COVID-19 AND MYASTHENIA GRAVIS RELATIONSHIP: A BRIEF LOOK

RELAÇÃO ENTRE COVID-19 E MIASTENIA GRAVE: UM BREVE OLHAR

RELACIÓN DEL COVID-19 Y MYSTHENIA GRAVIS: UNA BREVE MIRADA

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RESUMO: Introdução: Desde que a infecção pelo novo coronavírus, responsável pela Síndrome Respiratória Aguda Grave (SARS-CoV-2), foi declarada uma pandemia pela Organização Mundial da Saúde (OMS), vários esforços têm sido feitos nas áreas de diagnóstico e pesquisa em mecanismos fisiopatológicos e suas complicações. Um dos campos que mostraram mais complicações pelo SARS-CoV-2 é a neurologia. Até o momento, poucos estudos associam a Miastenia Gravis (MG) à doença infecciosa por coronavírus (COVID-19), mas é possível estabelecer essa correlação, principalmente em pacientes em terapia imunossupressora. **Objetivo:** Revisar brevemente relatos de casos e estudos observacionais da crescente literatura sobre a relação entre COVID-19 e Miastenia Gravis. **Método:** Foi realizada uma revisão integrativa com base na literatura disponível nas bases de dados PubMed e Google Scholar, utilizando os descritores "myasthenia gravis" e "COVID-19" e "SARS-CoV-2". Esta busca incluiu artigos publicados até 4 de novembro de 2020 em inglês ou espanhol. Após a leitura dos artigos disponíveis na íntegra, foram selecionados aqueles que mostraram relação entre COVID-19 e SARS-CoV-2 com um aspecto específico da MG. Inicialmente foi encontrado um total de 415 artigos e 10 foram finalmente selecionados. **Resultados:** O manejo clínico dos pacientes e uma atenção especial à condição respiratória e ao monitoramento dos efeitos colaterais dos medicamentos devem ser realizados. **Conclusão:** Apesar de na maioria dos casos haver recuperação e bom desfecho, é importante considerar que infecções virais precedentes podem desencadear eventos miastênicos.
Descritores: Myasthenia Gravis; Infecções por Coronavírus; SARS-CoV-2 ; Pandemia.

Abstract: Introduction: Since infection by the Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO), numerous efforts have been made in the fields of diagnosis and research into pathophysiological mechanisms and their complications. One of the fields that has shown the

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most complications by SARS-CoV-2 is neurology. So far, few studies have associated Myasthenia Gravis (MG) with Coronavirus infectious disease (COVID-19), but it is possible to establish this correlation, especially in patients undergoing long-term immunosuppression therapy. **Objective:** To briefly review case reports and observational studies of the growing literature regarding on the relantionship about COVID-19 and MG. **Method:** An integrative review was performed based on the literature available in the PubMed and Google Scholar databases, using the descriptors "myasthenia gravis" and "COVID-19" and "SARS-CoV-2". This search included articles published up until 4th November 2020 in English or Spanish. After reading the articles available in their entirety, those related specifically to relationship between COVID-19 and SARS-CoV-2 with a specific aspect of MG were selected. It was initially found a total of 415 articles and 10 were finally selected. **Results:** The clinical patients management and a special attention to the respiratory condition and the monitoration of drug side effects have occur. **Conclusion**: Besides most of the cases go to recovery and good outcome, it is important to consider that preceding viral infections could trigger to myasthenic events.
Keywords: Myasthenia Gravis; Coronavirus Infections; SARS-CoV-2; Pandemic.

RESUMEN: Introducción: Desde que la infección por el nuevo coronavirus, responsable del Síndrome Respiratorio Agudo Severo (SARS-CoV-2), fuera declarada pandemia por la Organización Mundial de la Salud (OMS), se han realizado varios esfuerzos en las áreas de diagnóstico y investigación de los mecanismos fisiopatológicos y sus complicaciones. Uno de los campos que mostró más complicaciones con el SARS-CoV-2 es la neurología. Hasta la fecha, pocos estudios han asociado la miastenia grave (MG) con la enfermedad infecciosa por coronavirus (COVID-19), pero es posible establecer esta correlación, especialmente en pacientes sometidos a terapia inmunosupresora. **Objetivo:** Revisar brevemente los informes de casos y los estudios observacionales de la creciente literatura sobre la relación entre COVID-19 y MG. **Método:** Se realizó una revisión integradora con base en la literatura disponible en las bases de datos PubMed y Google Scholar, utilizando los descriptores "myasthenia gravis" y "COVID-19" y "SARS-CoV-2". Esta búsqueda incluyó artículos publicados hasta el 4 de noviembre de 2020 en inglés o español. Después de leer los artículos disponibles en su totalidad, se seleccionaron aquellos que mostraban una relación entre COVID-19 y SARS-CoV-2 con un aspecto específico de MG. Inicialmente se encontraron un total de 415 artículos y finalmente se seleccionaron 10. **Resultados:** Se debe realizar un manejo clínico de los pacientes y especial atención a la condición respiratoria y monitoreo de efectos secundarios de los medicamentos. **Conclusión:** Aunque en la mayoría de los casos hay recuperación y buen pronóstico, es importante considerar que infecciones virales previas pueden desencadenar eventos miasténicos.

Palabras clave: Miastenia Gravis; Infecciones por Coronavirus; SARS-CoV-2; Pandemia.

1. INTRODUCTION

The Coronavirus infectious disease (COVID-19), caused by the Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) in March 2020. The Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, up to 20th September 2023, reports

676.609.955 global cases and 6.881.955 global deaths, were The United States, Brazil and Mexico are the countries with the highest number of deaths[1].

Pandemic has had a major impact in several sectors worldwide, from public health to economy. One of the major concerns of the infection, in addition to the management of serious situations that require intensive treatment, are the complications, especially neurological ones. The respiratory system is the principal that is affected, but several studies are showing the virus capacity to invade other groups of systems. The synapses between motor neurons and skeletal muscle fibers – characterizing the neuromuscular junction (NMJ) – are the responsible to allows, among other basic functions, the respiration[2]. NMJ dysfunctions, like the most frequent of them – Myasthenia gravis (MG) – can differ in etiology by genetic, toxic, or immunological causes, impacting the neuromuscular transmission, and may even be lethal.

MG is known to be and autoimmune disorder due to antibodies attack, in a direct mechanism, against postsynaptic acetylcholine receptor (AchR) – in 80% of the cases – or against postsynaptic membrane of the NMJ[3]. Since the beginning of COVID-19 pandemic, some studies are hypothesizing and studying mechanisms that could explain the impact of SARS-CoV-2 infection on neurologic illness.

One pathology that has been described its relation to COVID-19 is Guillain-Barré Syndrome (GBS), related as a complication of the virus infection. Further, individuals with neuromuscular diseases (NMDs), like GBS, are considered as a risk group more vulnerable to develop severe forms of COVID-19[4]. The clinical presentations suggest a parainfectious etiology of GBS, probably secondary to molecular mimicry in a post-infectious status or a hyperimmune response[4]. This hyperacute immune response can be explained, at least in part, by cytotoxic $CD8^+$ T cells indirect effects, cross-reaction in immune mediators or by exacerbation of inflammatory responses with “cytokine storm” event[5].

So far, few studies have associated MG with COVID-19, but it is possible to establish this relationship, especially in patients undergoing long-term immunosuppressive therapy. Most of the mechanisms remains unclear and it is unknown the real risk of amplification of cellular responses due to COVID-19 for NMDs[6].

Therefore, this review briefly focuses on case reports and observational studies of the growing literature regarding on the relationship about COVID-19 and MG.

2. METHODS

It was analyzed published reports regarding on COVID-19-associated to MG of PubMed and Google Scholar databases. Case reports and observational studies published up until 4th November 2020 were initially selected based on the abstracts and the studies classification and/or relevance. Full-text articles were acquired from journals' websites. Figure 1 shows a PRISMA flowchart representing the search in the databases and the chart 1 summarize the publications included in this review.

This integrative review used the descriptors "*myasthenia gravis*" and "*COVID-19*" and "*SARS-CoV-2*". Duplicate articles, letters to editors, guidance for clinical managements, current practice guidelines or specifics considerations for treatment were excluded, by exclusion criteria. After reading the articles available in their entirety, those linked to relationship between COVID-19 and SARS-CoV-2 with a specific aspect of MG were selected. Data extraction of research work selected was executed by independent researchers, using standard form.

The articles selected for review were analyzed and systematized in authors, year of publication, title, research type, objectives, and main findings.

Figure 1: PRISMA flowchart representing the search in the databases

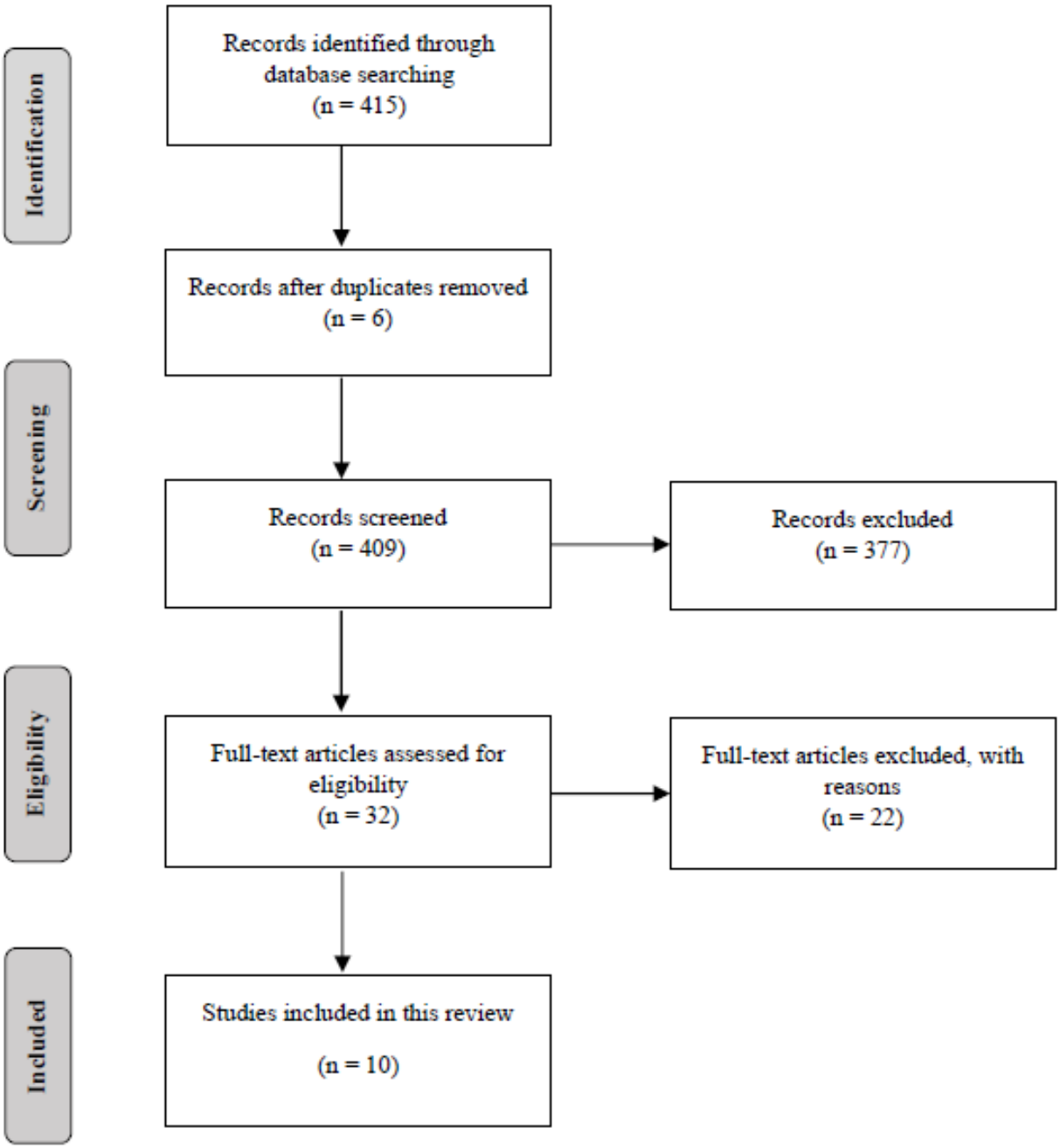

Table 1: Publications included in this review

(Abbreviations: COVID-19 - Coronavirus infectious disease 2019; MG - Myasthenia gravis; SARS-CoV-2 Severe acute respiratory distress syndrome coronavirus 2)

Authors/Year Data Base	Title	Research Type	Objectives	Main Findings
Huber et al. (2020) [7]	Postinfectious Onset of Myasthenia Gravis in a COVID-19 Patient	Case Report	To report the case of a young woman with postinfectious onset of MG after COVID-19	A 21-year-old female patient presented manifestations of myasthenic syndrome after SARS-CoV-2 diagnosed infection, assuming a preceding viral infection triggering post/infectious of MG as a neurological complication.
Moschella and Roth (2020) [8]	Isolated COVID-19 Infection Precipitates Myasthenia Gravis Crisis: A Case Report	Case Report	To report a single case of isolated COVID-19 infection that precipitated a myasthenic crisis with no other clinical sequelae	Besides recovery, even a mild infection aging studied can precipitate a myasthenic crisis event.
Anand et al. (2020) [9]	COVID-19 in patients with myasthenia gravis	Observational study	To describe the clinical course and outcomes of COVID-19 in 5 patients with pre-existing diagnoses of MG	The clinical course and outcomes in patients with MG and COVID-19 are highly variable.
Restivo et al. (2020) [10]	Myasthenia Gravis Associated with SARS-CoV-2 Infection	Case Report	To describe 3 patients without previous neurologic or autoimmune disorders who were diagnosed with MG after the onset of COVID-19	MG symptoms appeared within 5 to 7 days after fever onset in all 3 patients, similar to reports of other kinds of infections that could be associated with autoimmune disorders.
Delly et al. (2020) [11]	Myasthenic crisis in COVID-19	Case Report	To present a case of a woman who developed MG crisis and concomitant COVID-19	This is the first known case in the literature of MG crises simultaneously with COVID-19. This clinical situation, especially in patients immunosuppressed, needs a special attention regarding to drugs side effects and general management.
Camelo-Filho et al. (2020) [12]	Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes	Observational retrospective study	To describe characteristics and outcomes of 15 hospitalized patients with MG and COVID-19	Most patients with MG hospitalized for COVID-19 had severe courses of the disease, underwenting to intensive care unit and mechanical ventilation or even death. Immunoglobulin and plasma treatments were safe and immunosuppressive therapy seems to be associated with better outcomes.
Ramaswamya and Govindarajanb (2020) [13]	COVID-19 in Refractory Myasthenia Gravis- A Case Report of Successful Outcome	Case Report	To describe myasthenic patient who was infected COVID-19 and recovered without myasthenic crisis/exacerbation, and no COVID-19 complications despite chronic immunomodulatory therapy	The patient, who has refractory MG on multiple long-term immunosuppressive therapies, recovered successfully from COVID-19 without myasthenia exacerbation or crisis. There are any changes to her immunosuppressive therapy.
Sriwastava et al. (2020) [14]	New onset of ocular myasthenia gravis in a patient with COVID-19: a novel case report and literature review	Case Report	To report the first case of ocular MG developing secondary to COVID-19 infection in a woman	After tested positive for COVID-19, the 65-year-old woman also tested positive for antibodies against ACHR, with ocular symptoms.
Singh and Govindarajan (2020) [15]	COVID-19 and generalized Myasthenia Gravis exacerbation: A case report	Case Report	To present a generalized MG exacerbation with co-existing COVID-19 symptoms and its management	MG treatment in the context of COVID-19 should be tailored to the patient, with close monitoring of the patient's respiratory status given the possibility of complications from both - the infection and MG.
Maresma et al. (2020) [16]	Miastenia gravis asociada a la infección por SARS-CoV-2: una conjunción de factores	Case Report	To presente a case of MG in a elderly patient during the subacute phase of this infection	SARS-CoV-2 infection can be considered as possible triggering event for MG development, including other factors in an independent or associated mechanisms.

3. RESULTS

It was identified 415 articles of COVID-19-related MG. After exclusion, we selected 10 studies. In all the patients included in the clinical and observational studies it was performed a SARS-CoV-2 polymerase chain reaction (PCR) or antibody assays to confirm the infection.

A case report of a 21-year-old woman described symptoms like right-sided ptosis and double vision, after COVID-19 infection, with no family history of NMDs but for autoimmune diseases[7]. At the beginning of patient admission, the initial visual symptoms were unspecific with double vision progression. These symptoms were treated with oral pyridostigmine and intravenous immunoglobulins (IVIG), until ocular symptoms regression[7].

COVID-19 can precipitate a myasthenic crisis, in an atypical mechanism[8]. In November 2019, a 70-year-old male patient diagnosed with MG and other comorbidities, had AchR antibody positive controlled with prednisone, methotrexate and pyridostigmine daily[8]. This patient was successfully treated with stress-dose steroid therapy alone, and plasma exchange (PLEX)[8].

An observational study describes the course with five patients with MG, two man and three women, between 42 and 90 years of age[9]. The duration of MG diagnosis covered 1 to 20 years and the patients had comorbidities[9]. Patients had a high variation clinical course, requiring supplemental oxygen (intubation), exacerbation of MG (with diplopia, dysphagia, and neck weakness symptoms), specific needs of IVIG, steroids, corticoids, classic immunosuppressants and experimental therapies for SARS-CoV-2 infection like hydroxychloroquine and azithromycin[9].

Another work showed the course of 3 patients that presented MG after COVID-19. A 64-year-old man developed muscular fatigability and diplopia and was treated with prednisone and pyridostigmine bromide, with good response[10]. After 1 week of classic COVID-19 symptoms, a 68-year-old man developed general muscle weakness, dysphagia, and diplopia, receiving IVIG[10]. The third patient was a 71-year-old woman, who presented hypophonia, diplopia and bilateral ocular ptosis after 5 days of beginning of the SARS-CoV-2 infection symptoms; after 1 day, she needed mechanical ventilation because her dysphagia and respiratory failure, besides plasmapheresis[10].

In a case report of a 56-year-old woman with at least 5 years of MG diagnosis, it was possible to correlate a myasthenic crisis (dysphagia, ptosis, lower extremities weakness) and

concomitant COVID-19[11]. Her therapy maintenance consisted of IVIG, prednisone and pyridostigmine[11]. With pneumonia diagnosed, she started the antibiotics azithromycin, cefepime and vancomycin, that were stopped, and hydroxychloroquine resumed; the worsening of her extremity weakness required another IVIG[11].

An observational retrospective study was conducted with 15 female and male myasthenic patients with 9 years of median disease duration, treated with prednisone or prednisone associated with an immunosuppressant[12]. 86,7% of the patients had to be managed with intensive cares, where all had received antibiotic therapy and most of them had de exacerbation MG form (underwent intravenous IVIG or PLEX) and a bad respiratory course[12]. Unfortunately, 4 patients died; among them, they were not treated with PLEX, IVIG or any immunosuppressive drug in high doses[12].

A 42-year-old woman diagnosed with oculobulbar MG 9 months before COVID-19 infection maintained her pharmacological treatment based on mycophenolate and steroids[13]. During the infection course, she did not have exacerbation, crisis, complications, or therapy change, just a shortness of breath at the admission[13].

Another case described a 65-year-old woman with a significant cancer history that presented extreme fatigue, myalgia, and diarrhea in 14 days. With 3 days she evolved to left eyelid ptosis, mild eye closure weakness, diplopia, and generalized fatigue[14]. After one month, she still had residual symptoms of ocular MG and COVID-19, characterizing as a complication of SARS-CoV-2 infection, with good outcome treated with pyridostigmine[14].

Studies reinforce that MG treatment in patients with COVID-19 must be individually monitored and should be tailored[15]. A 36-year-old woman with 2 years of clinical history of MG presented exertional dyspnea, progressive limb weakness and dysphagia, exacerbated 6 months prior the COVID-19 infection, treated with pyridostigmine, prednisone and mycophenolate mofetil and IVIG[15]. At the hospitalization she received PLEX and stress dose steroids, continued mycophenolate mofetil and was intubated, but had a good outcome[15].

A last case report showed an 86-year-old man without cognitive impairment, with a clinical history of hypertension, type 2 diabetes, nonvalvular atrial fibrillation and hyperuricemia[16]. The patient was admitted for secondary bilateral pneumonia, by confirmation of SARS-CoV-2, with respiratory failure[16]. The man had a good evolution after completing treatment with ceftriaxone, azithromycin, and systemic corticosteroid pulses[16]. After 4 days he presented generalized weakness, ptosis mild eyelid predominantly left, jaw fatigue, severe

dysphonia, vertical diplopia and global hyporeflexia, without dysphagia or compromise respiratory[16]. The MG diagnosis was managed with a round of IVIG, systemic corticosteroids and pyridostigmine[16].

4. DISCUSSION

MG clinical management in COVID-19 context is a challenge. During the COVID-19 pandemic, several hypotheses emerged about the relationship between pathologies like GBS and MG and SARS-CoV-2 infection. Skeletal muscles and nervous system express the receptor for angiotensin-converting enzyme 2 (ACE2R), a key-protein to cell virus entry, and this explain the neurological and muscle involvement[17]. People affected by NMDs have further risk to develop more complications in response to COVID-19[18].

The authors sustain the idea that bacterial and viral infection can trigger for MG crisis in patients with pre-existing MG, despite of an unclear mechanism[14]. COVID-19 patients are prone to suffer from post-infectious neuroimmunological complications due to SARS-CoV-2 cell invasion[7]. Antibodies that are directly produced against virus proteins may cross-react with AChR subunit; virus has epitopes that are like components of the NMJ and the COVID-19 infection may break immunologic self-tolerance[10]. Some authors speculate that in MG is possible to consider that viral infection can trigger to an autoimmune response and specific mechanisms as immortalization of infected B-cells, molecular mimicry, bystander activation and epitope spreading can occur[18]. In fact, the main responsible for MG development could be the homology existing between viral surface proteins and AChR[10].

Regarding pathophysiology, the similarity between an antigen of the virus and an autoantigen leads to cross-reactivity of the T cells, B cells and antibodies by a mimicry phenomenon[16]. Although this mechanism has already been established in neuro autoimmune diseases postinfectious, this has not been shown to occur in the MG context[16]. Vaccination, for example, is another concern. Until now, scientific community still have doubts if a GBS history or other inflammatory neuropathy would preclude immunization against SARS-CoV-2 infection[6].

Inflammation always needs attention. Myasthenic patients have elevation on pro and anti-inflammatory cytokines levels that can mediate important pathogenic and inflammatory mechanisms at NMJ[19]. Between the initial symptoms and the complications, one possibility is

an autoimmunity induction response stimulated by SARS-CoV-2 and the immune system that can trigger to alloantibodies and autoantibodies to ACE2R[20].

Patients who underwent to an inflammatory storm status are more vulnerable to develop neuroaxis para-infective or post-infective complication[17]. The central nervous system (CNS) injury and inflammation amplification are directly and indirectly associated with cytokine storm, by lack of homeostasis[21,22].

In addition to T regulatory cells dysregulation (with loss of self-tolerance) and a huge chemokines, cytokines and inflammation mediators release, a significant break of blood-brain barrier (BBB) can be associate with neuroinflammatory process amplification caused by SARS-CoV-2[23].

It is still unknown whether COVID-19 can cause more severity disease in patients with NMDs, but this clinical situation deserve concern because its respiratory muscle weakness involvement and can cause failure consequent, especially for those who are immunosuppressed[9]. The fact is that complications can exist, like myopathy and neuropathies[14].

There is a considerable variability in MG patients' responses to SARS-CoV-2 infection, especially considering case reports, with one patient or smaller groups[9]. Ptosis and fatigability are common symptoms[14]. In a systematic review and meta-analysis regarding to neurological and musculoskeletal features of COVID-19, the authors described the prevalence of clinical manifestations on 35% and 33% for smell and taste impairment, respectively, 19% for myalgia, 12% for headache, 10% for back pain and dizziness, 3% for acute cerebrovascular disease, and 2% for impaired consciousness, exhibiting several clinical presentations, including muscular one[24].

Considered the specific drug management, authors emphasize the importance of preventive approach for MG patients and, in case of prolongation of intensive care, this condition can worsen the functional prognosis[25]. Clinicians should be vigilant for the diagnosis and treatment of patients with neurological symptoms[24]. Both – patients and caregivers – must be advised about specific recommendations, to prevent significative morbimortality[8,26]. Patients should be individualized monitored, particularly on drug management and neurological manifestations[26].

In the articles included in this review, some clinicians decided not to initiate or withdraw drugs like hydroxychloroquine because of its risks[8,9,10]. In fact, this drug is capable to worsen MG[6], alone or concomitantly with a macrolide like azithromycin, that can require additional

IVIG administration[11]. Myasthenic syndrome and toxic myopathy are related with hydroxychloroquine treatment[27,28].

A real challenge is involved on immunosuppression management, specifically in patients that requires intubation, tracheostomy, or oxygen, but it is possible to have favorable outcomes[16]. In fact, the decisions about initiate acute pharmacological interventions or continue with immunosuppressive drugs, must be made in an individual form, evaluating the particularities and the severity of MG and COVID-19, based on collaborative professional work[13,16,30]. Myasthenic symptoms can be affected using immunosuppression[30] and patients postinfectious analysis who underwent to immunosuppressive therapy is important.

The authors indicated that previous use of immunosuppressive drugs plus corticosteroids like prednisone appears to not impact a favorable outcome, including to prevent a mechanical ventilation[12]. A cohort study revealed 30% of lethality rate and 86.7% of intensive care unit (ICU) admission, probably related to worsening respiratory function associated with MG exacerbation and viral replication[12]. In contrast, a Cochrane review concluded that to assume MG corticotherapy treatment with benefic management, it is necessary more evidence[29].

Long-term therapy with corticosteroid should be avoided, even though good characteristics of cost, rapid effect, and reliability[30]. Protocols that associate stress steroids and corticosteroids, in a severe COVID-19 clinical condition, may demand to pause the immunosuppression in temporarily way[15]. Long-action drugs like azathioprine and mycophenolate mofetil can be continued[15].

Another drug class used on MG context is acetylcholinesterase inhibitors (AChEIs) that can, for several hours, improve muscular weakness, not affecting the disease clinical course[30].

Some studies included in this review cited the PLEX and stress-dose steroids in MG patient's treatment[8]. Particularly with the PLEX, this treatment can remove inflammatory mediators like cytokines, avoiding a myasthenic crisis[8], which can improve the weakness including IVIG[30]. When IVIG is required in MG patients in SARS-CoV-2 infection concomitant, demand a careful administration[11]. In general, after hospitalization, some patients continued their home medication regimen[15].

Maintaining patient follow-up is essential for the evaluation and monitoring of myasthenic symptoms and adverse effects of medications and vulnerability to viral infections.

MG patients may be more susceptible to infectious problems, and SARS-CoV-2 infection can be a trigger for the development of autoimmune conditions. This is certainly a two-way street.

5. FINAL CONSIDERATIONS

Clinical case reports and observational retrospective studies have some limitations, special to the low number of patients evaluated. Despite most of the cases go to recovery and good outcome, it is important to consider that preceding viral infections could trigger to myasthenic events, but little is known about relationship between COVID-19 and MG.

MG management is very complex, especially when we discuss the drugs and their potential side effects. People who are immunosuppressed for medications or specific conditions like cancer and other comorbidities, needs an individual care, considering that these factors can increase COVID-19 risk.

There are some speculative clues about the two pathologies, but further investigation is required to establish specific pathophysiological mechanisms that can possibility the correct clinical management and to decide the best patient conduct, to prevent worse outcomes, including a postinfectious analysis.

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