Neurological Sequelae of COVID-19 in Rehabilitation Settings

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ABSTRACT

Neurological symptoms of post-acute sequelae of COVID-19 (PASC), also known as Long COVID, are recognized. Four neurological syndromes (transverse myelitis, ischemic stroke, headache, and Guillain-Barré syndrome) associated with PASC are reviewed here, with a particular focus on issues related to rehabilitation.

KEYWORDS: Long COVID, neurological, rehabilitation

INTRODUCTION

The World Health Organization (WHO) defines Long COVID as symptoms lasting at least two months after a probable or confirmed diagnosis of COVID-19, usually starting within three months of COVID-19 onset.[1] This syndrome is also described as post-acute sequelae of COVID-19 (PASC). Neurological symptoms of PASC are variable and include fatigue, cognitive impairment, headache, myalgia, sensorimotor abnormalities, seizures, and dysautonomia.[1,2] Several neurological syndromes have been described in relation to PASC. In the absence of specific evidence for these syndromes, their treatment typically proceeds according to that for similar but non-COVID-related entities. For example, COVID-19-associated Guillain-Barré Syndrome (GBS) is treated in the same way as pre-pandemic GBS. Due to the prolonged symptoms in some COVID-19 cases, rehabilitation strategies are increasingly used to improve outcomes and hasten recovery.

In this review, we focus on four COVID-19-associated neurological syndromes that may benefit from inpatient or outpatient rehabilitation. These include GBS, transverse myelitis (TM), ischemic stroke, and headache. We will discuss the typical clinical presentation, theorized pathophysiology of these syndromes, and potential rehabilitation needs and treatments.

TRANSVERSE MYELITIS

Transverse myelitis (TM) is focal inflammation of the spinal cord, resulting in neurologic deficits (weakness, sensory loss, bowel/bladder dysfunction). Common causes include multiple sclerosis, neuromyelitis optical spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein associated disease (MOGAD), and neurosarcoidosis. A handful of cases of TM have been reported in the context of PASC,[3-8] and there are two theorized mechanisms for this condition. The first postulates viral invasion of the CNS via the ACE2 receptors on the brain/spinal glial cells and the endothelial cells of the blood brain barrier. The second proposed mechanism is a post-infectious autoimmune mediated response.[3]

TM presents clinically with acute to subacute focal neurologic deficits that correlate to the area of spinal cord inflammation. COVID-19-associated TM has been seen in both the acute phase of the illness as well as up to one month after the acute COVID-19 phase.[4,7] This time frame would support the proposed pathophysiology of direct viral invasion and post-inflammatory autoimmune response, respectively.

On MRI scans, both longitudinally extensive spinal cord lesions and multifocal cord lesions have been described in COVID-19-related TM. The cervical and thoracic segments of the spinal cord are most often implicated, and within the cord the ventral horns are most commonly affected. The ventral horn predominance correlates with patients typically presenting with primarily motor symptoms. Notably, this ventral horn predominance is also seen in other viruses that infect the spinal cord directly (e.g., polio, flaviviruses, and enterovirus).[3] The standard treatment of TM, including that associated with COVID-19, consists of high-dose steroids and frequently the addition of either plasmapheresis or intravenous immunoglobulin (IVIG). Patients with COVID-19-associated TM had various degrees of clinical improvement. One report showed complete recovery after a course of steroids and IVIG,[5] but most cases with COVID-19 TM do not fully recover over the first several days and require physical rehabilitation.

Given the small number of case reports describing TM with PASC, there are limited data regarding specific rehabilitation outcomes. In non-COVID TM, long-term follow up shows that approximately one-third of patients recover with minimal to no impairment; one-third have moderate disability (e.g., independent ambulation with mild spasticity, some manageable urinary/bowel changes, sensory deficits); and one-third have severe disability (e.g., inability to walk independently, no sphincter control).[9] The aim of physical rehabilitation in these patients is to maximize their independence and capabilities. Physical and occupational therapists focus on strength and range-of-motion to improve

tone, mitigate pain, and maximize functional mobility and independence with daily activities. Generally, in spinal cord injury rehabilitation, individuals with an injury at or below T12 may regain independent ambulation with assistive devices. Patients with cervical and high-thoracic lesions do not have as good a prognosis for ambulation. TM associated with COVID-19 is typically of the cervical and thoracic segments, but the outcomes data for this cohort are insufficient to make any generalizations about the prognosis for ambulation. Regardless, it is important to begin rehabilitation early and aggressively as about a third of patients with TM have a chance of near complete recovery.[10] Furthermore, the recovery process for TM can go on for a year or more, so it is important to periodically re-evaluate patients for additional courses of physical and occupational therapy. Overall, it appears that Long COVID-associated TM patients who are treated early on with high-dose steroids and IVIG in conjunction with a physical rehabilitation program will have the best prognosis and a chance for full recovery.

ISCHEMIC STROKE

Ischemic strokes have been associated with COVID-19. A systematic review during the first six months of the pandemic showed that the average incidence of ischemic stroke in COVID-19 patients was 1.5%[11] and a retrospective cohort study (March to April 2020) showed a 0.9% incidence of stroke, with a disproportionate number having strokes of uncertain etiology (cryptogenic).[12]

The theorized mechanisms of COVID-19-associated ischemic stroke are cardiomyopathy and/or hypercoagulability.[11,13] This hypercoagulability includes elevated D-dimer and fibrinogen levels or fibrin/fibrinogen degradation products as well as elevated pro-inflammatory cytokine levels and direct damage to endothelial cells.[11,13] In an early study, patients with COVID-19 had a much higher incidence of cryptogenic strokes as compared to non-COVID-19 patients.[12]

Depending on the location of the cerebral infarct, ischemic stroke can present with a variety of symptoms. Rehabilitation must be tailored to a patient's unique needs by an interdisciplinary team. Rehabilitation treatments after non-COVID stroke focus on improving mobility and activities of daily living (ADLs), often by helping patients practice and relearn basic activities.[14,15] The rehabilitation team will also address bowel and bladder function, pain management, psychological issues, and education of the patient and family. Most clinical recovery takes place in the first 3–6 months after stroke.[14]

There are no data about rehabilitation in patients with stroke related to COVID-19. An important consideration in discussing rehabilitation approaches is that patients with stroke in the context of COVID-19 had more severe strokes at admission and worse functional outcomes than those without the viral infection.[16] Therefore, they are likely to require more intensive and longer periods of inpatient rehabilitation.

HEADACHE

Headache is one of the most common neurological symptoms of COVID-19.[17,18] In patients with acute COVID-19, 11–34% reported a headache, and 5–55% of patients experienced headaches three months after the acute infection.[19] There is no known pathophysiology for these headaches, but a plausible mechanism is the release of cytokines and chemokines by macrophages during infection.[20] It is also theorized that the SARS-CoV-2 virus may activate trigeminal nerve endings, directly or indirectly, via vasculopathy and/or circulating cytokines/chemokines.[21]

The headaches described in COVID-19 are usually bitemporal, pressure-like or pulsatile, and may have associated migrainous photophobia/phonophobia.[19,21,22] They usually occur on a daily basis and are more prevalent in patients with underlying medical comorbidities (hypertension, coronary artery disease, diabetes, and hypothyroidism).[17] They are also difficult to control with standard treatments for tension or migraine headaches.

In some instances, COVID-19-associated headaches are refractory to standard management, and there is increasing interest in an interdisciplinary approach, similar to post-concussion headache management. There is wide variation in the structure of concussion clinics, but most have some combination of specialists in neurology, physical medicine and rehabilitation, sports medicine, social work, physical therapy, occupational therapy, and psychology.[23] In interdisciplinary concussion clinics, these clinicians work together to treat the complex causes of post-concussive headaches. The Mayo Clinic has been introducing Long COVID patients with headaches to their Brain Rehabilitation clinic that previously was reserved for concussion patients. Using the concussion clinic as a model, the interdisciplinary management of Long COVID headaches may be the best option for rehabilitation of these patients.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré Syndrome (GBS) is an autoimmune peripheral polyneuropathy characterized by ascending weakness and/or sensory loss.[24] Pre-pandemic GBS was frequently a post-infectious illness associated with campylobacter jejuni as well as Epstein Barr virus, mycoplasma pneumonia, Haemophilus influenzae and influenza A. It is thought to be caused by molecular mimicry, the theory in which foreign antigens have structural similarities to self-antigens and thereby trigger an autoimmune reaction.[24]

GBS associated with COVID-19 is considered primarily a post-infectious syndrome, but some studies have also shown

a para-infectious variant.[25-27] Molecular mimicry is the postulated pathological mechanism of GBS, and a study by Lucchese and Floel showed this mimicry between COVID-19 and human heat shock proteins.[28] The mechanism in the less frequent, para-infectious variant of COVID-19-associated GBS is thought to be caused by direct injury to nerves and/or an underlying immunodeficiency.[29]

As in conventional patients with GBS, those with COVID-19 are most often treated with IVIG or plasmapheresis. Follow-up and outcome data on patients with COVID-19 are limited, but a review noted that in an unspecified "short" time interval, 62% of patients with GBS had significantly improved or recovered.[25] Radisic et al showed that there was no difference in disability score between GBS patients with or without COVID-19 at three months after hospital discharge.[31] In a study of eight patients, Solaro et al showed that COVID-19-associated GBS had better outcomes than non-COVID-19 GBS.[32]

There are limited data on rehabilitation methods and outcomes for patients with COVID-19-associated GBS, but most case reports suggest an interdisciplinary approach with physical, occupational and speech/swallow therapy. Rehabilitation in these cases has mainly focused on functional training for safety and independence through exercises for strength, balance, and range-of-motion.[30,33]

Data on the rehabilitation of non-COVID-related GBS may be helpful. A study by Prada et al showed that continuing physical therapy for more than six months can improve functional outcomes in GBS.[34] A randomized controlled trial by Khan et al showed that at 12 months, patients with high intensity rehabilitation (three 1-hour sessions per week with PT, OT, psychology and speech therapy) scored better on scales of functional status and their perception of the disease.[35]

CONCLUSION

COVID-19 can be associated with long-lasting neurologic symptoms. In this article we discussed four neurologic syndromes associated with COVID-19 that may benefit from interdisciplinary rehabilitation strategies. There is limited data on outcomes of rehabilitation in these COVID-19-associated conditions, but using the non-COVID neurological syndromes as models is the first step toward more effective treatment of these patients.

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