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NEUROPATHIES IN PATIENTS WITH COVID-19: AN INTEGRATIVE REVIEW

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ABSTRACT

Introduction: December 2019, in the city of Wuhan, an outbreak of Severe Acute Respiratory Syndrome began. Although the respiratory system is the most affected, experimental studies show involvement of the nervous system. In view of the similarity in the SARS-CoV-2 genome with SARS-CoV and MERS-CoV, and the presence of reports of neuropathies in patients infected with these, the aim of this article is to describe the main evidence regarding the causal relation between COVID -19 and peripheral neuropathies, in addition to possible mechanisms involved in this process. **Methodology:** This is an integrative literature review, made through articles that discuss the relation between COVID-19 infection and the manifestation of neuropathies. The databases used were: PubMed, LILACS, BIREME, being considered important scientific bases of international scope. Searches were limited to articles from the year 2020, in English and Portuguese. **Discussion:** It is known that the involvement generated by the coronavirus is diffuse, even acting on the central and peripheral nervous systems. Although there are studies that propose a possible causal relation between the new human coronavirus and the manifestation of Guillain-Barré Syndrome, Miller-Fisher Syndrome, and cranial polyneuropathy, there is no evidence to prove this. **Conclusion:** The manifestation of neuropathies by patients with COVID-19 has been demonstrated in different studies. Even so, the mechanism responsible for the appearance of these clinical conditions must be better elucidated. Therefore, it is not yet possible to determine whether the relation between COVID-19 infection and presentation of neuropathies is causal or coincidental.

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INTRODUCTION

December 2019, in the city of Wuhan, an outbreak of Severe Acute Respiratory Syndrome began. It spread so rapidly to different continents that it led the World Health Organization (WHO) to declare a pandemic state in March 2020 (Cucinotta, 2020).

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Although the respiratory system is the most affected, numerous experimental studies and case reports have demonstrated the neurotropic potential of the virus (Montalvan *et al.*, 2020). A retrospective study with 214 patients positive for COVID-19 showed that 36.4% of them had neurological symptoms, 8.9% of which had involvement of the peripheral nervous system.[3] The main reported symptoms were: headache, altered consciousness, ataxia of gait, cerebrovascular diseases, seizures, hyposmia, hypogeusia and neuralgia (Mao, 2020).

In addition, it was observed that patients with more severe conditions were more likely to have neurological symptoms than patients with mild conditions (Mao, 2020). SARS-CoV-2 shares approximately 80% of its genome with other known human coronaviruses, MERS-CoV and SARS-CoV (Dalakas, 2020). Studies carried out with patients with SARS-CoV have shown acute neuromuscular disorders, such as: weakness, hyporeflexia, and symptoms sensory and motor peripherals (Dalakas, 2020; Tsai *et al.,* 2005). Guillain-Barré Syndrome (GBS) and axonal polyneuropathy were observed in patients infected with MERS-CoV (Dalakas, 2020; Algahtani *et al.*, 2016; Kim, 2017). In addition, reports of GBS were found in a child with beta-coronavirus infection (HCV-OC43) (Dalakas, 2020; Turgay *et al.*, 2015). Considering the genetic similarity between the viruses, it is believed that SARS-CoV-2 infection may also trigger neuropathies. It is still unclear whether COVID-19 gains access to the nervous system, thereby inducing neurological disease, or whether the infection triggers autoimmune diseases and from there leads to neurological conditions (Mao, 2019; Desforges, 2014). It is believed that the involvement of cranial nerves may reflect its neurovirulence, since anosmia affects up to 50% of infected patients (Dalakas, 2020). The objective of this article is to describe, based on the current literature, the main evidences regarding the causal relation between COVID-19 and peripheral neuropathies, in addition to possible mechanisms involved in this process.

METHODOLOGY

This is an integrative literature review, made through articles that address the relation between COVID-19 infection and the neuropathies' manifestation.

The databases used were: PubMed, LILACS, BIREME, being considered important scientific bases of international scope. Searches were limited to articles from the year 2020, in English and Portuguese. The inclusion criteria for the sample were: articles that addressed the manifestation of neuropathies in patients infected with COVID-19. And the exclusion criteria were articles that were not in agreement with the proposed theme. For the search, the descriptors indexed in the MESH and in the DeCS "COVID-19" AND "Neuropathy" were used. The process of eligibility of articles for the sample of this review followed three stages: reading the title to suit the theme; reading the summary to investigate your ability to answer the guiding question; and reading the full articles in order to extract the data for later summarization of the outcomes.

All articles included in the sample addressed neurological aspects of COVID-19 infection, and the data were analyzed based on the results. Besides that, it was decided to perform the reverse search, which consists of an article search technique based on the investigation of the references of the articles selected for the sample, in order to expand the search and diversify the results.

RESULTS

By crossing the descriptors in the databases, a total of 22 publications were found. Among these, according to the inclusion and exclusion criteria, 12 were excluded and 10 were selected to compose the sample. In addition to these, 13 articles were found through reverse search. Thus, the sample consisted of 23 articles, between systematic reviews, case reports and editorials.

DISCUSSION

It is known that the involvement generated by the coronavirus is diffuse, acting, even, in the central and peripheral nervous systems (Finsterer, 2020). A recent manifestation was evidenced, which comprises a series of disorders in autoimmunity, the Guillain-Barré syndrome (GBS), also known as acute polyradiculoneuritis (Zhao, 2020). This is evidenced by clinical findings in the nervous conduction of the central nervous system (CNS), in which it is possible to highlight acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and Acute sensorimotor axonal neuropathy (AMSAN), which experiences similarities in its pathophysiology with AMAN, however, associated with sensory involvement (Finsterer, 2020; Skott *et al.,* 2011). In addition to Acute Inflammatory Demyelinating Polyneuropathy, reports of Miller Fisher syndrome (MFS) and cranial polyneuropathy (Gutiérrez-Ortiz *et al.,* 2020). A case report published in The Lancet described Guillain-Barré Syndrome in a 61-year-old patient recently arrived from the city of Wuhan (Shen, 2020). The patient initially did not have a respiratory condition, developing a dry cough and fever just 8 days after admission. Although it cannot be said that the infection was present since admission due to the absence of initial microbiological tests, there was no report of patients with COVID-19 in the neurological ward, nor in the team that attended it, which makes the hypothesis of nosocomial infection less likely. Thus, the article suggests that the GBS may be an initial manifestation of COVID-19. In addition, it is worth noting that in this case the Guillain-Barré Syndrome did not manifest itself as post-viral, as is its classic form and seen in other reports of GBS and COVID-19 (Finsterer, 2020), but in a para-infectious form, as also reported in cases of Zika virus infection (Shen, 2020; Parra, 2016; Brasil, 2016). The prevalence of GBS concomitant with SARS-CoV-2 is low, but it can be said that it exists, and is more prevalent in the elderly male population. Among the subtypes, Acute Inflammatory Demyelinating Polyneuropathy was the most commonly observed. [2] Increasing evidence suggests that the appearance of GBS and the involvement of cranial nerves in COVID-19 represent autoimmunity.[17] One of the arguments that corroborate this hypothesis is the fact that the cerebrospinal fluid was negative for the presence of SARS-CoV-2 in most patients with GBS who underwent lumbar puncture (Costello, 2020; Dalakas, 2020). In addition, the improvement observed in patients after the use of intravenous immunoglobulin suggests a continuous immune response, as in other autoimmune diseases (Costello, 2020; Dalakas, 2020). A 36-year-old patient, living in an endemic region for COVID-19, was described as the first presumptive case of Miller-Fisher syndrome associated with COVID-19 (Lantos, 2020). In this patient, progressive ophthalmoparesis was observed, which included the left oculomotor nerve and the abducent nerve bilaterally, in addition to ataxia and hyporeflexia. In the MRI images of this patient, including images of the orbits and retro-orbital region, with and without gadolinium, a T2 hyperintense signal from the left cranial nerve was notable. It is worth noting that the serological ganglioside antibody test showed negative anti-GQ1b, and when the antibody test is negative in patients with MFS, the symptoms may be due to viral neurotropism, and not to immunity-mediated injury, which demonstrates the absence of consensus on the mechanism that the virus affects the nervous system (Lantos, 2020; de Silva , 2019). A study carried out at the university

hospital in Madrid, documented a case of Cranial Polyneuritis, or also known as Multiple Isolated Cranial Neuropathy, in a patient previously positive for Covid-19.[14] It is believed that SARS-CoV-2 is responsible for such occurrence, in view of the temporal relation. The pathophysiological mechanism that manages cranial polyneuritis in the Covid-19 scenario includes an aberrant immune response or direct viral neuropathogenic effects. However, no SARS-CoV-2 was found in cerebrospinal fluid (CSF) (Shen, 2020). Another study published in Northern Ireland described peripheral neuropathy in a 69-year-old patient (Abdelnour, 2020). The patient reported spontaneous resolution paraparesis three days before visiting the hospital for a chronic cough. Upon admission, the patient tested positive for COVID-19 and was admitted. Peripheral neuropathy could not be better characterized because no lumbar puncture or nerve condition test was performed, given the risk due to covid-19 status. The S proteins of the new human coronavirus bind to respiratory cells not only through receptors of Angiotensin-Converting Enzyme 2 (ACE-2), but also through glycoproteins that contain sialic acid and gangliosides (Costello, 2020; Fantini, 2020). In view of the molecular mimicry between peripheral nerve glycolipids and infections by *Campylobacter jejuni* and Zika virus, are known triggers for GBS, the role of gangliosides in the condition of peripheral nerve autoimmunity becomes intriguing (Costello, 2020; Dalakas, 2015). In summary, there were no reports of other neuropathies related to patients with COVID-19. Although the studies shown above propose a possible causal relation between the new human coronavirus and the manifestation of Guillain-Barré Syndrome (Shen, 2020; Finsterer, 2020; Sedaghat, 2020), Miller-Fisher Syndrome (Gutiérrez-Ortiz, 2020; Lantos, 2020), and cranial polyneuropathy (Gutiérrez-Ortiz, 2020), there is no evidence to support this. Thus, it is not possible to define whether SARS-CoV-2 infection is a triggering factor for neuropathies or just coincidental.

CONCLUSION

The manifestation of neuropathies from patients with COVID-19 has been demonstrated in different studies. Even so, the mechanism responsible for the appearance of these clinical conditions should be better elucidated, given that there is no evidence as to the virus's ability to reach the nervous system and induce neurological diseases or these manifestations being related to autoimmune processes. Therefore, it is not yet possible to determine whether the relation between COVID-19 infection and presentation of neuropathies is causal or coincidental. Experimental studies should be performed in order to explore the pathophysiological mechanism associated with the appearance of neurological symptoms in patients infected with SARS-CoV-2. Thus, there will be a greater understanding of viral pathogenicity, allowing new control and treatment measures to be established.

REFERENCES

Abdelnour L, Eltahir Abdalla M, Babiker S. 2020. COVID 19 infection presenting as motor peripheral neuropathy. *J Formos Med Assoc*., 119(6):1119-1120. doi:10.1016/ j.jfma. 2020.04.024

Algahtani H, Subahi A, Shirah B. 2016. Neurological Complications of Middle East Respiratory Syndrome Coronavirus: A Report of Two Cases and Review of the Literature. *Case Rep Neurol Med*., 2016:3502683. doi: 10.1155/ 2016/3502683

Brasil P, Sequeira PC, Freitas AD, *et al*. 2016. Guillain-Barré syndrome associated with Zika virus infection. *Lancet*. 387(10026):1482. doi:10.1016/S0140-6736(16)30058-7

Costello F, Dalakas MC. 2020. Cranial Neuropathies and COVID-19: Neurotropism and Autoimmunity. Neurology. 2020. DOI: https://doi.org/10.1212/ WNL.000 000000 00 09921.

Cucinotta D, Vanelli M. 2020. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 91(1):157-160. Published 2020 Mar 19. doi:10.23750/abm.v91i1.9397

Dalakas MC. 2015. Pathogenesis of immune-mediated neuropathies Biochimica et Biophyisca Acta., 1852(4):658-666

Dalakas MC. 2020. Guillain-Barré syndrome: The first documented COVID-19-triggered autoimmune neurologic disease: More to come with myositis in the offing. Neurology(r) Neuroimmunology & Neuroinflammation. Sep;7(5). DOI: 10.1212/nxi.0000000000000781.

de Silva NL, Weeratunga P, Umapathi T, *et al*., 2019. Miller Fisher syndrome developing as a parainfectious manifestation of dengue fever: a case report and review of the literature. J Med Case Rep., 13:120 doi:10. 1186/ s13256-019-2066-z pmid:31043165

Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. 2014. Human coronaviruses: Viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Research*, 194: 145–158

Fantini J, Di Scala C, Chahinian H, Yahi N. 2020. Structural and molecular modeling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection, International Journal of Antimicrobial Agents, doi: https://doi.org/10.10 16/j.ijantimicag.2020.1059

Finsterer J, Scorza FA, Ghosh R. 2020. COVID-19 polyradiculitis in 24 patients without SARS-CoV-2 in the cerebro-spinal fluid. *J Med Virol*., 10.1002/jmv.26121. doi: 10. 1002/jmv.26121

Finsterer J, Stollberger C. 2020. Update on the neurology of COVID-19. J Med Virol. 2020. https://doi.org/ 10.1002/ jmv26000

Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, Pedro-Murillo ES, Bermejo-Guerrero L, Gordo-Mañas R. 2020. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. Neurology. DOI: 10.1212/WNL.0000000000009619.

Kim JE, Heo JH, Kim HO, *et al*. 2017. Neurological Complications during Treatment of Middle East Respiratory Syndrome. *J Clin Neurol*., 13(3):227-233. doi:10.3988/jcn.2017.13.3.227

Lantos JE, Strauss SB, Lin E. 2020. COVID-19–Associated Miller Fisher Syndrome: MRI Findings. *American Journal of Neuroradiology*. DOI: https://doi.org/ 10.3174/ ajnr. A6609

Mao L, Jin H, Wang M, *et al*., 2020. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China [published online ahead of print, Apr 10]. *JAMA Neurol*. 2020;77(6):1-9. doi:10.1001/jamaneurol.2020.1127

Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. 2020. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. *Clin Neurol Neurosurg*. 194:105921. doi:10.1016/j. clineuro. 2020.105921

Parra B, Lizarazo J, Jiménez-Arango JA. *et al*., 2016. Guillain-Barré Syndrome Associated with Zika Virus Infection in

Colombia. *N Engl J Med*., 375(16):1513-1523. doi:10.1056/ NEJMoa1605564

Sedaghat Z, Karimi N. 2020. Guillain Barre syndrome associated with COVID-19 infection: A case report. *J Clin Neurosci*. 2020;76:233-235. doi:10.1016/j. jocn.2020. 04.062

Skott H, Muntean-Firanescu C, Samuelsson K. *et al*., 2019. The cerebelar phenotype of Charcot-Marie-Tooth neuropathy type 4C. Cerebellum Ataxias.6:9. https://doi.org/ 10.1186/s40673-019-0103-8

Tsai LK, Hsieh ST, Chang YC. 2005. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*., 14(3):113-119.

Turgay C, Emine T, Ozlem K, Muhammet SP, Haydar AT. 2015. A rare cause of acute flaccid paralysis: Human coronaviruses. *J Pediatr Neurosci*., 10(3):280-281. doi:10.4103/1817-1745.165716

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

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