Neuromuscular Disorders Associated With COVID-19

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ABSTRACT: The coronavirus disease 2019 (COVID-19) pandemic has had an enormous impact on practically every aspect of daily life, and those with neuromuscular disorders have certainly not been spared. The effects of COVID-19 infection are far-reaching, going well beyond respiratory symptoms alone. From simple myalgias to debilitating critical illness neuromyopathies, we continue to learn and catalog the diverse pathologies presented by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as it relates to the neuromuscular system. Complications have been documented both as a direct result of primary infection but also in those with pre-existing neuromuscular disorders from myasthenia gravis to devastating critical illness neuromyopathies. In this review, we will discuss the relationship between COVID-19 infection and critical illness neuromyopathy, peripheral nerve palsies, myalgias, positional compressive neuropathy, myasthenia gravis, and Guillain-Barré syndrome.

KEYWORDS: COVID-19, neuromuscular, neuropathy, myasthenia gravis, palsy

Introduction

Though much had been postulated regarding neuromuscular disorders during the height of the COVID-19 pandemic, objective large-scale datasets were scarce and as new variants formed, so too did the phenotypical presentation of those ill with SARS-CoV2. Previously, much of the published literature focused on the direct effects of SARS-CoV2 on the nervous system but failed to categorize the downstream effects of a COVID-19 illness. This review serves to summarize the known data about the direct effects of the SARS-CoV2 on the neuromuscular system. It also seeks to incorporate information on indirect impacts such as the avoidance of care out of concern for contracting illness, peripheral neuropathies obtained due to positioning during prolonged pronation, and medications that can alter transmission rates in myasthenia gravis. Arguably, the indirect impacts have done more to alter individual and population health than those directly caused by the SARS-CoV2, as most individuals experienced mild or asymptomatic illness associated with contracting the virus.

Critical Illness Neuropathy and Myopathy

Early in the pandemic, the heterogeneity of disease was vast. The majority of cases involved mild upper respiratory symptoms, though some developed lower respiratory symptoms resulting in severe hypoxic respiratory failure and acute respiratory distress syndrome (ARDS). Critical illness neuromyopathy (CIN) is one of the most feared complications in the ICU, as it results in prolonged weaning from ventilators and impairs functional recovery for potentially years following discharge from the ICU. Though this disease can be subdivided into purely myopathy or purely neuropathy, many times they occur together and result in similar courses for recovery with treatment being the same for both. For simplicity, they will be referred to as a combination throughout much of the article. Historically, there have been 6 recognized risk factors associated with the development of critical illness polyneuromyopathy (CIPNM), all of which tended to be present in persons critically ill with COVID-19. Most individuals that developed ARDS related to their COVID-19 infections required prolonged ventilation. One review during an early wave of the pandemic between March 2020 and April 2020 demonstrated the median ventilator free days for those that had progressed to ARDS to be 0 (IQR 0-15) at 28 days.[1] At the time, steroids were the only treatment identified to demonstrate mortality benefit.[2] In addition to being an independent risk factor for the development of CIPNM, glucocorticoid steroids tend to result in increased blood glucose levels which is also a separate risk factor itself.[3] One of the mainstays of the management of ARDS involves paralytic use to reduce metabolic demand and maintain compliance with mechanical ventilation.[4] Finally, systemic inflammatory response syndrome (SIRS) is its own independent risk factor, and those critically ill with COVID-19 infections tended to have profoundly elevated systemic inflammatory markers.[2,4] The above combination would seem to place individuals at an exceptionally high risk of developing CIPNM. The actual incidence is difficult to identify though. Pre-COVID-19 era reports indicate numbers as high as 50% of those that are critically ill and undergoing mechanical ventilation for longer than 7 days.[5,6] In terms of diagnosis, from a clinical exam standpoint, CIPNM tends to spare bulbar muscles and does not involve autonomics.[7] The most commonly identified electrodiagnostic abnormality in critical illness myopathy is a reduction of the compound muscle action potential (CMAP) to below 50% of the lower limit of normal.[7] Sensory

nerve action potentials (SNAPs) should be unaffected. As for critical illness neuropathy, there is evidence of an axonal sensorimotor neuropathy, primarily in the form of decreased SNAP and CMAPs with normal distal latency times.[7] In the author's mind, the easiest way to think of this is to consider the nerve as a wire: a reduction in the wire size should result in less information being sent through the wire, though the speed with which that information travels is unaffected. In all forms, positive sharp waves are found on needle EMG.[7] It should be noted that some changes related to electrodiagnostic testing can occur very early, within 24 hours.[8] Likewise, another study demonstrated measurable differences in diaphragmatic thickness 18 hours after initiation of mechanical ventilation with a mean decrease in thickness of 32%.[9]

Muscle biopsy is a rarely utilized way to obtain a definitive diagnosis, demonstrating loss of myosin and relatively more loss of type II than type I fibers.[10] There are also characteristic findings for CIP on muscle biopsy, including evidence of denervation/reinnervation.[10] CIPNM presents a considerable challenge for those that it affects. Recovery is slow, resulting in an incredibly prolonged convalescence requiring considerable resources such as around the clock nursing care, long-term mechanical ventilation, and tracheostomy and gastrostomy tube placements.

Several strategies have been utilized as preventative measures in CIPNM. Though most involved non-randomized cohort groups, there are some promising trends. As consistent with literature on all-cause ICU admissions, it is clear that daily physical therapy provides benefits in the form of decreased length of stay and improved functional outcomes in CIPNM but does not appear to decrease the overall incidence and with non-randomization, and the treatment effect is difficult to quantify.[11-13]

A more innovative treatment involving direct electrical muscle stimulation on a daily basis in the ICU has been evaluated and though it included small cohorts, it did demonstrate a decrease in the diagnosis of CIPNM and resulted in more rapid weaning from the ventilator and improved motor muscle testing scores for blinded examiners.[14]

Cranial Nerve Palsies

Cranial nerve deficits are the most common peripheral nerves affected. Olfactory dysfunction is seen in up to 80% of patients with COVID-19.[15] Aside from this, the most common cranial nerve affected is the facial nerve (CN VII), commonly referred to as Bell's Palsy, though by definition Bell's palsy is idiopathic in nature.[15] Paralysis of the facial nerve has been commonly associated with other viruses such as varicella zoster virus (VZV) and herpes simplex virus type 1 (HSV-1)[16] as well as many common upper respiratory tract infection causing viruses. During the pandemic, the incidence of diagnosed Bell's palsy increased.[17,18] However, with testing variability, proving that COVID-19 was the causative agent was

difficult with only 8/34 testing positive in one study and only 56% of patients being tested for COVID-19 in another.[17,18] A systematic review found 46 cases of Bell's palsy as the only neurological symptom in COVID-19. Facial paralysis was the presenting symptom in 37% of cases and 21.7% showed only partial recovery.[19] The high rate of partial recovery along with case reports showing other complications such as aberrant nerve regeneration,[20] Wernicke's encephalopathy,[21] and sudden hearing loss[22] convey the complexity and morbidity of COVID-19 associated facial nerve palsy. A systematic review found a pool of 32 patients who had been treated for Bell's palsy, and a combination of antivirals and steroids led to a faster resolution of symptoms than steroids or antivirals alone.[23] Other cranial nerve deficits have occurred in association with COVID-19 infection including oculomotor (CN III) and abducens (CN VI).[15] The vestibulocochlear nerve (CN VIII) was affected in the form of tinnitus or hearing changes in 13.2% of severe COVID-19 survivors, though this may be confounded by commonly used medications such as furosemide in severe infections.[24]

Peripheral Nerve Palsies and Neuropathy

The effect of COVID-19 on the peripheral nervous system is poorly understood due to the relative rarity of the conditions; however, there is significant morbidity for those afflicted. Peripheral nerve palsies in the setting of COVID-19 can both be the presenting symptom or a later complication.

Unilateral recurrent laryngeal nerve palsy (branch of CN X) was reported in a patient who experienced severe COVID-19, prolonged hospitalization, but no endotracheal intubation.[25] Another case report showed bilateral recurrent laryngeal nerve paralysis but with a remote history of endotracheal intubation.[26] With the risk of vocal cord paralysis with endotracheal intubation,[27] there is certainly going to be an increase of cases, but cases without the history of intubation could represent an additional extra-pulmonary manifestation of COVID-19.

Phrenic nerve paralysis has also been reported.[28] This should be suspected especially if there is a pronounced difficulty in weaning from a respirator or if there are other neurologic manifestations.

Additionally, reports of bilateral peroneal nerve paralysis[28] and Parsonage-Turner Syndrome (brachial plexus-based neuritis) in individuals recovering or recovered from COVID-19 implicate the virus in these peripheral nerve disorders.[29,30] This is further confounded by known brachial plexopathies following prone positioning, commonly utilized in severe COVID-19 respiratory infections, though these tend to occur without pain, separating them from a typical neuritis.[31]

Nearly 30% of those infected with SARS-CoV2 report symptoms consistent with a peripheral neuropathy.[32] This rate is far above reported rates in other respiratory viruses, suggesting that perhaps the immune dysregulation contributes to a sensitization that predisposes to neuropathic pain.

Peripheral Nerve Palsies Related to COVID-19 Vaccination

Peripheral nerve palsies have also rarely been attributed to COVID-19 vaccination. Case reports have been published showing cranial nerve palsies, peripheral nerve palsies, and variations of Guillain-Barre Syndrome.[33-36] These adverse events have been reported with the BNT162b2 (Pfizer)[33] and ChAdOx1 nCoV-19 (Oxford-AstraZeneca)[4] vaccines. The timeline from vaccination to symptom presentation varied among the cases, from 2 days after the first dose[36] to 3 weeks after the second dose.[37]

A variety of mechanisms were postulated depending on the time to symptom onset. A longer time to symptom onset could be explained by a humoral immune response, as in one patient who was found to have GQ1b antibodies a week after his second injection of his vaccine.[38] Alternatively, a short time to symptom onset could be explained by an increased inflammatory response. In a patient with a past medical history of ischemic heart disease, the authors speculated that this inflammatory state created microthrombotic disease leading to nerve palsy.[36]

Outside of case reports, few studies have been performed because of the rarity of this outcome. An analysis of the U.S. Vaccine Adverse Event Reporting System found comparable rates of facial nerve palsies to influenza vaccination,[39] and a case control study found no statistically significant association between vaccination and facial nerve palsy.[40] Because of these initial studies, vaccination should still be recommended for the prevention of COVID-19, but more research needs to be performed to further clarify the potential impact of this adverse event given the massive administration of vaccines worldwide.

Myalgia/Myositis

Early symptoms of COVID-19, including musculoskeletal symptoms such as myalgias, have been reported extensively in the literature, with some studies reporting a prevalence in nearly two-thirds of COVID-19 patients. For further context, in a prospective observational cohort study of 1150 patients hospitalized for COVID-19 in New York City, it was found that 26% of patients reported myalgia.[41] Another epidemiologic study of 1420 patients in Europe with mild-to-moderate COVID-19 infections found that 62.5% reported myalgia.[42] While the mechanism of myalgia in COVID-19 patients is not well understood, it has been postulated that those with COVID-19 can experience an aggressive inflammatory response with elevated levels of pro-inflammatory signaling molecules which may play a role in contributing to muscle damage.[43] The effects of these responses can be persistent and long-lasting as shown by a study by Karaarslan et al which found that 56.3% of COVD-19 patients reported musculoskeletal complaints, including fatigue, myalgia, and arthralgia, 1 month after discharge.[44] Another case series following COVID-19 patients in Italy found that 23.7% of patients had persistent complaints of joint pain over a month following discharge,[45] and a large prospective cohort study of 1733 COVID-19 patients admitted to the hospital found that 63% were still experiencing fatigue/myalgia at 6 months post-discharge.[46] In a different study investigating the association between COVID-related myalgia experienced by patients at hospital admission and the presence of post-COVID symptoms, a higher proportion of patients presenting with myalgia exhibited musculoskeletal post-COVID pain when compared to those without myalgia.[47] In addition, 50% of individuals with preexisting musculoskeletal pain experienced a worsening of their symptoms after COVID-19.[47] Given these statistics, it is important to consider the management of patients with musculoskeletal complaints as they may require further treatment including NSAIDS and/or rehabilitation.[43]

In addition to myalgias, COVID-19 has been associated with myositis but may be varied in presentation. It is thought that COVID-19-induced myositis may be caused by direct infection of the muscle which may trigger an autoimmune response.[48] COVID-19-induced myositis is reported to vary in terms of severity and includes symptoms of general muscle weakness, back pain, dermatomyositis, rhabdomyolysis, and a paraspinal affliction with back pain.[48] In cases in which COVID-19 leads to acute myositis, it has been shown that nearly half of patients have prolonged recovery that spans over weeks to several months.[48] In particular, it has been highlighted that patients who exhibit paraspinal myositis have prolonged hospital stays.[48] As mentioned earlier, presentations of myositis may vary and this is evidenced in a case report detailing the clinical course of a COVID-19 patient who experienced myositis involving the proximal limb, bulbar, and facial muscles.[49] In addition to these findings, the use of imaging modalities to aid in determining the severity of the disease in patients has played a complementary role in the management of patients with COVID-19. For example, in cohort of 9 patients with COVID-19 who underwent MR imaging of the spine, there was evidence of paraspinal myositis characterized by intramuscular edema and/or enhancement in 7 patients; of these 7 patients, 5 had prolonged hospital stays of greater than 25 days.[50] While there may be confounding variables in the COVID-19 patient population who experience myalgias and myositis symptoms, it is recommended to base treatment on recorded histories and imaging findings as appropriate to formulate individualized treatment plans for managing these patients.

Positional Compressive Neuropathy

Patients with severe COVID-19 often develop respiratory failure and require ventilatory support. Adult respiratory distress syndrome (ARDS), a fatal complication, occurs in response to hypoxia, inflammation, and resulting pulmonary edema.[51] Approximately 5% of patients with COVID-19 progress to severe ARDS.[52] Complications such as pressure ulcers and

neuropathy from traction injury and nerve compression from prolonged immobilization can occur independent of additional risk factors such as obesity and diabetes mellitus.[53] In cases of severe ARDS, prone positioning is commonly used to improve aeration and oxygenation.

Early implementation of prone positioning has been shown to be more effective than supine positioning at reducing the 28-day and 90-day mortality when done for at least 16 hours a day.[54] Prone positioning during the pandemic became widely adopted as standard of care for COVID-19 patients, leading to accumulation of the known risks with exposure to prone positioning. In one report, patients treated in prone positions, anywhere from 7 to 19 days developed peripheral neuropathies ranging from focal neuropraxia, to axonal damages involving multiple nerves, as well as brachial plexopathy and lumbosacral plexopathy. Implementation of appropriate measures such as preventative padding and alternating cycles of prone/supine positioning is advised to minimize the incidence of positional palsies.

Myasthenia Gravis

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction that is characterized by muscle weakness which is aggravated by continued use.[55] Ocular symptoms such as ptosis and diplopia are the presenting signs in two-thirds of patients. Within 2 to 3 years of presentation, around 75% of patients will develop generalized weakness. Up to 40% of patients develop respiratory muscle weakness, and 15% to 20% of patients will experience a myasthenic crisis.[56] Because of advances in directed therapies as well as respiratory support, the mortality has improved dramatically in the last century. Currently, the mortality rate is approximately 5% to 9%.[56]

With the knowledge that comorbidities such as cardiovascular disease or diabetes mellitus predispose individuals to a more severe course of COVID-19,[57] there is concern that individuals with myasthenia gravis may also be predisposed, especially those receiving immunomodulatory therapies. Clinical evidence is limited because of the ongoing and evolving nature of the pandemic along with the overall rarity of the disease. To date, case reports and case series predominate the literature. Two systematic reviews of these descriptive studies and a handful of cohort or cross-sectional studies have been performed. One pooled the patient data and found no definitive evidence that COVID-19 exaggerates the neurological symptoms of people with MG.[58] However, they did suggest that monotherapy with corticosteroids may lead to worse outcomes, but a larger sample size is needed to definitively reach this conclusion. Another recent publication highlights a case study and references a case series of several individuals diagnosed with MG shortly after infection with SARS-CoV2. They surmised that the immune dysregulation created by infection with SARS-CoV2 resulted in histologically verified thymic dysfunction, resulting in the expression of anti-acetylcholine receptor antibodies.[59,60] The other systematic review reported the outcomes of the studies that it included.[61] They summarized that MGFA class greater than IV,[62] older age, and long-term use of corticosteroids[63] were associated with more severe COVID-19. Higher forced vital capacity (FVC) at onset of COVID-19 was found to be protective.[63] This same study also suggested that current treatment with rituximab at onset of COVID-19 was associated with increased risk of death. In most cases, however, treatment should be continued because the risk of COVID-19 is smaller than leaving MG untreated.[64]

Larger studies have also been performed more recently. A French multicenter cross-sectional study found that patients with diabetes, hypertension, or severe forms of neuromuscular disease had a higher risk of developing moderate or severe COVID-19.[65] A retrospective review of electronic health records in the United States found that dysphagia and an age over 75 were associated with increased mortality, but recent treatment for MG was not associated with increased mortality.[66]

Most of the published studies are limited by small sample sizes, but the general theme that older patients with comorbidities and a more progressed disease process are more susceptible to severe COVID-19 has arisen. Additionally, the use of immunomodulatory treatments has been found to be safe, with the exception of monotherapy with corticosteroids, and should be continued per local treatment guidelines.

Recovery from COVID-19

The CARE-MG database was started early in the COVID-19 pandemic to track the effect of the disease on the population that has myasthenia gravis. Preliminary data released shows a mortality rate of 24%, with 40% of the patients requiring rescue therapy. Only 43% of patients made a complete recovery in this registry.[67] This registry was released early in the pandemic, when therapeutic strategies were uncertain and even contained azithromycin and hydroxychloroquine which are known to exacerbate myasthenia gravis.[68] Mortality rates from other studies range between 10.6% and 30%.[61,66] The data shows that there is an increased burden of mortality in patients with MG.

Patients with MG are also more likely to be hospitalized than healthy individuals.[8] When the hospitalization is due to a myasthenic crisis, infection with COVID-19 lead to significantly longer hospital stays than those who are not infected.[69] This increased burden of hospitalization and mortality has an unknown long-term effect on the disease process of MG. Further studies are required to show if a myasthenic crisis precipitated by COVID-19 infection has a long-term effect on the MG disease course.

Risk of developing COVID in MG patients compared to general population

While it is thought that patients with MG are more at risk of developing COVID-19 due to their immunocompromised

states, the consensus is uncertain. Based on preliminary studies investigating this question, the risk of COVID-19 in MG patients does not appear to be higher than that of the general population. A study by Businaro et al which had 162 patients enrolled found that COVID-19 prevalence was not statistically different between MG patients and the general population.[70] Furthermore, they found that the type of treatment received did not influence the occurrence of COVID-19 and that the only subgroup of patients who were more likely to develop COVID-19 were MG patients with oncologic/autoimmune comorbidity.[70]

Impact of COVID-19 on hospitalization rates, exacerbation/crisis

While several studies have not revealed any unusual impacts of COVID-19 on hospitalization rates of patients with either MG or COVID-19,[58] one study showed a slight increase in atrial fibrillation (11%vs 5%) and COPD (11%vs 4%), with higher prevalence in MG patients with COVID-19 compared to those who did not have COVID-19.[71] Another study with 13 hospitalized patients found that the mean length of hospitalization for the group with MG patients and COVID-19 was 8.28 days, and that of the group with MG patients and non-COVID-19 was 4.33 days, revealing a statistically significant increase in the mean length of hospitalization associated with MG patients who were admitted with COVID-19.[69] In a separate observational study by Gummi et al in 2019 investigating acute exacerbations of MG patients, it was found that the average admission for MG patients was 6.5 days.[72] Comparing these 2 studies, it is consistent with the notion that COVID-19 exacerbates the hospitalization stay of MG patients. In addition to these higher-than-average hospitalization stays, a large case series in mainland China with 72 314 cases has shown that MG patients with COVID-19 were frequently admitted to the hospital, have disease exacerbations, and have a higher mortality than the general population.[73]

Intravenous immunoglobulin (IVIg)/treatment role in MG exacerbation with COVID

Intravenous immunoglobulin (IVIg) treatment has anti-inflammatory and immunomodulating effects and has shown efficacy in the treatment of patients with MG. However, there is concern regarding its use for MG exacerbation in patients with COVID-19 due to its immunosuppressive and thromboembolic properties.[74,75] Consequently, healthcare providers must be aware of the risk of thromboembolic complications associated with IVIg treatment. Despite these concerns, the data from several recent studies have shown that treatment of MG patients and COVID-19 patients with IVIg is safe.[76-78]

According to a single-institution case series of 8 MG patients with COVID-19, treatment was successful for seven, 6 of whom were discharged without any MG symptoms.[77] In

another series in which 3 patients experienced myasthenic exacerbations due to COVID-19 were treated with IVIG, none had major side effects.[78] Lastly, in an observational retrospective study of MG patients with COVID-19, 1 MG patient with COVID-19 who presented with an MGFA score ⩾II in the last month before admission received IVIg and had a favorable outcome.[76] Collectively, these reports support the notion that IVIG treatment is safe and does not appear to worsen outcomes for MG patients with COVID-19 who experience worsening symptoms.

Guillain–Barré syndrome

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy which is related to previous infectious exposure. This critical illness is characterized by ascending paralysis and respiratory failure and is typically associated with gastrointestinal infection, viral upper respiratory tract infection, or Zika virus. GBS is classified into several subtypes, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN). There have been increased cases of GBS after the COVID-19 pandemic.[79] However, the strength of this association remains unclear.

A retrospective review of 37 patients from 28 publications demonstrates a mean age of 58.7 years for patients with COVID-19-associated GBS.[80] 65% of these patients were male. The latency period between neurological symptoms and COVID-19 symptoms was 11 ± 6.5 days. The most common COVID-19 symptoms were fever and cough, and common symptoms on presentation of GBS were limb paresthesia, pain, and/or weakness. Over a third of these patients required mechanical ventilation. In the patients who had a lumbar puncture, albuminocytologic dissociation in the cerebrospinal fluid was found more than three-fourths of the time. Protein levels ranged from 44 to 313 mg/dL. Upon electrodiagnostic evaluation, 65% of the patients had AIDP as the GBS subtype. Eighty-nine percent of the patients in this retrospective study were treated with intravenous immunoglobulin (IVIg). Other treatments included plasma exchange, acetaminophen, hydroxychloroquine, and azithromycin. Eighty-nine percent of patients showed a response to therapy.

Another systematic review identified 109 GBS cases, 99 of which had confirmed COVID-19 infection.[81] The average age in this review was 56.1 years, with the mean time to onset of neurological manifestations from COVID-19 symptoms being 12.2 days. Common COVID-19 symptoms included fever, cough, dyspnea, and GI symptoms, and the most frequent GBS manifestations were ascending motor weakness, diminished reflexes, paresthesia, and facial palsy. Thirty patients had respiratory failure. 74 of 86 patients who underwent cerebrospinal fluid analysis had albuminocytologic dissociation. Of 77 patients in whom electromyography was performed, the prevalent GBS subtype was AIDP. Seventy-two patients received

IVIg, 10 underwent plasmapheresis, and 7 received both treatments. In regard to outcome, 40 patients were admitted to the ICU, 33 patients required mechanical ventilation, and 6 patients expired.

The reported frequency of GBS in COVID-19 patients is about 0.15%, which is more than 13-fold higher than in non-COVID-19 patients.[79] Nerve damage is thought to be a result of an immune cross-reaction through the formation of antibodies against surface glycoproteins of the virus, which may damage peripheral nerves that have a similar protein structure.[82] In summary, studies demonstrate that Guillain-Barré syndrome may be associated with COVID-19 illness, and favorable outcomes are seen with treatment of IVIg and plasmapheresis.

Author Contributions

All authors contributed to the planning and writing of the original manuscript.

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REFERENCES

1. Hazard D, Kaier K, von Cube M, et al. Joint analysis of duration of ventilation, length of intensive care, and mortality of COVID-19 patients: a multistate approach. *BMC Med Res Methodol*. 2020;20:206.
2. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *New Engl J Med*. 2021;384:693-704.
3. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288:2859-2867.
4. Schweickert WD, Hall J. ICU-acquired weakness. *Chest*. 2007;131:1541-1549.
5. Koch S, Spuler S, Deja M, et al. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. *J Neurol Neurosurg Psychiatry*. 2011;82:287-293.
6. Witt A, Bostock H, Z'Graggen WJ, et al. Muscle velocity recovery cycles to examine muscle membrane properties. *J Vis Exp*. 2020;156. doi:10.3791/60788
7. Shepherd S, Batra A, Lerner DP. Review of Critical Illness Myopathy and Neuropathy. *Neurohospitalist*. 2017;7:41-48.
8. Fink MP, Evans TW. Mechanisms of organ dysfunction in critical illness: report from a round table conference held in Brussels. *Intensive Care Med*. 2002;28:369-375.
9. Schepens T, Verbrugghe W, Dams K, Corthouts B, Parizel PM, Jorens PG. The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study. *Crit Care*. 2015;19:422.
10. Di Giovanni S, Mirabella M, D'Amico A, Tonali P, Servidei S. Apoptotic features accompany acute quadriplegic myopathy. *Neurology*. 2000;55:854-858.
11. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med*. 2008;36:2238-2243.
12. Nordon-Craft A, Schenkman M, Ridgeway K, Benson A, Moss M. Physical therapy management and patient outcomes following ICU–acquired weakness. *J Neurol Phys Ther*. 2011;35:133-140.
13. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373:1874-1882.
14. Routsi C, Gerovasili V, Vasileiadis I, et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Crit Care*. 2010;14:R74.
15. Taga A, Lauria G. COVID-19 and the peripheral nervous system. A 2-year review from the pandemic to the vaccine era. *J Peripher Nerv Syst*. 2022;27:4-30.
16. Zhang W, Xu L, Luo T, Wu F, Zhao B, Li X. The etiology of Bell's palsy: a review. *J Neurol*. 2020;267(7):1896-1905. doi:10.1007/s00415-019-09282-4
17. Zammit M, Markey A, Webb C. A rise in facial nerve palsies during the coronavirus disease 2019 pandemic. *J Laryngol Otol*. 2020;134:905-908. 2020.
18. Egilmez OK, Gündoğan ME, Yılmaz MS, Güven M. Can COVID-19 cause peripheral facial nerve palsy? *SN Compr Clin Med*. 2021;3:1707-1713.
19. Gupta S, Jawanda MK. Surge of Bell's Palsy in the era of COVID-19: systematic review. *Eur J Neurol*. 2022;29:2526-2543.
20. Alrajhi F, Seraj H, Taher NO, Alnabihi AN. Bell's palsy in a patient after contracting COVID-19 with signs of aberrant nerve regeneration. *Am J Ophthalmol Case Rep*. 2022;27:101679.
21. Alexandri M, Reynolds BZ, Smith H, Golden BM, Gross H, Switzer JA. Wernicke's encephalopathy and cranial nerve VII palsy in a 24-year-old patient with COVID-19. *Int J Emerg Med*. 2022;15:6.
22. Ozer F, Alkan O. Simultaneous sudden hearing loss and peripheral facial paralysis in a patient with Covid-19. *Ear Nose Throat J*. 2021;1455613211028094. doi:10.1177/01455613211028094
23. Turki A, Abbas KS, Makram AM, et al. Epidemiology, clinical features, and treatment modalities of facial nerve palsy in COVID-19 patients: a systematic review. *Acta Neurol Belg*. 2022;122:1419-1432.
24. Munro KJ, Uus K, Almufarrij I, Chaudhuri N, Yioe V. Persistent self-reported changes in hearing and tinnitus in post-hospitalisation COVID-19 cases. *Int J Audiol*. 2020;59:889-890.
25. Tin S, Foo F, Breitling M, Saverimuttu J, Lisi C. A new and rare presentation of unilateral recurrent laryngeal nerve palsy in a COVID-19 patient with no recent history of endotracheal intubation. *Cureus*. 2021;13:e17700.
26. Jungbauer F, Hülse R, Lu F, et al. Case report: bilateral palsy of the vocal cords after COVID-19 infection. *Front Neurol*. 2021;12:619545.
27. Maresch KJ. AANA journal course - vocal cord paralysis: implications for anesthesia care. *AANA J*. 2021;89:443-448.
28. Morawiec N, Chyra D, Boroń A, et al. Bilateral paralysis of peroneal nerve after COVID-19 disease: a case report. *BMC Neurol*. 2022;22:91.
29. Khan AJ, Szczepura A, Palmer S, et al. Physical therapy for facial nerve paralysis (Bell's palsy): an updated and extended systematic review of the evidence for facial exercise therapy. *Clin Rehabil*. 2022;36:1424-1449.
30. Fortanier E, Le Corroller T, Hocquart M, Delmont E, Attarian S. Shoulder palsy following SARS-CoV-2 infection: two cases of typical Parsonage-Turner syndrome. *Eur J Neurol*. 2022;29:2548-2550.
31. Goettler CE, Pryor JP, Reilly PM. Brachial plexopathy after prone positioning. *Crit Care*. 2002;6:540-542.
32. Odozor CU, Kannampallil T, Ben Abdallah A, et al. Post-acute sensory neurological sequelae in patients with severe acute respiratory syndrome coronavirus 2 infection: the COVID-PN observational cohort study. *Pain*. 2022;163:2398-2410.
33. Shemer A, Pras E, Hecht I. Peripheral Facial Nerve Palsy Following BNT162b2 (COVID-19) Vaccination. *Isr Med Assoc J*. 2021;23:143-144.
34. Pawar N, Ravindran M, Padmavathy S, Chakrabarty S. Acute abducens nerve palsy after COVID-19 vaccination in a young adult. *Indian J Ophthalmol*. 2021;69:3764-3766.
35. Cicalese MP, Ferrua F, Barzaghi F, et al. Third cranial nerve palsy in an 88-year-old man after SARS-CoV-2 mRNA vaccination: change of injection site and type of vaccine resulted in an uneventful second dose with humoral immune response. *BMJ Case Rep*. 2022;15:e246485.
36. Kim SI, Seok HY, Yi J, Cho JH. Leg paralysis after AstraZeneca COVID-19 vaccination diagnosed as neuralgic amyotrophy of the lumbosacral plexus: a case report. *J Int Med Res*. 2021;49:3000605211056783.
37. Amjad MA, Hamid Z, Patel Y, et al. COVID-19 vaccine-induced Parsonage-Turner syndrome: a case report and literature review. *Cureus*. 2022;14:e25493.
38. Nanatsue K, Takahashi M, Itaya S, Abe K, Inaba A. A case of Miller Fisher syndrome with delayed onset peripheral facial nerve palsy after COVID-19 vaccination: a case report. *BMC Neurol*. 2022;22:309.
39. Sato K, Mano T, Niimi Y, Toda T, Iwata A, Iwatsubo T. Facial nerve palsy following the administration of COVID-19 mRNA vaccines: analysis of a self-reporting database. *Int J Infect Dis*. 2021;111:310-312.
40. Shemer A, Pras E, Einan-Lifshitz A, Dubinsky-Pertzov B, Hecht I. Association of COVID-19 vaccination and facial nerve palsy: A Case-control study. *Otolaryngol Head Neck Surg*. 2021;147:739-743.
41. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395:1763-1770.
42. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med*. 2020;288:335-344.
43. Hasan LK, Deadwiler B, Haratian A, Bolia IK, Weber AE, Petrigliano FA. Effects of COVID-19 on the Musculoskeletal System: Clinician's Guide. *Orthop Res Rev*. 2021;13:141-150.
44. Karaarslan F, Demircioğlu Güneri F, Kardeş S. Postdischarge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19: prospective follow-up by phone interviews. *Rheumatol Int*. 2021;41:1263-1271.
45. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324:603-605.

46. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397:220-232.

47. Fernández-de-Las-Peñas C, Rodríguez-Jiménez J, Fuensalida-Novo S, et al. Myalgia as a symptom at hospital admission by severe acute respiratory syndrome coronavirus 2 infection is associated with persistent musculoskeletal pain as long-term post-COVID sequelae: a case-control study. *Pain*. 2021;162(12):2832-2840. doi:10.1097/j.pain.0000000000002306

48. Saud A, Naveen R, Aggarwal R, Gupta L. COVID-19 and myositis: What We Know so far. *Curr Rheumatol Rep*. 2021;23:63.

49. Zhang H, Charmchi Z, Seidman RJ, Anziska Y, Velayudhan V, Perk J. COVID-19-associated myositis with severe proximal and bulbar weakness. *Muscle Nerve*. 2020;62:E57-E60.

50. Mehan WA, Yoon BC, Lang M, Li MD, Rincon S, Buch K. Paraspinal myositis in patients with COVID-19 infection. *AJNR Am J Neuroradiol*. 2020;41:1949-1952.

51. Barakat-Johnson M, Carey R, Coleman K, et al. Pressure injury prevention for COVID-19 patients in a prone position. *Wound Pract Res*. 2020;28:50-57.

52. Alhazzani W, Evans L, Alshamsi F, et al. Surviving sepsis Campaign guidelines on the management of adults with Coronavirus disease 2019 (COVID-19) in the ICU: First Update. *Crit Care Med*. 2021;49:e219-e234.

53. Mano T, Fujimura S. Brachial plexus injury and musculocutaneous nerve palsy during prone positioning in a patient with COVID-19. *Cureus*. 2022;14:e24931.

54. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *New Engl J Med*. 2013;368:2159-2168.

55. Hehir MK, Silvestri NJ. Generalized Myasthenia Gravis: classification, Clinical Presentation, natural history, and epidemiology. *Neurol Clin*. 2018;36:253-260.

56. Grob D, Arsura EL, Brunner NG, Namba T. The course of myasthenia gravis and therapies affecting outcome. *Ann N Y Acad Sci*. 1987;505:472-499.

57. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.

58. Abbas AS, Hardy N, Ghozy S, et al. Characteristics, treatment, and outcomes of myasthenia gravis in COVID-19 patients: A systematic review. *Clin Neurol Neurosurg*. 2022;213:107140.

59. Tereshko Y, Gigli GL, Pez S, De Pellegrin A, Valente M. New-onset myasthenia gravis after SARS-CoV-2 infection: case report and literature review. *J Neurol*. 2023;270:601-609.

60. Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med*. 2020;173:1027-1028.

61. Tugasworo D, Kurnianto A, Retnaningsih R, Andhitara Y, Ardhini R, Budiman J. The relationship between myasthenia gravis and COVID-19: a systematic review. *Egypt J Neurol Psychiatry Neurosurg*. 2022;58:83.

62. Solé G, Mathis S, Friedman D, et al. Impact of Coronavirus Disease 2019 in a French cohort of myasthenia gravis. *Neurology*. 2021;96:e2109-e2120.

63. Jakubíková M, Týblová M, Tesař A, et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival. *Eur J Neurol*. 2022;28:3418-3425.

64. International MG/COVID-19 Working Group, Jacob S, Muppidi S, Guidon A, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci*. 2020;412:116803.

65. Pisella LI, Fernandes S, Solé G, et al. A multicenter cross-sectional French study of the impact of COVID-19 on neuromuscular diseases. *Orphanet J Rare Dis*. 2021;16:450.

66. Kim Y, Li X, Huang Y, et al. COVID-19 outcomes in Myasthenia Gravis Patients: analysis from Electronic Health Records in the United States. *Front Neurol*. 2022;13:802559.

67. Muppidi S, Guptill JT, Jacob S, et al. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). *Lancet Neurol*. 2020;19:970-971.

68. Županić S, Lazibat I, Rubinić Majdak M, Jeličić M. Treatment of myasthenia gravis patients with Covid-19: review of the literature. *Acta Clin Croat*. 2022;60:496-509.

69. Digala LP, Prasanna S, Rao P, Qureshi AI, Govindarajan R. Impact of COVID-19 infection among myasthenia gravis patients- a Cerner Real-World Data™ study. *BMC Neurol*. 2022;22:38.

70. Businaro P, Vaghi G, Marchioni E, et al. COVID-19 in patients with myasthenia gravis: Epidemiology and disease course. *Muscle Nerve*. 2021;64:206-211.

71. Stascheit F, Grittner U, Hoffmann S, et al. Risk and course of COVID-19 in immunosuppressed patients with myasthenia gravis. *J Neurol*. 2023; 270:1-12.

72. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. *Muscle Nerve*. 2019;60: 693-699.

73. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-1242.

74. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res*. 2020;194:101-115.

75. van Dam LF, Kroft LJM, van der Wal LI, et al. Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: A different phenotype of thrombotic disease? *Thromb Res*. 2020;193:86-89.

76. Camelo-Filho AE, Silva AMS, Estephan EP, et al. Myasthenia Gravis and COVID-19: clinical characteristics and outcomes. *Front Neurol*. 2020;11: 1053.

77. Županić S, Perić Šitum M, Majdak M, Karakaš M, Bašić S, Sporiš D. Case series of COVID-19 in patients with myasthenia gravis: a single institution experience. *Acta Neurol Belg*. 2021;121:1039-1044.

78. Rodrigues CL, de Freitas HC, Lima PRO, et al. Myasthenia gravis exacerbation and myasthenic crisis associated with COVID-19: case series and literature review. *Neurol Sci*. 2022;43:2271-2276.

79. Fragiel M, Miró Llorens P, et al. Incidence, clinical, risk factors and outcomes of Guillain-Barré in Covid-19. *Ann Neurol*. 2021;89:598-603.

80. Caress JB, Castoro RJ, Simmons Z, et al. COVID-19-associated Guillain-Barré syndrome: the early pandemic experience. *Muscle Nerve*. 2020;62:485-491.

81. Aladawi M, Elfil M, Abu-Esheh B, et al. Guillain Barre Syndrome as a complication of COVID-19: A Systematic Review. *Can J Neurol Sci*. 2022;49:38-48.

82. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry*. 2021;92:751-756.