Neuromuscular complications by COVID-19: a systematic literature review

Complicações neuromusculares pela COVID-19: uma revisão sistemática de literatura

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ABSTRACT: Introduction: Coronaviruses are zoonotic RNA viruses, and are also a family of viruses that cause respiratory infections. One of the known types is SARS-CoV-2, a new coronavirus described in late 2019, responsible for causing the COVID-19. Besides the respiratory tract, such pathology can affect several organ systems and among these, the neuromuscular system has been pointed out as a target of SARS-CoV-2. Objective: To determine whether there is a relationship between COVID-19 and the emergence of neuromuscular diseases. Methodology: Systematic review using the PRISMA method, with data collection carried out in PubMed and BVS, verifying the relationship between COVID-19 and the emergence or intensification of neuromuscular diseases. The collected articles were published between January 2020 and March 2021. A total of 1366 articles were found and 56 were approved for the systematic review. Results: 56 studies pointed out a link between COVID-19 and the development of neuromuscular pathologies, highlighting: Guillain-Barré syndrome and its variations (n=37), Gravis myasthenia (n=4), Myelitis (n=2). Discussion: Regarding Guillain-Barré Syndrome and its association with COVID-19, it was observed that the main neuromuscular signs and symptoms reported were: quantitative reflex deficits (hyporeflexia or areflexia), paresthesia, paralysis, decreased muscle strength, numbness and tingling. Therefore, it was noted that there are several relationships between COVID-19 and the development of neuromuscular diseases or syndromes. Conclusion: It is possible to see that there is strong evidence of a relationship between the pathophysiology of COVID-19 and the emergence of neuromuscular syndromes, with Guillain-Barré Syndrome being the most reported dysfunction in different locations around the world. In this sense, it is interesting the development of research with a larger sample size, as well as the need to understand the mechanism of viral action on the nervous system in order to obtain more efficient treatments for these clinical pictures.

Keywords: Covid-19; Neuromuscular diseases; Systematic review.

RESUMO: Introdução: O Coronavírus é um vírus zoonótico de RNA, tratando-se também de uma família de vírus que causam infecções respiratórias, em que um dos tipos conhecidos é o SARS-CoV-2, que é um novo coronavírus descrito no final de 2019, sendo responsável por provocar a doença chamada de COVID-19. Além do trato respiratório, tal patologia pode afetar vários sistemas orgânicos e dentre esses, o sistema neuromuscular tem sido apontado como alvo do SARS-CoV-2. Objetivo: Verificar se há relação entre a COVID-19 e o surgimento de doenças neuromusculares. Metodologia: Revisão sistemática pelo método PRISMA, com coleta de dados realizada nas bases PubMed e BVS, verificando a relação entre a COVID-19 e o surgimento...
or intensification of the neuromuscular diseases. The articles colected were published between January 2020 and March 2021. They were found 1366 articles and approved 56 for the revision sistemática. Resultados: 56 studies apontaram ligaqação entre a COVID-19 and the development of pathologies neuromuscular, destacando-se: Síndrome de Guillain-Barré and its variações (n=37), Miastenia de Gravis (n=4), Mielite (n=2). Discussão: Em relação a Síndrome de Guillain-Barré and sua associação com a COVID-19, observou-se que os principais sinais e sintomas neuromusculares relatados foram: déficits quantitativos of the muscles and the ventromedial pathways responsible for the postural and the descending tracts of the spinal cord, whose lateral pathways are responsible for controlling the distal muscles and the ventromedial pathways responsible for the postural muscles. It reveals that various neuromuscular disorders are differentiated by the topographical regions where the lesions occur in the motor units. The Guillain-Barré syndrome was observed, in this panorama, as the most habitually present in these cases, defined as a pathology affecting the cranial and peripheral nerves by an acute inflammatory condition leading to limb weakness.

INTRODUCTION

Coronavirus is a zoonotic virus, an RNA virus of the Nidovirales order, in the Coronavirus family. It is a family of viruses that causes respiratory infections, among which the most widespread nowadays, due to the current pandemic, is the severe acute respiratory syndrome (SARS). The types of coronaviruses, in this conjunction, are known up to now as alpha coronavirus HCoV-229E and alpha coronavirus HCoV-NL63, beta coronavirus HCoV-OC43, and beta coronavirus HCoV-HKU1, SARS-CoV (causing SARS), MERS-CoV (causing Middle East respiratory syndrome or MERS), and SARS-CoV-2, a new coronavirus described in late 2019 after cases were reported in China, responsible for generating the disease called COVID-19.

In this context, in December 2019, the new coronavirus (SARS-CoV-2) emerged, responsible for disseminating the COVID-19 pandemic in China, which resulted in a severe global health crisis. The virus spread quickly, starting on the Asian continent and spreading throughout the planet. And for that reason, the World Health Organization (WHO) declared a Public Health Emergency of International Importance on January 30, 2020, and later, on March 11, 2020, it was declared as a pandemic status.

Considering this, according to data published by the WHO, as of October 23, 2021, there were a total of 242,348,657 cumulative cases of COVID-19 and a total of 4,927,723 cumulative deaths on the planet in around 210 countries and territories worldwide.

Additionally, neuromuscular disorders have been reported in patients with COVID-19 related to the somatic motor system, which consists of neurons controlling the muscles that perform movements. Meanwhile, the somatic motor system is divided into the central and peripheral, whereas, the peripheral motor control is coordinated by the information pathways from the central level, through the descending tracts of the spinal cord, whose lateral pathways are responsible for controlling the distal muscles and the ventromedial pathways responsible for the postural muscles. It reveals that various neuromuscular disorders are differentiated by the topographical regions where the lesions occur in the motor units. The Guillain-Barré syndrome was observed, in this panorama, as the most habitually present in these cases, defined as a pathology affecting the cranial and peripheral nerves by an acute inflammatory condition leading to limb weakness.

METHODOLOGY

This study performed a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendation. Searches were conducted from May 20, 2021, to June 30, 2021, in the U.S. National Library of Medicine (PubMed) and Virtual Health Library (VHL) databases. The search strategy was based on Boolean operators with the following keyword combinations: ‘covid-19 AND muscle-skeletal system’; ‘covid-19 AND neuromuscular disorders’; ‘covid-19 AND neuromuscular manifestations’. The collected articles were published from January 2020 to March 2021 and were screened, in the first phase, by title, abstract, and methodology, to identify whether they were appropriate for the proposed topic and had consistent methods; then, in the second screening, repetitions were excluded, and then those included were analyzed by different researchers; thus, each included article was thoroughly examined by two independent reviewers.

Inclusion criteria were: (1) Articles in English, Portuguese, or Spanish; (2) Open access articles; (3) Papers relating to the triggering of neuromuscular disorders and covid-19; (4) Articles associated with intensifying signs and symptoms of neuromuscular disorders and covid-19; (5) Typology studies: case series, case reports, and primary articles. The exclusion criteria adopted were: (1) Articles tangentially related to the onset or intensification of neuromuscular disorders, their signs, and symptoms with COVID-19; (2) Articles on neuromuscular disorders concerning psychological and psychiatric dysfunctions caused by COVID-19; (3) Repetitions. Therefore, in the third analysis, papers were stratified according to the findings of the relationship between COVID-19 and neuromuscular disorders.

Our study analyzed each article separately; its data were extracted and then grouped, and after this step was performed, the agreements and disagreements among the
findings from all the papers were sorted. It was possible this way to prepare the review based on its leading question: “What is the relationship between COVID-19 and the emergence of neuromuscular disorders?”.

The present work is a systematic review of literature; thus, there was no need for approval by a research ethics committee.

RESULTS

This search uncovered 1194 articles in PubMed and 172 articles in VHL. The researchers selected primary research studies, case reports, and case series. There was a total of 208 selected studies. Thirty-six studies were excluded due to repetitions, and the research included 176 for the second screening. After the second review, 56 papers were approved to compose this systematic review.

The studies included in this review were from different locations in a short period, demonstrating the rapid spread of SARS-CoV-2. Thus, the review included articles from the following countries: United States of America - USA (15), Italy (6), United Kingdom (5) Germany (4), Spain (4), France (3) Iran (3), India (2), Turkey (2), Japan (2) China (1), Brazil (1), Denmark (1), Romania (1), Philippines (1), Colombia (1), Israel (1), and Australia (1). In addition, there were studies conducted jointly by two countries: Italy and Germany (1) and India and the USA (1).

![Flowchart of the systematic review phases](Source: Authors’ data)

**Figure 1:** Flowchart of the systematic review phases

This study included 50 case reports, 2 case series, 1 clinical trial, 1 cohort, and 2 case-controls. The review described 76 patients aged 22 to 89 years old in the case reports and case series. Each report was analyzed separately to prepare this review and grouped its data. The cohort study examined the medical data from 47 patients. In the case-control study, 41 patients with COVID-19 were followed up.

Thus, sixty studies found and reported an association between COVID-19 and the development of neuromuscular pathologies. The most prominent manifestations identified were: Guillain-Barré Syndrome (GBS) and its variations (n=37), Gravis Myasthenia (n=4), Myelitis (n=2), Demyelination and Polyradiculoneuritis (n=2), Diaphragmatic Myoclonia and Brachial Plexopathy (n=2), Myopathy (n=2), Myositis and Bulbar Weakness (n=1), Peripheral Polyneuropathy (n=1), Acute Demyelinating Encephalomyelitis (ADEM) (n=2), Amyotrophy (n=2), Bell’s Palsy (n=2) and Rhabdomyolysis (n=2).

The review observed the results demonstrated
that the new beta-enveloped coronavirus’s viral pathophysiology interfered in the central nervous system (CNS) and peripheral nervous system (PNS), muscles, and neuromuscular junctions. The researchers noted that there are several relationships between COVID-19 and the development of neuromuscular disorders or syndromes based on that context.

DISCUSSION

Guillain-Barré syndrome

Studies show that CGS is associated with COVID-19. Due to the absence of other clinical findings related to neuromuscular symptoms, it is closely considered if SARS-CoV-2 infection would be the cause of such manifestation. Furthermore, in the study by Fragiel et al., the research identified 11 cases of GBS among patients infected with the new coronavirus, and the relative frequency of GBS was higher in patients diagnosed with COVID-19 compared to patients who had tested negative for the disease.

The case report by Hirayama et al. related to the onset of the first neurological symptoms of GBS observed that such manifestations started in the lower limbs, resembling neuropathies; GBS is classified as polyradiculoneuritis, which has an acute or subacute onset, responsible for generalized flaccid paralysis, initially affecting the digital extremities of the lower limbs. However, it is worth noting that this study states that patients with GBS associated with SARS-CoV-2 infection may present negative results for antiganglioside antibodies.

Based on this perspective, the main neuromuscular signs and symptoms observed reported quantitative reflex deficits (hyporeflexia or areflexia), paresthesia, paralysis, numbness, tingling, and decreased muscle strength. The latter was verified by the Medical Research Council (MRC) scale in recent studies. Furthermore, Rajdev et al. study show no significant difference between proximal and distal muscle groups. Thus, GBS-related COVID-19 causes decreased muscle strength, and in some patients, this decrease is uniform in the upper limbs (ULs) or lower limbs (LLs). Other symptoms observed were facial nerve involvement and radicular muscle pain, but this characteristic is not often presented in cases of GBS after COVID-19.

As for the evolution of neurological symptoms, the case report by Padroni et al. demonstrates that the development of such symptoms is associated with a post-infectious condition. Moreover, clinical signs related to inflammatory laboratory parameters after infection by COVID-19 are associated with neurological symptoms in patients. Thus, neurological symptoms may begin in patients after SARS-CoV-2 infection.

However, it is worth noting that some studies presented divergence as to the onset of signs and symptoms of GBS. However, most case reports and case series point out that the neuromuscular symptoms appear after the viral symptoms, such as fever, cough, and headache. A study by Zhao et al. demonstrated that neuromuscular symptoms began before the symptoms of COVID-19, suggesting that GBS associated with SARS-CoV-2 infection may follow a para-infection pattern rather than the classic post-infection profile.

Although the case report by Zhao et al. has displayed limitations, such as the absence of microbiological tests upon patient admission and the fact that the respiratory symptoms appeared 7 days after the onset of GBS symptoms, making it prudent to consider the hypothesis the patient developed GBS from an unknown cause and coincidentally acquired SARS-CoV-2 infection. In this study, the researchers pointed out this bias related to the possibility of COVID-19 and GBS symptoms occurring concomitantly, which may be linked to an unusual accentuated immune response or a direct neuropathogenic effect on the nervous system. Also, the possibility of both problems occurring in a post-infectious nature has been questioned. Thus, there is a possibility of no direct relationship between COVID-19 and GBS.

Furthermore, it is worth noting that although studies point to the existence of an association between infection by the new coronavirus and neuromuscular diseases, there is still no understanding of the pathogenesis of such manifestation. However, researchers observed that most studies reported cough, dyspnea, fever, and olfactory changes as the main symptoms preceding the development of GBS.

In parallel, such symptoms are related to the reported hypotheses on the pathophysiology of SARS-CoV-2 infection and its effects on the nervous and muscular systems, such as stimulation of inflammatory cells and cytokine production, creating immune-mediated mechanisms that may be associated with the development of GBS; and neurotropism that may occur through the circulation or via the olfactory epithelium, enabling the new coronavirus to reach encephalic regions and bind to the ACE receptor.

Furthermore, because of the recognition of neurological findings associated with COVID-19 infection, a possible association between SARS-CoV-2 infection and Miller Fisher syndrome (MFS), a GBS variant, has been observed. Such an association is understood from the viewpoint of imaging examinations since MRI results point to the first presumptive case of this relationship. In other studies with similar neurological findings, the medical staff verified records of manifestations such as oculomotor nerve palsies (III), ataxia, and anosmia in patients who tested positive for COVID-19 and were later diagnosed with SMF.
**Myasthenia gravis**

As for the relationship between SARS-CoV-2 infection and Myasthenia Gravis (MG), a case report that aimed to understand the neurological implications resulting from COVID-19 infection reported a patient with MG infected by the new coronavirus and after four days presented a suggestive exacerbation of the condition, characterized by generalized weakness, predominantly proximal, mild palpebral ptosis, especially on the left, with palpebral and mandibular fatigue, as well as dysphonia, diplopia, and hyporeflexia. Such a finding is convergent with the study by Sripastava et al., which hypothesized that the manifestation of MG is effectively a specific neurological complication of COVID-19 infection, which can manifest, for example, clinical findings such as ptosis and fatigue.

Furthermore, it is noteworthy that a study carried out with five patients diagnosed with COVID-19 and who had MG concluded that only one case presented a myasthenic exacerbation. However, it is worth mentioning that the authors make some reservations concerning this condition since the diagnosis of COVID-19 and the associated therapies such as azithromycin and hydroxychloroquine can contribute to this exacerbation scenario. Thereby the cautious use of these drugs is essential in patients with MG. Moreover, in a similar study involving 3 patients with MG diagnosed with COVID-19, the researchers found only one patient who presented exacerbation. This recurrence highlights the need to understand the association between SARS-CoV-2 infection and complications of neurological conditions.

**Myelitis**

Related to the association between COVID-19 and myelitis, clinical findings suggest an association with acute transverse myelitis in a patient who, after getting infected by SARS-CoV-2, presented a condition of increased tonus, as well as hyperreflexia and reduced proprioception of the lower limbs. In addition, bilateral irregular paresthesia was recorded at the level of the umbilicus, reduced anal tonus to the rectal touch, findings consistent with upper motor neuron damage. This finding is consistent with a case report that included, besides a similar clinical presentation, magnetic resonance imaging, cerebrospinal fluid (CSF), and laboratory findings, which indicated acute transverse myelitis as a probable complication of the COVID-19 viral infection; and a case report that reported a patient presenting neurological deficit, which started jointly with the viral symptoms of the new coronavirus infection, whose magnetic resonance imaging suggested myelitis.

**Demyelination and polyradiculoneuritis**

The researcher sought to understand the association between viral infection and a demyelinating neurological condition regarding demyelination and polyradiculoneuritis. A study found mild distal latency in tibial nerves, partial conduction blockage, rare or absent F waves, suggestive of bilateral motor demyelinating tibial neuropathy, making it possible to understand the evidence of neurological impact associated with respiratory disease and symptoms such as fatigue, transient memory loss, and myalgia. In another review, a study by Pfefferkorn et al. reported a patient with a clinical condition pointing to substantial tetraparesis, including the loss of muscle strength and generalized areflexia electoneuromyography suggested peripheral demyelination, while MRI indicated a polyradiculoneuritis at numerous levels of the spine.

Concerning the association between infection by the new coronavirus and the conditions of diaphragmatic myoclonus and brachial plexopathy, a study comprising the case report from two patients found the appearance of persistent involuntary paroxysmal movements in the abdomen after treatment for COVID-19 in both analyses. The first case was diagnosed with myoclonus or Van Leeuwenhoek diaphragmatic disease and in the second case, the researchers found the involvement of the diaphragm to generate incapacitating shortness of breath, through an electroencephalogram (EEG) showing lateralized periodic discharges, suggesting a direct association between the treatment of the disease and the neurological condition. Furthermore, the relationship between the treatment of the disease and neurological impacts is observed in a case report of a patient presenting severe weakness of the left upper extremity and neuropathic pain, with hyporeflexia of the left biceps and left brachioradialis and triceps areflexia, as well as generalized muscle strength loss, and marked reduction in nerve conduction studies.

**Myopathy**

Related to the level of myopathic changes associated with SARS-CoV-2 infection, in a clinical trial, such manifestations were found in one or more muscles in 55% of patients, and a shorter potential motor unit duration was observed in the control group compared to healthy controls. Furthermore, a case report reported a patient presenting with severe weakness and muscle loss; the complementary examination findings indicated critical illness myopathy due to COVID-19, congruent with the possibility of an association between the two pathological conditions.

**Myositis and Bulbar Weakness**

Concerning myositis and bulbar weakness and COVID-19, a study by Zhang et al. observed that the patient with dysarthria, dysphagia, odynophagia, and other neurological symptoms was diagnosed with myositis and bulbar weakness. In this context, the association of these
Peripheral polyneuropathy

As for the association between polyneuropathy and new coronavirus infection, a case report of post-SARS-CoV-2 infection in which the patient presented neuromuscular symptoms after 4 months of COVID-19 treatment, with involvement of parts of the lower and upper limbs, was diagnosed with sensory axonal polyneuropathy. In this context, the onset of neurological symptoms resembles chronologically the findings of post-infection conditions as reported in other studies.

Acute Demyelinating Encephalomyelitis (ADEM)

Concerning Acute Demyelinating Encephalomyelitis (ADEM) and its association with COVID-19, the researchers noticed that studies on this relationship are scarce. McCuddy et al. report that their patients suffered from fatigue, cough, and fever leading to acute respiratory distress syndrome secondary to SARS-CoV-2 infection. Several findings were presented that prove ADEM diagnosis from the MRI. Congruent to that, Lopes et al. narrate in their report that their patients suffered from fatigue, cough, and fever leading to acute respiratory distress syndrome secondary to SARS-CoV-2 infection. Several findings were presented that prove ADEM diagnosis from the MRI. Congruent to that, Lopes et al. narrate in their two reports, there was compatibility with ADEM related to COVID-19, since, besides the clinical presentation and neuroimaging showing multifocal abnormalities in the white matter, there was also previously confirmed viral infection, CSF study ruling out CNS infection, negative oligoclonal bands, and lack of the previous history related to demyelinating diseases in both patients. In this bias, the need for good clinical propaedeutic and the performance of imaging exams that can previously capture these alterations and correlate them with coronavirus infection is perceptible.

Amyotrophy

It is related to the relationship between new coronavirus infection and amyotrophy condition, a case report of a 52-year-old patient who presented neuromuscular symptoms after SARS-CoV-2 infection describes a probable association between neuralgic amyotrophy and COVID-19. This finding converges with the study by Ismail et al., which reports a case of severe asymmetric bilateral neuritic amyotrophy in a 32-year-old man related to a laboratory-confirmed SARS-CoV-2 infection. Thus, it is possible to verify the existence of a relationship between amyotrophy and SARS-CoV-2, which was confirmed in the previously mentioned studies.

Bell’s facial palsy

Pertaining to the association between SARS-CoV-2 infection and Bell’s facial palsy, a case report reported a twenty-eight-year-old pregnant patient diagnosed with lower motor neuron paralysis of the right facial nerve after presenting viral symptoms and testing positive for COVID-19. Such a finding is congruent with the case series of eight patients with COVID-19, demonstrating that peripheral facial paralysis can occur during the clinical course of the disease or anticipate other typical manifestations, such as fever and respiratory symptoms. Thus, although the incidence is extremely small, it is possible to relate the pathophysiology of SARS-CoV-2 to facial nerve affection.
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