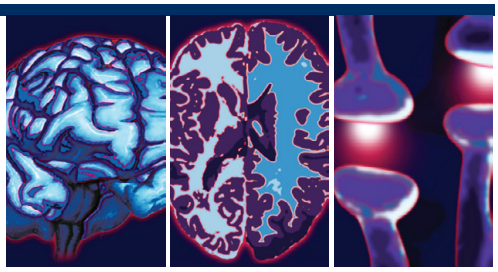

# COVID-19 and neuromuscular disorders

## Introduction

The coronavirus 2019 (COVID-19) pandemic has potential to disproportionately and severely affect patients with neuromuscular disorders. This article reviews potential neuromuscular complications of COVID-19, assessment and mitigation of COVID-19-related risk for patients with preexisting neuromuscular disease, guidance for management of immunosuppressive and immunomodulatory therapies, practical guidance regarding neuromuscular care delivery, telemedicine, and education, and effect on neuromuscular research. We outline key unanswered clinical questions and highlight the need for team-based and interspecialty collaboration. Primary goals of clinical research during this time are to develop evidence-based best practices and to minimize morbidity and mortality related to COVID-19 for patients with neuromuscular disorders.

Whereas several human coronaviruses, including hCoV-229E, OC43, NL63, and HKU1, are associated with mild respiratory symptoms, more severe coronavirus infections have appeared over the last 2 decades. These newer coronavirus infections can result in severe acute respiratory syndrome (SARS) and include Middle East Respiratory Syndrome (MERS) and most recently coronavirus disease 2019 (COVID-19). It is possible that associated Neuromuscular Disorders (NMDs) have occurred previously but have been overshadowed by systemic manifestations. During the current COVID-19 pandemic, we need to be vigilant for neuromuscular complications that may be directly or indirectly related to coronavirus infection. We should also plan to adjust our clinical practices to prevent the spread of COVID-19 and to care for patients with NMDs and the complications they experience during this time. Finally, since the effects of the pandemic are expected to persist for longer than several weeks, we will want to adapt neuromuscular educational training programs. This article reviews the current state of knowledge and practice in these 3 areas, provides guidance, and raises clinical questions for future investigation.

There is a known risk of Guillain-Barr´e syndrome (GBS) attributable to viral infections (e.g., influenza, H1N1, Zika, Epstein-Barr virus). The rationale is that molecular mimicry exists between specific viral proteins and proteins on peripheral nerves (e.g., gangliosides) leading to an innocent bystander attack against the myelin or axon of peripheral nerves. There is 1 reported case of GBS in association with COVID-19; however, direct causality is uncertain. GBS has been reported rarely with other coronavirus infections. There is no current evidence of direct viral invasion with inflammation and degeneration of motor neurons and peripheral nerves as seen in some viral infections (e.g., poliovirus, enterovirus D68, West Nile, herpes zoster, cytomegalovirus). In the literature, there is 1 report of a 3-year-old child with acute flaccid paralysis who was coinfected with coronaviruses (HCoV 229E and OC43). However, the diagnosis was questionable; the

child had normal EMG and nerve conduction studies 1 and 3 weeks after onset, normal CSF, and normal brain and spinal cord MRI. Coronavirus infections may be associated with myopathies. No additional workup such as EMG, muscle imaging, or histopathology was reported. Likewise, as many as a third of patients infected with other coronavirus infections manifested with myalgias and elevated CKs.

There are no data regarding magnitude of risk of exacerbation due to COVID-19 or prior coronaviruses for rare NMDs. Infection is a common trigger of exacerbation or disease progression in many NMDs, both inherited and immune-mediated. For example, infection has been the leading cause of exacerbation of myasthenia gravis (MG) in a retrospective study. As such, we expect that we will observe both increased rates of disease worsening and an increased incidence of new presentations during the COVID-19 pandemic. Considerations for exacerbation in acquired and inherited disorders are primarily related to degree of baseline cardiac and respiratory dysfunction, bulbar weakness, underlying pathophysiology of disease, and related comorbid conditions. Patients with motor neuron disease (e.g., amyotrophic lateral sclerosis [ALS], spinal muscular atrophy) and hereditary neuropathies with ventilatory muscle involvement may be particularly susceptible to infection. Those with metabolic myopathies (e.g., lipid storage diseases and mitochondrial disorders) are at increased risk of rhabdomyolysis with fever, infection, or fasting (attributable to loss of appetite). In addition, patients with various muscular dystrophies, including myotonic dystrophy, and metabolic diseases (e.g., Pompe disease) who have ventilatory muscle weakness or cardiomyopathy are likely at increased risk for severe COVID-19. Patients who develop COVID-19 may not return to their prior baseline.

Patients with NMDs who use immunosuppressive therapies (ISTs) are likely at increased risk of contracting COVID-19 or having a more severe course of the virus. This risk is variable even among patients on ISTs and with the same disease. Published experience from Wuhan, China, to date has not examined neuromuscular comorbidities or patients on ISTs.5,6 In looking to similar immunocompromised populations where there has been work published, recent data suggest a trend toward increased incidence rate of COVID-19 and increased rate of severe disease in patients with cancer and cancer survivors in China.17 As a result, the authors made recommendations for this population that may be applicable to immunocompromised patients with NMD at highest risk: intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer in endemic areas, stronger personal protection provisions for patients with cancer or cancer survivors, and consideration of more intensive surveillance or treatment when patients with cancer are infected with SARS coronavirus 2 (SARS-CoV-2), especially in older patients or those with other comorbidities.

Several antiviral drugs are in clinical trial for treatment of COVID-19, including lopinavir/ritonavir, used for HIV infection, and remdesivir, which inhibits viral RNA polymerases and appears to show potent activity in vitro against members of the filoviruses (e.g., Ebola virus) and coronaviruses (e.g., SARSCoV, MERS-CoV).24 A recently published trial from China found no efficacy of lopinavir/ritonavir in COVID-19,but other trials are ongoing and in preparation. With this in mind, certain protease inhibitors may increase the risk of peripheral neuropathy in patients with HIV,26 but other studies have found lopinavir/ritonavir does not increase the risk and may actually reduce

the risk of distal sensory polyneuropathy in HIV-infected individuals.

In the United States, we are in the early stages of these modifications. Approach has been tailored by geographic location, local COVID-19 prevalence, patient population, and practice or institutional structures. Currently, the volume of elective or nonurgent outpatient care has been significantly reduced. The goal is to limit exposure to patients, communities, and medical staff. No data regarding the scope of this effect have been generated. The American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM) published guidance regarding clinical visits, electrodiagnostic testing, and telemedicine during COVID-19.57 Currently, the AANEM encourages physicians to "discuss issues related to patient care with their hospitals and provide their recommendations regarding which patients need to be seen vs those that can be delayed without impact on patient care or outcomes" Most outpatient electrodiagnostic studies and muscle and nerve biopsies may be postponed unless in case of urgent need and the results would change management (e.g., new ALS, MG, immune-mediated neuropathy or myopathy). Relevant patient-related and disease-specific outcomes and systems-based measurements of care metrics should be evaluated to assess the effect of these modifications.

In addition to professional and personal challenges for trainees and teaching faculty and clinical reassignments, the COVID-19 pandemic has posed limitations on formal neuromuscular training in residencies and fellowships. We see the immediate effect for this year's cohort, but anticipate that next year will also be affected, either by ongoing reallocated clinical volume or the need to catch up on differed routine outpatient care. To adapt to these changes in real time and plan for the months ahead, we have added new or modified fellowship activities, and involved fellows in creating and testing these new structures (table 7). We have found that new communication platforms (e.g., Microsoft Teams or other) have been essential for ongoing formal and informal communications and to facilitate synchronous supervision of fellows remotely in clinic. Readers of Neurology® will have developed additional novel educational strategies. We anticipate that there will be future collaboration around these innovations to build and, after COVID-19, continuing those that have positively affected training.

Data from the current COVID-19 pandemic regarding specific risks and outcomes for patients with neuromuscular disease are unknown. We will need new clinical structures including robust telemedicine platforms and procedures to care for our patients and to continue to educate trainees during this time. Expedited publication of updated evidence-based guidance will be informative. In the meantime, we can be vigilant in assessing patients with neuromuscular disease for potential neuromuscular complications of COVID-19 and work towards mitigation of COVID-19-related risk for patients with preexisting neuromuscular disease. Collaborative efforts among institutions will help generate the data needed to inform management of rare NMDs in the setting of COVID-19 and maintain clinical trials and research despite current challenges.