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# Main Neurological Manifestations arising from COVID-19: an integrative review

Principales Manifestaciones Neurológicas derivadas del COVID-19: una revisión integradora

Principais Manifestações Neurológicas decorrentes do COVID-19: uma revisão integrativa

## ABSTRACT

**Objective:** To identify the main neurological manifestations and their implications in the patient's clinical condition as well as the pathophysiology of SAR-CoV-2 in the central nervous system. **Methods:** An integrative literature review was conducted based on 14 articles extracted from the PUBMED and LILACS database. **Results:** It was found that headache, vertigo, taste and olfactory disorders and stroke are the most prevalent symptoms. **Conclusion:** The pathophysiology of neurological involvement by COVID-19 remains inconclusive and knowing the neurological symptoms associated with the most severe conditions can assist in early interventions and in improving prognosis.

**DESCRIPTORS:** Nervous System; Neurologic Manifestations; Coronavirus Infections.

## RESUMEN

**Objetivo:** Identificar las principales manifestaciones neurológicas y sus implicaciones en la situación clínica del paciente, así como la fisiopatología del SAR-CoV-2 en el sistema nervioso central. **Métodos:** Se realizó una revisión integradora de la literatura a partir de 14 artículos extraídos de la base de datos PUBMED y LILACS. **Resultados:** Se encontró que la cefalea, el vértigo, los trastornos del gusto y olfativos y el ictus son los síntomas más prevalentes. **Conclusión:** La fisiopatología de la afectación neurológica por COVID-19 sigue sin ser concluyente y conocer los síntomas neurológicos asociados con las condiciones más graves puede ayudar en las intervenciones tempranas y en la mejora del pronóstico.

**DESCRIPTORES:** Sistema Nervioso; Manifestaciones Neurológicas; Infecciones por Coronavirus.

## RESUMO

**Objetivo:** Identificar as principais manifestações neurológicas e suas implicações no quadro clínico do paciente bem como a fisiopatologia do SAR-CoV-2 no sistema nervoso central. **Métodos:** Uma revisão de literatura integrativa foi conduzida com base em 14 artigos extraídos da base de dados PUBMED e LILACS. **Resultados:** Foi constatado que cefaleia, vertigem, disfunções gustativas e olfatórias e AVC são os sintomas mais prevalentes. **Conclusão:** A fisiopatologia do envolvimento neurológico pelo COVID-19 permanece inconclusiva e conhecer a sintomatologia neurológica associada aos quadros mais graves e severos pode auxiliar em intervenções precoces e na melhora de prognósticos.

**DESCRITORES:** Sistema Nervoso; Manifestações Neurológicas; Infecções por Coronavirus.

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### Lília Tereza Diniz Nunes

Medical student at FAHESA/ITPAC Palmas, Graduated in Fashion at the University Center of Faculdades Metropolitanas Unidas (2010). Post-Graduate Student in Higher Education Teaching at ITOP-Palmas. Master in Design from Universidade Anhembi Morumbi.

ORCID: 0000-0002-8571-3039

### Luiz Eduardo Cunha Felipe

Medical student at FAHESA/ITPAC Palmas, Incomplete Superior Education.

ORCID: 0000-0001-6906-7201

**Itamar Magalhães Gonçalves**

Graduated in Medicine at the Federal University of Uberlândia, Medical Residency in General Surgery and Urology at the Federal University of Uberlândia and Master in Teaching in Health Sciences at the Federal University of São Paulo. He has already served as professor of the Medicine course at the Federal University of Tocantins and Coordinator of the Teles-saúde Tocantins Redes Program. Currently, he works as a Forensic Medical Expert at the Tocantins State Secretariat of Public Security and serves as Professor of Medicine at Instituto Tocantinense Presidente Antônio Carlos - ITPAC Palmas. He is interested in Health Sciences Teaching, Information and Communication Technologies, Simulation Exercises and Medical Skills.

ORCID: 0000-0003-2276-6288

**Oscar Nunes Alves**

Graduated in Medicine from the Federal University of Espírito Santo, title of Neurosurgeon by the Brazilian Society of Neurosurgery. He has already served as Professor of Medicine at Instituto Tocantinense Presidente Antônio Carlos - ITPAC Porto Nacional and as Head of the Neurosurgery Service at Hospital Geral de Palmas. Currently competing as a Neurosurgeon at Hospital Geral de Palmas, also serving private hospitals and is a partner of the Institute of Neurosciences of Tocantins.

ORCID: 0000-0002-6443-6853

**INTRODUCTION**

The new coronavirus and the pandemic it generated drastically changed the world and the health system. Some studies carried out early in the pandemic have shown symptoms of a predominance of breathing including fever, cough, dyspnoea and fatigue<sup>1</sup>. With the development of the disease and new cases worldwide, it was possible to identify the tropism of the virus also by neural cells through mechanisms that are still being studied.

“By the end of Epidemiological Week (SE) 35 of 2020, on August 29th, 24.761.119 cases of COVID-19 in the world were confirmed. The United States was the country with the highest number of accumulated cases (5.917.439), followed by Brazil (3.846.153)”<sup>2</sup>.

This research aims to analyze, by means of a survey of data published in 10 articles collected in the PUBMED database in the period from December 2019 to August 2020, which are the main neurological symptoms presented by patients affected by SARS-CoV-2. A multiplicity of neurological symptoms were found when analyzing articles chosen from nonspecific symptoms such as headache, nausea and vomiting to specific symptoms such as stroke, Guillain Barré syndrome and peripheral nerve diseases.

Several studies have been dedicated to understanding how SARS-CoV-2 ac-

cesses the brain causing the neurological manifestations presented by patients, Whittaker et al.<sup>3</sup> proposes two theories, the first being through systemic vascular dissemination and the second and more local through the cribriform lamina of the ethmoid bone.

Something is certain, the neurotropism of the virus is familiar as the one presented by SARS-CoV that penetrates the cell via a protein called ECA2, expressed in the epithelium of the upper and lower airways, as well as in the endothelial epithelium of the central nervous system.

*SARS-CoV-2 uses the angiotensin-converting enzyme receptor 2 (ECA2) to enter host cells, the same as the SARS-CoV infection did in 2003. The pathological mechanism that COVID-19 has in the nervous system can happen by various pathways, including hematogenous pathway, retrograde neural pathway, hypoxia, immune damage and ECA2 enzyme. The virus entering the bloodstream can cause the immune system to produce cytokines as a physiological response; the increase in the production of cytokines can cause an increase in the permeability of the blood-brain barrier, thus facilitating the entry of the virus into the CNS. This may explain why patients with more severe CO-*

*VID-19 may have Cytokine Storm Syndrome.*<sup>4</sup>

Regarding the progression of the virus in the nervous system, some studies have postulated a neuronal spread of the coronavirus in which the virus infects a peripheral neuron and through the active transport machinery, synaptic terminal and retrograde transport is taken from the neuronal cell body to remote areas of the brain. This trans-synaptic transfer mechanism is supported by studies involving the 67 N hemagglutinating strain of the encephalomyelitis virus, the first CoV strain found to invade the brain.<sup>5</sup>

Adjuvant evidence for neurological involvement in COVID-19 includes CSF examination, electrophysiology, and radiological findings. The characteristic change in CSF after COVID-19 is the slight increase in cell counts and protein levels, especially immunoglobulins, which suggests an inflammatory or infectious state.<sup>6</sup>

In this integrative review, we will present the main neurological symptoms involved in the course of the disease, its pathophysiology and delve into the four most prevalent symptoms in patients with COVID-19.

**METHOD**

To carry out this study, we opted for an integrative literature review, based on the studies of Ganong<sup>7</sup>, Broome<sup>8</sup> and

Whittemore and Knalf.<sup>9</sup>

For the elaboration of this integrative review, the following steps were taken: establishment of the hypothesis and objectives of the integrative review; establishment of inclusion and exclusion criteria for articles (sample selection); definition of the information to be extracted from the selected articles; analysis of results; discussion and presentation of results and the last step consisted of presenting the review.

To guide the integrative review, the following question was asked: what are the main neurological symptoms resulting from coronavirus infection?

For the selection of articles, two databases were used, PubMed and Lilacs, seeking to expand the scope of the research and avoid bias.

The inclusion criteria initially defined for the review were: articles in Portuguese, English and Spanish, with abstracts available in the selected databases, published between December 2019 and August 2020, published articles whose adopted methodology allowed obtaining data thus concise, literature reviews, letter to the editor, opinion articles and articles without clinical data or outside the theme addressed were excluded.

The health descriptors Nervous System, Coronavirus Infections and the Boolean operator AND were used. Initially, 638 results were found, which were refined with the following filters: “Clinical Trial”, “Meta-Analysis”, “Randomized Controlled Trial and Sistematic Review. After reading its contents in full, it was decided to use 14 articles that met the

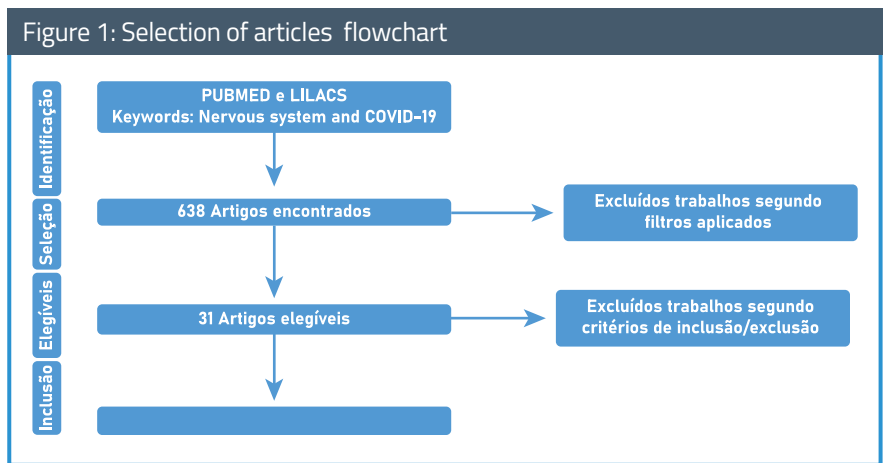
criteria listed above.

To assess the data, an instrument for collecting information was designed to answer the guiding question of this review. The analysis and interpretation of the data were carried out in an organized and synthesized manner through the elaboration of a synoptic table that comprised the following items: study identification; objectives, year and publication period; study design; thematic; and, main results and recommendations. The selected articles were analyzed in full and grouped by thematic areas. The data was validated using the PRISMA instrument verified by two professional health researchers.

The presentation of the results and discussion of the data obtained was done in a descriptive way, through tables and graphs allowing the reader to evaluate the applicability of the integrative review elaborated, in order to achieve the objective of this method.

RESULTS

A tabulation of the neurological symptoms found in the chosen researches was performed and these symptoms were divided firstly by their articles in order to know the different neurological manifestations according to the table below. Subsequently, a graph was made to know the prevalence of the 10 symptoms most described in table 1 and of these 4 were



Source: Own authorship (2020)

Table 1: Neurological Symptoms

Autor	Tipo de Estudo	Sintomas Neurológicos Encontrados
WHITTAKER, ANSON e HARKY, 2020	Revisão Sistemática	Ataxia, Síndrome de Guilan Barré, Cefaleia, Vertigem, Convulsões, Encefalopatia, Desorientação, Anosmia, Disfunção olfatórias e gustativas, Agnosia, Alucinações, AVC Isquêmico, Ataxia, Hiporeflexia, Confusão mental, EEG alterado, Perda da consciência, Redução do Nível de Consciência, Status Epiléptico, Fraqueza bilateral dos membros inferiores e dormência, Olhar sustentado para cima, Endurecimento bilateral da perna
ASADI-POOYA, SIMANI, 2020	Revisão Sistemática	Cefaleia, Vertigem, Redução do nível de consciência, Doenças cerebrovasculares agudas, Ataxia, Convulsões, AVC isquêmico, Trombose do seio venoso cerebral, Hemorragia cerebral, Confusão mental
WANG et. al, 2020	Revisão Sistemática com Meta- Análise	Consciência prejudicada, Doença cerebrovascular aguda, Sinais de liberação do trato corticoespinal, Ataxia, Vertigem, Disfunção gustativa e olfatória, Disfunção visual e dores nos nervos.

NEPAL et al, 2020	Revisão Sistemática com Meta-Análise	Cefaleia, Encefalopatia, AVC isquêmico, Hemorragia Intracerebral, Encefalite, Encefalomielite, Mielite Aguda, Disfunção gustatória e olfativa, Paralisia de Bell, Síndrome de Guillain Barré, Mialgia, Miosite, Rabdomiólise
MONTALVAN et al, 2020	Revisão Sistemática	Encefalite, Polineuropatia, Miopatia, AVC, Esclerose Múltipla
CHEN et al, 2020	Revisão Sistemática	Cefaleia, Vertigem, Disfunções gustativas e olfatórias, redução do nível de consciência, Doenças cerebrovasculares agudas, Convulsões, Encefalite, Meningite, Síndrome de Guillain Barré, Síndrome de Miller Fisher e Paralisia do Nervo Oculomotor
FÁTIMA et al, 2020	Revisão Sistemática	AVC Isquêmico, AVC Hemorrágico, Trombose.
ROMOLI et al, 2020	Revisão Sistemática	Disfunção gustativa e olfatória, Disfunção visual, Cefaleia, Mudanças de humor, Febre, Convulsões, Meningite, Encefalopatia, Oftalmoparesia internuclear direita, Neuropatias craniais múltiplas, Confusão mental, Agitação, Sinais piramidais, Síndrome disexecutiva, Vertigem, Dor em nervo, Manifestações musculoesqueléticas, Coma, Rigidez de pescoço, Fraqueza simétrica e distal de membros moderada, Perda de reflexos, Quadriplegia aguda simétrica progressiva, Tetraplegia de arreflexia flácida, Paralisia, Diplegia facial, Parestesia de membro, Fraqueza simétrica, Arreflexia, Diminuição da sensação termodolorosa distal, Parestesia flácida, Incontinência urinária e fecal
WILSON e JACK, 2020	Revisão Sistemática	Cefaleia, Vertigem, Redução do nível de consciência, Hipoalgesia, Disfunções olfatórias ou anosmia e Neuralgia, AVC agudo, epilepsia e ataxia
PINZON et al, 2020	Revisão Sistemática com Meta-Análise	Cefaleia, Vertigem, Disfunções olfatória e gustativas, Disfunções visuais, Fraqueza muscular, Doença cerebrovascular aguda, Convulsões, Ataxia, Neuralgia, AVC, Miopatia, Polineuropatia, Rabdomiólise, Convulsões, Redução do nível de consciência e Encefalopatia
MSIGWA et al, 2020	Revisão Sistemática	Estado de mal epiléptico, convulsão com duração de 5 a 30 minutos ou mais sem anulação automática, convulsões reaparecendo repetidamente sem restauração total da consciência; Confusão, Convulsão generalizada; encefalite e meningite associadas a confusão e perda de consciência e sinais de irritação meníngea; AVC agudo; Infartos cerebrais de grandes vasos; trombose e estado hipercoagulável; encefalomielite disseminada aguda; Estado mental alterado, com ataxia e déficits motores focais; coma, Distúrbios neuromusculares; Polineuropatia crítica, Miopatia, Rabdomiólise; Neuropatia olfatória; Anosmia e Ageusia, paralisia do nervo abducente bilateral, arreflexia e dissociação albuminocitológica,
ROMÁN et al, 2020	Revisão Sistemática	Doença cerebrovascular; Hipoperfusão frontotemporal (agitação; sinais do trato corticoespinal, como reflexos tendinosos acelerados, clônus do tornozelo e respostas plantares extensoras bilaterais; delírium; e hipertermia com febre, encefalopatia); tromboes arteriais e venosas, hemorragia subaracnóide e coagulopatias; Encefalopatia necrosante hemorrágica aguda; Encefalopatia, meningite, encefalite, convulsões; Síndrome de Guillain-Barré; Síndrome de Miller Fisher, Polineurite cranial; Mielite; Miastenia Gravis; Miopatias, Cefaleia, Disfunções Gustativas e Olfatórias, AVC agudo (isquêmico e hemorrágico)
KREMER et al, 2020	Estudo retrospectivo	AVC isquêmico, Hemiplegia esquerda; Sinais do trato piramidal bilateral; Fraqueza do lado esquerdo, Desatenção sensorial do lado esquerdo; Disartria; Afasia, Hemiplegia direita, Fraqueza do lado direito, Queda facial direita, Hemianopsia homônima esquerda, Meningoencefalite, Confusão, Agitação, Vigília patológica quando a sedação foi interrompida, Consciência prejudicada, Cefaleia, Vertigens, Ataxia, Distúrbios do movimento.
ROMERO-SANCHEZ et al, 2020	Revisão Sistemática	Mialgias; Cefaleia; Vertigem; Síncope; Anosmia; Disgeusia; Desordens de consciência; Sonolência; Estupor; Coma; Bradicipsíquia, Desorientação; Síndrome confusional aguda; Convulsões; Disautonomia; Lesões musculares (Hipercalemia, Rabdomiólise, Miopatia); AVC isquêmico; Hemorragia intracraniana; Distúrbios do movimento (hipercinético); Encefalite; Neurite óptica; Sintomas neuropsiquiátricos (ansiedade, depressão, insônia, psicose)

Source: Own Authorship, 2020

highlighted to be analyzed in thematic categories due to their high incidence.

A wide range of neurological symptoms can be seen, but some symptoms stood out, ten of them were present in at least three of the chosen studies and were distributed in Graph 1.

Among these, four Headache, Vertigo, Taste and Olfactory Dysfunctions and Stroke due to their high prevalence among the articles studied (mentioned in at least 10 of the 14 articles studied) were analyzed separately in thematic categories according to the quantitative approach presented in researches studied and will be addressed below.

#### 4.1 HEADACHE:

Of the 31 articles studied by Whittaker et al<sup>3</sup> 12 of them had cases where headache was reported to be one of the prevalent symptoms among patients, in one of the retrospective studies analyzed, the prevalence reached 35% being described as one of the most common neurological symptoms. Asadi-Pooya<sup>10</sup>, shows findings similar to Whittaker's<sup>3</sup> when showing the prevalence of headache ranging from 6 to 13% and of the 6 articles studied there was the presence of headache as a neurological manifestation in 5 of them. According to Nepal et al<sup>4</sup>, eight retrospective studies reported COVID-19 patients with headache, which represents an average of 19,88%.

The research by Chen et al<sup>11</sup> reports

important data by pointing out that headache was found in 51 studies involving 16.446 thousand patients with COVID-19, of which headache was reported in 20,1% of the studied population and also reports the presence of headache associated with vertigo in 8 more cases that involved 654 patients with COVID-19.

Romoli et al<sup>12</sup> described the presence of headache in 4 of the 27 articles analyzed. Wilson and Jack<sup>1</sup>, found headache among the most common neurological symptoms with a prevalence of<sup>11</sup> to 13%. Pinzon et al<sup>13</sup> reported the presence of headache in 21 studies (out of 33) being the most common symptom presented shortly after myalgia with a prevalence of 34%.

Román et al<sup>14</sup>, 2020 describes that in a cohort study of 262 confirmed cases in Beijing hospitals, 6,5% had headache compared to 6 to 8% in Wuhan.

Kremer et al<sup>15</sup>, 2020 found headache in the universe of the most common neurological symptoms resulting from COVID-19, among the 64 patients studied 10 present this symptom which corresponds to 16%.

Romero-Sanchez et al<sup>16</sup>, 2020 classified headache as a nonspecific neurological symptom and, along with myalgia, it was the most common symptom found, in a universe of 841 patients, 119 of them presented headache, which represents 14,1% prevalence, corroborating statistics presented by the above-mentioned authors.

#### 4.2 VERTIGO:

Along with headache, it was shown to be the most common neurological symptom observed in patients with COVID-19, a fact confirmed by Whittaker et al<sup>3</sup> in a prevalence of 13% in case studies conducted in China. Corroborating these findings, Asadi-Pooya<sup>10</sup> observed the presence of vertigo in 2 of the 6 articles studied, but with a high incidence (17%). Wang et al<sup>6</sup>, classified vertigo as a nonspecific neurological symptom - just like Romoli et al<sup>12</sup> - and was found in 4 of the 41 articles studied. Chen et al<sup>11</sup> reports that vertigo was investigated in 13 studies including 2236 patients with COVID-19 and approximately 7% of them reported the presence of the symptom without distinction of the severity of the condition. Wilson and Jack<sup>1</sup> reached the variation in the prevalence of vertigo to 8 to 17%. Pinzon et al<sup>13</sup>, reports the presence of vertigo in 6 of the 33 studies surveyed with a prevalence of 8,77%, being the most prevalent neurological symptom followed by headache.

Kremer et al<sup>15</sup>, 2020 found 2 cases of patients (in a universe of 19) with vertigo associated with COVID-19 and meningoencephalitis which corresponds to 10,5% incidence similar to that presented by Romero-Sanchez et al<sup>16</sup>, 2020 that reported 51 cases of patients with vertigo (841 studied) prevalence of 6,1%.

#### 4.3 TASTING AND OLFACTORY DYSFUNCTIONS:

Whittaker et al<sup>3</sup> reported that taste and olfactory dysfunctions along with headache and vertigo are the key symptoms reported in research, this type of dysfunction alone or in association was found in 4 of the 31 articles studied. Wang et al<sup>6</sup> points out that this dysfunction had a prevalence of 30 to 80% among patients with COVID-19.

Nepal et al<sup>4</sup> highlights that 5 cases (in a universe of 37) presented the prevalence of olfactory dysfunction (59,45%), in addition four studies presented the prevalence of taste dysfunction (56,48%).

Graph 1: Main Neurological Manifestations



Source: Own Authorship, 2020



Chen et al <sup>11</sup> reports that olfactory dysfunction was reported in 59,2% of cases and taste in 50,8%, being more frequent in patients with mild or moderate COVID-19 when compared to severe and severe cases.

Romoli et al <sup>12</sup> found even higher rates of taste and olfactory dysfunctions ranging from 85,6% to 88%. Pinzon et al <sup>13</sup> in turn, reports only one study with a prevalence of 5%. Wilson and Jack <sup>1</sup> also found a prevalence of 5% for cases of anosmia and hyposmia.

Msigwa et al <sup>17</sup>, 2020 reports that anosmia and ageusia occur in > 80% among COVID-19 cases, either as a first presentation or as the only neurological sign in mild cases.

Román et al <sup>14</sup>, 2020 demonstrated to find a big difference between the frames of anosmia and dysgeusia in the studies made in China and in Europe, while in China in the city of Wuhan this symptom was prevalent in 5,1% of the cases studied in 3 hospitals in Europe there was a prevalence of 85,6% in 12 hospitals, the same pattern occurs for dysgeusia which in Wuhan had a prevalence of 5,6% in 3 hospitals and in Europe 88% in 12 hospitals.

Romero-Sanchez et al <sup>16</sup>, 2020 reports more similar percentages to the Chinese in its research with 841 cases 41 of them had anosmia and 52 dysgeusia which corresponds to 4,9% and 6,2% respectively.

#### 4.4 STROKE

Whittaker et al <sup>3</sup>, points out the presence of 6 articles with a stroke report among the 31 studied and in one of the studies 5 patients under 50 years of age including two who had no previous medical history presented the condition. Fatima et al <sup>18</sup> reviewed 39 patients, of which 36 had ischemic stroke (92,3%) and 2 patients had hemorrhagic stroke (5,1%).

Asadi-Pooya et al <sup>10</sup> found lower percentages of ischemic stroke in one of his studies with 221 patients 5% of them had such an event. Nepal et al <sup>4</sup> presented results of varied studies on ischemic strokes with a prevalence of 2,8 to 5% of ische-

**Symptoms of the central nervous system (vertigo, ataxia, headache, stroke, etc.) were more common than those of the peripheral nervous system. Nonspecific symptoms, vertigo, headache, and gustatory and olfactory dysfunctions, despite being present in other viral pictures, have become quite characteristic of the initial symptoms of COVID-19...**

mic events, a prevalence similar to that presented by Wilson and Jack <sup>1</sup> 3% for acute cerebrovascular events.

According to Montalvan et al <sup>5</sup> strokes are uncommon complications of viral infections of the central nervous system, diseases of large vessels have been reported in 5 out of 206 COVID-19 patients and have been reported in a study of a series of 14 stroke cases in 214 patients with COVID-19.

Román et al <sup>14</sup>, 2020 approaches the authors by reporting a 5% incidence of acute stroke including ischemic and hemorrhagic strains in case series studied in China.

Kremer et al <sup>15</sup>, 2020 promoted a study with patients who had an ischemic stroke due to COVID and found 17 patients out of 64 studied, which represents 26% given that it differs greatly from those found by Romero-Sanchez <sup>16</sup> when reporting 11 cases out of the 841 studied leading to a prevalence of 1,3%.

#### DISCUSSION

Symptoms of the central nervous system (vertigo, ataxia, headache, stroke, etc.) were more common than those of the peripheral nervous system. Nonspecific symptoms, vertigo, headache, and gustatory and olfactory dysfunctions, despite being present in other viral pictures, have become quite characteristic of the initial symptoms of COVID-19, suggesting levels of central nervous system involvement.

Strokes of the ischemic and hemorrhagic strokes were described in 12 of the 14 articles studied, gustatory and olfactory dysfunctions in 10 of 14, followed by headache and followed by vertigo.

Anosmia, hyposmia, hypogeusia, and dysgeusia are very common symptoms among COVID-19 patients worldwide, reaching rates of 88% 12 in general, but when isolated olfactory dysfunction predominates and it has been suggested that anosmia could indicate the neurotropic potential of the coronavirus to reach the brain through the olfactory nerve. <sup>14</sup>

When we analyze the data presented on headache we are faced with two extremes, Whittaker et al <sup>3</sup>, 2020 reported 35% headache in the studied patients

and Román et al.<sup>14</sup> 6,5% this may be due to the fact that often this symptom is not easily linked as a neurological manifestation being treated as a general symptom and more common to viral infections than related to a typical clinical picture of COVID, however the “early onset headache and decreased responsiveness are indicators of potential neurological involvement in COVID-19 patients”.<sup>14</sup>

We emphasize, as well as the authors, that these nonspecific neurological manifestations that commonly appear early in the disease may prove to be important predictors of a future deterioration of the clinical picture.<sup>3</sup>

Strokes are due to the thrombo-inflammatory nature of SARS-Cov-2 which

predisposes patients to a state of hypercoagulability due to an increased production of pro-clotting factors and damage to the capillary endothelium which results in a deregulation of its anti-thrombotic properties<sup>3</sup>, - besides Whittaker et al.<sup>3</sup> in his research he found the hemorrhagic type of stroke to be the most prevalent (92%) - coupled with this is the fact that both diseases have similar risk factors predisposing to the disease of the great vessels.<sup>5</sup>

COVID-19 may therefore increase the risk of venous and arterial thromboembolism associated with inflammation, hypoxia, and diffuse intravascular coagulation<sup>14</sup> being more severe in elderly patients, who present risk factors in more severe conditions of the disease.

## CONCLUSION

The complete understanding of the pathophysiological mechanisms of neural invasion of SARS-CoV-2 remains a challenge to medicine, the growing number of neurological symptomatological findings of the most varied types raises the question that this virus could be a new type of underdiagnosed neuropathogen. Through this research it was possible to review the main neurological symptoms and delve into the main types, knowledge that can be a predictor of early interventions, a better understanding of the virus's performance and consequently of achieving better prognosis in affected patients. ■

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