 reaches the brainstem through trans synaptic mechanisms, starting from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways, resulting in cardiorespiratory dysfunction (Y. C. Li et al., 2020; Natoli et al., 2020).

Another possible route to contribute to CNS infection is through blood circulation, supported by the observation that SARS-CoV infiltrates immune cells, such as monocytes, macrophages, T lymphocytes and dendritic cells (Gu et al., 2005; Law et al., 2005; Spiegel et al., 2006).

This via suggests SARS-CoV and, subsequently, SARS-CoV-2 drive immunopathogenesis by direct infection of immune cells. Conversely, there is still no consensus regarding this transmission route, provided that, on SARS-CoV and MERS-CoV studies, a large majority of non-neuronal cells did not present the virus particles on the infected brain areas (Ding et al., 2004; Y. C. Li et al., 2020).

In more severe cases, COVID-19 may lead to dysfunctional immune response, and, therefore, an insight on angiotensin conversion is required (Tay et al., 2020). This process depends on the actions of two receptors: angiotensin type 1 receptor (AT1R) and angiotensin

type 2 receptor (AT2R), associated, respectively to deleterious and anti-inflammatory responses (Biancardi et al., 2016; Gheblawi et al., 2020).

Once Angiotensin II activates AT1R, a signaling cascade culminates in p38 Mitogen-Activated Protein Kinases activation and ADAM metallopeptidase domain 17 (ADAM-17) phosphorylation by Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase 2-induced reactive oxygen species formation (Gheblawi et al., 2020; Patel et al., 2014). ADAM-17 is a transmembrane protein which promotes extracellular domain shedding and activation of Tumor Necrosis Factor alpha (TNF-α), conferring a chronic inflammatory response.

Furthermore, as ADAM-17 mediates proteolysis and ectodomain shedding of ACE2, and its functionality is enhanced in COVID-19, a high shedding of ACE2 occurs (Alenina & Bader, 2019; Gooz, 2010). This not only causes the ACE2 loss at the membrane, but also a decreased enzymatic function, generating harmful effects mediated by renin angiotensin system (RAS) overactivation in a positive feedback cycle (Gheblawi et al., 2020; Patel et al., 2014).

If the immune system is overactivated, disfunction of T Helper 17 and regulatory T cells happens, prompting an enhanced secretion of pro-inflammatory cytokines, able to cause multiple organs failure and death, and compromising blood brain barrier (BBB) permeability, in COVID-19 severe cases (Gheblawi et al., 2020; Ruan et al., 2020)

This process is called “cytokine storm”, an unsuppressed local inflammation provoked by pathogen and damage associated molecular patterns’ detection, which leads to a systemic inflammatory response syndrome. Additionally, this state is marked by an increased secretion of pro-inflammatory cytokines and chemokines, such as interleukins 1, 2, 6, 7, interferon gamma, among other factors (X. Li et al., 2020). Hence, either by direct CNS infection or systemic inflammation, COVID-19 can destabilize the BBB, promoting SARS-CoV-2 entry in the brain as well as neuronal damage (Wu, Xu, Chen, Duan, Hashimoto, & Yang, 2020).

3.2 Covid-19 And Neurovascular Disruption

Both purinergic signaling system and RAS play important roles in cardiovascular regulation in the brain. The first system exerts such task by autonomic modulation, also being responsible for controlling communication among astrocytes as well as the interaction between astrocytes and neurons (Haspula & Clark, 2018). In agreement, RAS components are expressed in glial cells and neurons, with astrocytes being the main angiotensinogen source in the brain (Haspula & Clark, 2018).

In neuroinflammation conditions, glial cells morphofunctionality disrupt, resonating in the cardiovascular regulation (Haspula & Clark, 2018). On the one hand, AT1R activation produces a rise in oxidative stress and inflammatory cytokines, especially in cardioregulatory centers of the hypothalamus and brainstem (Haspula & Clark, 2018; Jiaxi Xu et al., 2018). On the other, AT2R is more expressed in neurons, having a cerebroprotective effect, since it promotes the oxidative stress reduction and attenuates neuronal apoptosis due to the release of some Nitric Oxide Synthase (NOS) isoforms, thus stabilizing BBB (Haspula & Clark, 2018; Jiaxi Xu et al., 2018).

Angiotensin II mediates reactive oxygen species production, through interaction between AT1R and Toll-like receptor 4 of microglial cells in the paraventricular nucleus (Biancardi et al., 2016). Accordingly, microglia shift to proinflammatory phenotype whereas astrocytes become overactive, a feature observed in a wide scope of neurological disorders (Biancardi et al., 2016; Haspula & Clark, 2018).

Owing to the reactive glial cells pattern, glutamate homeostasis is compromised, and such overstimulation is neurotoxic. Additionally, AT1R activation can hamper synaptic strength and activity, as this receptor modulates the impulses generated by neurotransmitters such as glutamate, gamma aminobutyric acid (GABA), and norepinephrine (Haspula & Clark, 2018).

In a riveting perspective, glutamate excitotoxicity is involved in the pathogenesis of some brain disorders, such as Alzheimer disease and Parkinson's disease, as it decreases ACE2 activity through ADAM-17 (Jiaxi Xu et al., 2018). This implies that decreased ACE2 function contributes to the development of neurodegenerative disorders, as it reinforces mechanisms, as inflammation and apoptosis (Alenina & Bader, 2019; Jiaxi Xu et al., 2018).

Consistently, ACE2 activation generates angiotensin 1-7 which, after binding to the mitochondrial assembly receptor, causes an anti-inflammatory and antifibrotic effect. Therefore, in case SARS-CoV-2 reaches human CNS, the virus is able to reduce the ACE2 protective effect, based on the described mechanisms, aggravating neuronal injury (Lu et al., 2020).

Nonetheless, post-infection systemic inflammation by SARS-CoV-2 further corroborates to neuroinflammatory processes, as it increases the probability to thrive neurological syndromes, including severe encephalitis which produces intermittent damage to doparminergic neurons, which can have implications on Parkinson’s disease (Wu, Xu, Chen, Duan, Hashimoto, Yang, et al., 2020).

3.3 Management and Treatment

On the ground of the current evidence, in case a patient is charged presenting neurological symptoms, physicians should consider SARS-CoV-2 infection as a differential to avoid delayed or misdiagnosis (Mao et al., 2020). During screening, patients reporting early neurological symptoms must be tested for COVID-19 and kept under observation, since the latency period may be enough for SARS-CoV-2 to annihilate medullary neurons and lead to life threatening consequences (Das et al., 2020).

In terms of physical examination, it is crucial to perform detailed neurological examination, especially cognitive assessment, to detect possible impairments (De Felice et al., 2020). In patients who develop severe neurological complications, whenever possible, investigation of CSF samples to assess the presence of viral antigen and inflammatory mediators must be performed, in order to determine direct CNS infection (De Felice et al., 2020).

Concerning hyposmia and anosmia management, 66-80% of patients with smell impairment associated with COVID-19 reported improvement or spontaneous resolution within days-weeks after recovery from a clinical illness, whereas 2.5%-5.0% of patients with COVID-19 have strokes, with ischemic stroke (5%) being more common than intracerebral hemorrhage (0.5%) (Mao et al., 2020; Vaira et al., 2020).

Stroke was associated with older age; risk factors such as hypertension, diabetes, prior cerebrovascular disease; elevated C-reactive protein; and elevated D-dimer (Aggarwal et al., 2020). Although severe cases have a stronger relation to stroke incidence, some patients may have asymptomatic strokes incidentally discovered on brain magnetic resonance imaging (Aggarwal et al., 2020; Helms et al., 2020). Accordingly, general protocol for stroke management should be followed. As COVID-19 can induce a hypercoagulable state, therapeutic anticoagulation is ought to be opted (Williams et al., 2020).

About COVID-19 laboratory findings, during incubation phase, which lasts three to five days, an early infection marker is lymphopenia, even in the absence of fever and cough (Zhou et al., 2020). When neurological symptoms occur, complete hemogram should be checked routinely. If the infection is not controlled, a severe infection stage emerges. Once virus replication and consequent lung damage reach critical proportions, symptoms such as fever, coughing and shortness of breath ensue, requiring ventilatory support. D-dimer can be used as a marker of infection severity, owing that high levels were related to COVID-19 advanced stages, but should not be accounted for prognosis (Školoudík et al., 2010; Zhou et

al., 2020). In severe cases, SARS-CoV-2 induces a cytokine storm and coagulation cascade activation, causing thrombotic phenomena (Dolhnikoff et al., 2020).

Because cerebrovascular complications may be caused by SARS-CoV-2 infection, anticoagulation plays a pivotal role on the treatment of neurological conditions at systemic level. American Society of Hematology indicates that all hospitalized patients with COVID-19 receive pharmacologic thromboprophylaxis with low molecular high heparin (LMWH) or fondaparinux, unless the risk of bleeding is judged to exceed the risk of thrombosis (Kreuziger et al., 2020). Due to the COVID-19 severe cases high mortality, heparin application is recommended for these patients to reduce the risk of disseminated intravascular coagulation and venous thromboembolism (Tang et al., 2020).

One study compared groups composed by critically ill patients diagnosed with COVID-19, to analyze the effect of heparin administration during 28 days hospitalization, assessing the risk of coagulophilia, prothrombin time, platelet count and sequential organ failure assessment (Tang et al., 2020). In both groups, prothrombin time was positive whereas platelet count was negative, results that correlated with 28-day mortality (Tang et al., 2020). Nevertheless, mortality in the same period was lower among heparin users when compared to patients who did not use anticoagulant. Taking these into account, anticoagulant therapy, especially with LMWH, seems to be associated with a better prognosis in COVID-19 critically ill patients (Tang et al., 2020).

Strikingly, heparin has been implicated in binding to SARS-CoV-2 spike protein as well as down-regulating interleukin 6, which has been shown to be elevated in COVID-19 patients, and, therefore, unfractionated heparin or LMWH remains as the best choice for admitted patients (Atallah et al., 2020).

4. Conclusions

Emerging evidence suggests that SARS-CoV-2 presents a neurotropism feature, in similarity to previous coronaviruses outbreaks, an observation supported by the prevalence of neurological manifestations on COVID-19 patients, and on enriching preclinical and clinical studies.

SARS-CoV-2 infection on the CNS can precipitate direct neurological alterations, worsen pre-existing neurological conditions, and aggravate damage caused by other insults, as well as increasing its susceptibility. With respect to transmission routes, olfactory bulb via trans synaptic is the most likely to take place, while the hematogenous pathway require

clarifications. In the pathological point of view, SARS-CoV-2 effects on the CNS arise from direct or indirect mechanisms, including encephalitis, encephalopathy, coagulation cascade activation and systemic inflammation.

Provided the lack of specific antiviral treatment able to prevent the disease's progression, anticoagulants should be deemed for clinical management. Rapid public health interventions with antibodies, antivirals or novel vaccine strategies are highly essential to contain SARS-CoV-2 infection and disease transmission (Shanmugaraj et al., 2020). Major research is focusing on anti-viral molecules targeting the spike protein as it mediates viral entry and induces host immune responses (Shanmugaraj et al., 2020).

ACE2 plays a key role on viral entry into healthy host cells, including on nervous tissue, and noteworthy progress has been made in understanding the main interactions between ACE2 and spike protein's RBD, so antibody drugs could be designed targeting SARS-CoV-2 RBD (Das et al., 2020). Structure-guided therapeutics as small molecules or peptides that interfere with viral receptor recognition could possibly halt the disease progression, so strategies to block AT1R and balance the function RAS components deserve further attention.

Because long-term consequences of COVID-19 are uncertain, follow-up on patients who had neurological manifestations must be performed, initially through observational studies such as cohorts and case-control studies, to analyze if SARS-CoV-2 infection promotes accelerated aging phenotypes in survivors in the brain and other organs, as well as its involvement with aging-associated conditions (De Felice et al., 2020; Lippi et al., 2020).

In the light of these data, new studies should be carried on the SARS-CoV-2 viral phenotype, main symptoms at the CNS, peripheral nervous system, and skeletal muscle, as well as the emergence of new treatments effective in mitigating symptoms, thus bringing benefits to the patient's health and quality of life.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

This study was intellectually supported by the following Brazilian fostering agencies: *Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)*, *Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco (FACEPE)*, and the Academic Support Program from *Universidade de Pernambuco*.

References

Aggarwal, G., Lippi, G., & Michael Henry, B. (2020). Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. *International Journal of Stroke*, *15*(4), 385–389. https://doi.org/10.1177/1747493020921664.

Alenina, N., & Bader, M. (2019). ACE2 in Brain Physiology and Pathophysiology: Evidence from Transgenic Animal Models. *Neurochemical Research*, *44*(6), 1323–1329. https://doi.org/10.1007/s11064-018-2679-4.

Atallah, B., Mallah, S. I., & AlMahmeed, W. (2020). Anticoagulation in COVID-19. *European Heart Journal. Cardiovascular Pharmacotherapy*, 1–2. https://doi.org/10.1093/ehjcvp/pvaa036.

Biancardi, V. C., Stranahan, A. M., Krause, E. G., de Kloet, A. D., & Stern, J. E. (2016). Cross talk between AT1 receptors and Toll-like receptor 4 in microglia contributes to angiotensin II-derived ROS production in the hypothalamic paraventricular nucleus. *American Journal of Physiology. Heart and Circulatory Physiology*, *310*(3), H404–H415. https://doi.org/10.1152/ajpheart.00247.2015.

Bohmwald, K., Gálvez, N. M. S., Ríos, M., & Kalergis, A. M. (2018). Neurologic alterations due to respiratory virus infections. *Frontiers in Cellular Neuroscience*, *12*(October), 1–15. https://doi.org/10.3389/fncel.2018.00386.

Das, G., Mukherjee, N., & Ghosh, S. (2020). Neurological Insights of COVID-19 Pandemic. *ACS Chemical Neuroscience*, *11*(9), 1206–1209. https://doi.org/10.

1021/acschemneuro.0c00201.

De Felice, F. G., Tovar-Moll, F., Moll, J., Munoz, D. P., & Ferreira, S. T. (2020). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Central Nervous System. *Trends in Neurosciences*, *43*(6), 355–357. https://doi.org/10.1016/j.tins.2020.04.004.

Ding, Y., He, L., Zhang, Q., Huang, Z., Che, X., Hou, J., Wang, H., Shen, H., Qiu, L., Li, Z., Geng, J., Cai, J., Han, H., Li, X., Kang, W., Weng, D., Liang, P., & Jiang, S. (2004). Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: Implications for pathogenesis virus transmission pathways. *Journal of Pathology*, *203*(2), 622–630. https://doi.org/10.1002/path.1560.

Dolhnikoff, M., Duarte-Neto, A. N., de Almeida Monteiro, R. A., da Silva, L. F. F., de Oliveira, E. P., Saldiva, P. H. N., Mauad, T., & Negri, E. M. (2020). Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *Journal of Thrombosis and Haemostasis*, *18*(6), 1517–1519. https://doi.org/10.1111/jth.14844.

Doobay, M. F., Talman, L. S., Obr, T. D., Tian, X., Davisson, R. L., & Lazartigues, E. (2007). Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, *292*(1). https://doi.org/10.1152/ajpregu.00292.2006.

Gandhi, S., Srivastava, A. K., Ray, U., & Tripathi, P. P. (2020). Is the Collapse of the Respiratory Center in the Brain Responsible for Respiratory Breakdown in COVID-19 Patients? *ACS Chemical Neuroscience*, *11*(10), 1379–1381. https://doi.org/10.1021/acschemneuro.0c00217.

Gheblawi, M., Wang, K., Viveiros, A., Nguyen, Q., Zhong, J. C., Turner, A. J., Raizada, M. K., Grant, M. B., & Oudit, G. Y. (2020). Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circulation Research*, 1456–1474. https://doi.org/10.1161/CIRCRESAHA.120.317015.

Gooz, M. (2010). ADAM-17: the enzyme that does it all. *Critical Reviews in Biochemistry*

and Molecular Biology, *45*(2), 146–169. https://doi.org/10.3109/10409231003628015.

Graham, R. L., Donaldson, E. F., & Baric, R. S. (2013). A decade after SARS: Strategies for controlling emerging coronaviruses. *Nature Reviews Microbiology*, *11*(12), 836–848. https://doi.org/10.1038/nrmicro3143.

Gu, J., Gong, E., Zhang, B., Zheng, J., Gao, Z., Zhong, Y., Zou, W., Zhan, J., Wang, S., Xie, Z., Zhuang, H., Wu, B., Zhong, H., Shao, H., Fang, W., Gao, D., Pei, F., Li, X., He, Z., … Leong, A. S. Y. (2005). Multiple organ infection and the pathogenesis of SARS. *Journal of Experimental Medicine*, *202*(3), 415–424. https://doi.org/10.1084/jem.20050828.

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D. S. C., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., Zhong, N. S. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England Journal of Medicine*, 1–13. https://doi.org/10.1056/NEJMoa2002032.

Harmer, D., Gilbert, M., Borman, R., & Clark, K. L. (2002). Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Letters*, *532*(1–2), 107–110. https://doi.org/10.1016/S0014-5793(02)03640-2.

Haspula, D., & Clark, M. A. (2018). Molecular basis of the brain renin angiotensin system in cardiovascular and neurologic disorders: Uncovering a key role for the astroglial angiotensin type 1 receptor AT1R. *Journal of Pharmacology and Experimental Therapeutics*, *366*(2), 251–264. https://doi.org/10.1124/jpet.118.248831.

Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Collange, O., Boulay, C., Fafi-Kremer, S., Ohana, M., Anheim, M., & Meziani, F. (2020). Neurologic Features in Severe SARS-CoV-2 Infection. *The New England Journal of Medicine*, *382*(23), 2268–2270. https://doi.org/10.1056/NEJMc2008597.

Hoch, D. H., Akiyama, S., Suyama, K., & Takano, T. (2020). Guillain–Barré Syndrome Associated with SARS-CoV-2. In *New England Journal of Medicine*. https://doi.org/10.56/NEJMc1509759.

Kim, J. M., Chung, Y. S., Jo, H. J., Lee, N. J., Kim, M. S., Woo, S. H., Park, S., Kim, J. W., Kim, H. M., & Han, M. G. (2020). Identification of coronavirus isolated from a patient in Korea with covid-19. *Osong Public Health and Research Perspectives*, *11*(1), 3–7. https://doi.org/10.24171/j.phrp.2020.11.1.02

Kreuziger, L. B., Lee, A., Garcia, D., Cuker, A., Cushman, M., DeSancho, M., & Connors, J. M. (2020). *COVID-19 and VTE/Anticoagulation: Frequently Asked Questions*. American Society of Hematology. Recuperado de www.hematology.org/covid-19/covid-19-and-vte-anticoagulation.

Law, H. K. W., Cheung, C. Y., Ng, H. Y., Sia, S. F., Chan, Y. O., Luk, W., Nicholls, J. M., Peiris, J. S. M., & Lau, Y. L. (2005). Chemokine up-regulation in SARS-coronavirus – infected, monocyte-derived human dendritic cells. *Blood*, *106*(7), 2366–2374. https://doi.org/https://doi.org/10.1182/blood-2004-10-4166.

Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis*, *10*(2), 102–108. https://doi.org/10.1016/j.jpha.2020.03.001.

Li, Y. C., Bai, W. Z., & Hashikawa, T. (2020). The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of Medical Virology*, *92*(6), 552–555. https://doi.org/10.1002/jmv.25728.

Li, Y. C., Bai, W. Z., Hirano, N., Hayashida, T., & Hashikawa, T. (2012). Coronavirus infection of rat dorsal root ganglia: Ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. *Virus Research*, *163*(2), 628–635. https://doi.org/10.1016/j.virusres.2011.12.021.

Lippi, A., Domingues, R., Setz, C., Outeiro, T. F., & Krisko, A. (2020). SARS-CoV-2: At the Crossroad Between Aging and Neurodegeneration. *Movement Disorders*, *35*(5), 716–720. https://doi.org/10.1002/mds.28084.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N.,

Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*, *395*(10224), 565–574.

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurology*, 1–8. https://doi.org/10.1001/jamaneurol.2020.1127.

Matsuda, K., Park, C. H., Sunden, Y., Kimura, T., Ochiai, K., Kida, H., & Umemura, T. (2004). The vagus nerve is one route of transneural invasion for intranasally inoculated influenza A virus in mice. *Veterinary Pathology*, *41*(2), 101–107. https://doi.org/10.1354/vp.41-2-101.

Mattos, R. De, Rafael, R., Ii, M. N., Maria, M., Carvalho, B. De, Maria, H., Leal, S., Iv, D., V, S. A., Guimarães, M., & Faria, D. A. (2020). Epidemiology, public policies and Covid-19 pandemics in Brazil: what can we expect ? *Rev Enfrem UERJ, Rio de Janeiro*, *28*, e49570. https://doi.org/10.12957/reuerj.2020.49570.

McCray, P. B., Pewe, L., Wohlford-Lenane, C., Hickey, M., Manzel, L., Shi, L., Netland, J., Jia, H. P., Halabi, C., Sigmund, C. D., Meyerholz, D. K., Kirby, P., Look, D. C., & Perlman, S. (2007). Lethal Infection of K18-hACE2 Mice Infected with Severe Acute Respiratory Syndrome Coronavirus. *Journal of Virology*, *81*(2), 813–821. https://doi.org/10.1128/jvi.02012-06.

Moriguchi, T., Harii, N., Goto, J., Harada, D., Sugawara, H., Takamino, J., Ueno, M., Sakata, H., Kondo, K., Myose, N., Nakao, A., Takeda, M., Haro, H., Inoue, O., Suzuki-Inoue, K., Kubokawa, K., Ogihara, S., Sasaki, T., Kinouchi, H., … Shimada, S. (2020). A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*, *94*(May), 55–58. https://doi.org/10.1016/j.ijid.2020.03.062.

Nadeem, M. S., Zamzami, M. A., Choudhry, H., Murtaza, B. N., Kazmi, I., Ahmad, H., & Shakoori, A. R. (2020). Origin, Potential Therapeutic Targets and Treatment for Coronavirus Disease (COVID-19). *Pathogens 2020, Vol. 9, Page 307*, *9*(4), 307.

https://doi.org/10.3390/PATHOGENS9040307.

Nakagawa, P., & Sigmund, C. D. (2017). How Is the Brain Renin-Angiotensin System Regulated? *Hypertension*, *70*(1), 10–18. https://doi.org/10.1161/HYPRTENSIONAHA.117.08550.

Natoli, S., Oliveira, V., Calabresi, P., Maia, L. F., & Pisani, A. (2020). Does SARS-Cov-2 invade the brain? Translational lessons from animal models. *European Journal of Neurology*, 0–2. https://doi.org/10.1111/ene.14277.

Ogier, M., Andéol, G., Sagui, E., & Bo, G. D. (2020). How To Detect and Track Chronic Neurologic Sequelae of Covid-19? Use of Auditory Brainstem Responses and Neuroimaging for Long-Term Patient Follow-Up. *Brain, Behavior, & Immunity - Health*, 100081. https://doi.org/10.1016/j.bbih.2020.100081.

Patel, V. B., Clarke, N., Wang, Z., Fan, D., Parajuli, N., Basu, R., Putko, B., Kassiri, Z., Turner, A. J., & Oudit, G. Y. (2014). Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: A positive feedback mechanism in the RAS. *Journal of Molecular and Cellular Cardiology*, *66*, 167–176. https://doi.org/10.1016/j.yjmcc.2013.11.017.

Pereira, A. S. (2018). Metodologia da pesquisa científica [eBook]. UAB / NTE / UFSM.

Romero-Sánchez, C. M., Díaz-Maroto, I., Fernández-Díaz, E., Sánchez-Larsen, Á., Layos-Romero, A., García-García, J., González, E., Redondo-Peñas, I., Perona-Moratalla, A. B., Del Valle-Pérez, J. A., Gracia-Gil, J., Rojas-Bartolomé, L., Feria-Vilar, I., Monteagudo, M., Palao, M., Palazón-García, E., Alcahut-Rodríguez, C., Sopelana-Garay, D., Moreno, Y., Segura, T. (2020). Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*, 10.1212/WNL.0000000000009937. https://doi.org/10.1212/wnl.0000000000009937.

Rother, E. T. (2007). Systematic literature review X narrative review. *ACTA Paulista de Enfermagem*, *20*(2), 7–8. https://doi.org/10.1590/s0103-21002007000200001.

Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*, *46*(5), 846–848. https://doi.org/10.1007/s00134-020-05991-x.

Shanmugaraj, B., Malla, A., & Phoolcharoen, W. (2020). Emergence of novel coronavirus 2019-nCoV: Need for rapid vaccine and biologics development. *Pathogens*, *9*(2), 1–10. https://doi.org/10.3390/pathogens9020148.

Školoudík, D., Bar, M., Šaňák, D., Bardoň, P., Roubec, M., Langová, K., Herzig, R., & Kaňovský, P. (2010). D-dimers increase in acute ischemic stroke patients with the large artery occlusion, but do not depend on the time of artery recanalization. *Journal of Thrombosis and Thrombolysis*, *29*(4), 477–482. https://doi.org/10.1007/s11239-009-0372-9.

Spiegel, M., Schneider, K., Weber, F., Weidmann, M., & Hufert, F. T. (2006). Interaction of severe acute respiratory syndrome-associated coronavirus with dendritic cells. *Journal of General Virology*, *87*(7), 1953–1960. https://doi.org/10.1099/vir.0.81624-0.

Steardo, L., Steardo, L., Zorec, R., & Verkhratsky, A. (2020). Neuroinfection may potentially contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiologica (Oxford, England)*, *March*, e13473. https://doi.org/10.1111/apha.13473.

Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis*, *March*, 1094–1099. https://doi.org/10.1111/jth.14817.

Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. P. (2020). The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews Immunology*, 1–12. https://doi.org/10.1038/s41577-020-0311-8.

The WHO MERS-CoV Research Group. (2013). State of Knowledge and Data Gaps of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Humans. *PLoS Currents*, *5*(October), 1–31. https://doi.org/10.1371/currents.outbreaks.0bf719e352e 7478f8ad8 5fa30127ddb8.

Tortoric, M. A., & Veesler, D. (2020). Structural insights into coronavirus entry. *Advances in Virus Research*, *105*(January), 93–116. https://doi.org/https://doi.org/10.1016/bs.aivir.2019.08.002 .

Vaira, L. A., Deiana, G., Fois, A. G., Pirina, P., Madeddu, G., De Vito, A., Babudieri, S., Petrocelli, M., Serra, A., Bussu, F., Ligas, E., Salzano, G., & De Riu, G. (2020). Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. *Head and Neck*, *42*(6), 1252–1258. https://doi.org/10.1002/hed.26204.

Williams, E., Bevers, M., & Feske, S. (2020). *Stroke*. Brigham And Women's Hospital Covid-19 Clinical Guidelines. Recuperado de https://covidprotocols.org/protocols/neurology/#stroke.

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., & Yang, L. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*, *March*. https://doi.org/https://doi.org/10.1016/j.bbi.2020.03.031.

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., & Yang, C. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*, *87*(March), 18–22. https://doi.org/10.1016/j.bbi.2020.03.031.

Xu, J., Zhong, S., Liu, J., Li, L., Li, Y., Wu, X., Li, Z., Deng, P., Zhang, J., Zhong, N., Ding, Y., & Jiang, Y. (2005). Detection of Severe Acute Respiratory Syndrome Coronavirus in the Brain: Potential Role of the Chemokine Mig in Pathogenesis. *Clinical Infectious Diseases*, *41*(8), 1089–1096. https://doi.org/10.1086/444461.

Xu, Jiaxi, Sriramula, S., & Lazartigues, E. (2018). Excessive Glutamate Stimulation Impairs ACE2 Activity Through ADAM17-Mediated Shedding in Cultured Cortical Neurons. *Cellular and Molecular Neurobiology*, *38*(6), 1235–1243. https://doi.org/10.1007/s10571-018-0591-8.

Yamashita, M., Yamate, M., Li, G. M., & Ikuta, K. (2005). Susceptibility of human and rat neural cell lines to infection by SARS-coronavirus. *Biochemical and Biophysical Research*

Communications, *334*(1), 79–85. https://doi.org/10.1016/j.bbrc.2005.06.061.

Yan, Y., Shin, W. I., Pang, Y. X., Meng, Y., Lai, J., You, C., Zhao, H., Lester, E., Wu, T., & Pang, C. H. (2020). The first 75 days of novel coronavirus (SARS-CoV-2) outbreak: Recent advances, prevention, and treatment. *International Journal of Environmental Research and Public Health*, *17*(7). https://doi.org/10.3390/ijerph17072323.

Ye, Z. W., Yuan, S., Yuen, K. S., Fung, S. Y., Chan, C. P., & Jin, D. Y. (2020). Zoonotic origins of human coronaviruses. *International Journal of Biological Sciences*, *16*(10), 1686–1697. https://doi.org/10.7150/ijbs.45472.

Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, *46*(4), 586–590. https://doi.org/10.1007/s00134-020-05985-9.

Zhao, H., Shen, D., Zhou, H., Liu, J., & Chen, S. (2020). Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *The Lancet Neurology*, *19*(5), 383–384. https://doi.org/10.1016/S1474-4422(20)30109-5.

Zhou, Y., Li, W., Wang, D., Mao, L., Jin, H., Li, Y., Hong, C., Chen, S., Chang, J., He, Q., Wang, M., & Hu, B. (2020). Clinical time course of COVID-19, its neurological manifestation and some thoughts on its management. *Stroke and Vascular Neurology*, svn-2020-000398. https://doi.org/10.1136/svn-2020-000398.

Porcentagem de contribuição de cada autor no manuscrito

Letícia Nunes Campos– 12%

Ana Clara Santos Costa– 11%

Débora Dantas Nucci Cerqueira- 11%

Gabriele Rodrigues Rangel- 11%

Isabela Cristina de Farias Andrade- 11%

Stella Costa Batista de Souza - 11%

Julio Cesar Dias de Melo Silva - 11%

Brayan Marques da Costa - 11%

Sura Wanessa Santos Rocha - 11%