Neuromuscular Complications in COVID-19: A Review of the Literature

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Introduction

Coronavirus disease of 2019 (COVID-19) is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the betacoronavirus family which includes severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV).[1] All viruses from the betacaronavirus family pose a public health threat as they are known to cross species barriers and lead to high pathogenicity and mortality in humans.[1] The COVID-19 global health pandemic has resulted in 8,242,999 cases and 445,535 deaths worldwide as of June 18, 2020.[2] There are currently no vaccines available to prevent infection with COVID-19 and no proven drug therapies. While the central nervous system complications of COVID-19 are becoming increasingly recognized including headache, seizure, encephalopathy, and cerebrovascular event, neuromuscular complications of COVID-19 are just beginning to be documented.[3-4] Patients with several neuromuscular disorders may also be at increased risk for exacerbation or progression of underlying disease due to COVID-19 associated respiratory muscle injury and long-term usage of immunosuppressive or immunomodulatory therapies.[5]

In this review we focus our discussion on two ways that COVID-19 critically impacts neuromuscular medicine: (1) serious complications and outcomes associated with the viral infection and; (2) management considerations for neuromuscular patients on immunotherapies during the COVID-19 pandemic. A comprehensive PUBMED literature search was completed on June 13, 2020 using keywords "coronavirus" and "neurology," yielding a total of 547 publications. All articles in the English language were reviewed, and those with detailed information on neuromuscular manifestations were included.

Neuromuscular Complications of COVID-19

Guillain-Barré syndrome (GBS)

At the time of this literature search, the most commonly reported neuromuscular complication of COVID-19 was GBS. While GBS has been infrequently described in SARS-CoV-1 and MERS-CoV, it seems to be relatively common in COVID-19.[5] Up to the search date, 27 cases of COVID-19 associated GBS were reported, 3 of whom were described as the Miller Fisher variant.[7-25] Report origins were worldwide including Austria (1),[11] China (1),[23] France (1),[9] Germany (1),[17] Italy (10),[7-8, 14,16,21] Iran (1),[18] Morocco (1),[20] Spain (3), [24-25] Switzerland (3),[12] Turkey (1),[1] and United States (4).[10,15,19,22] Table 1 shows the essential characteristics and clinical courses of the 27 GBS cases. The mean age was 59.8 years, with male cases (63%) predominating over females (37%). The mean interval duration between the initial onset of COVID-19 symptoms and the appearance of neurologic symptoms was 10.7 days. Fever preceded GBS symptoms in 17 (63%) patients. In 2 (7.4%) GBS patients, there were no preceding symptoms suggesting COVID-19 infection. Eleven patients were tested for anti-ganglioside antibodies, and only one returned positive for GD1b-IgG.[24] SARS-CoV-2 viral PCR was performed in cerebrospinal fluid (CSF) of 15 patients, and all were negative. On MRI, nerve root enhancement was observed in four, and bilateral facial nerve enhancement was seen in one patient.[21] Electrodiagnostic (EDX) testing was completed in 23 patients. Among them, 16 (69.6%) were found to reveal demyelinating, 6 (26%) axonal, and 1 (4.3%) mixed axonal and demyelinating features. Mechanical ventilation was administrated in 12 (44%) patients.

The most common immunotherapy was intravenous immunoglobulin (IVIG), administered in 24 (88.9%) patients; and plasmapheresis was used in 2 (7.4%). Hydroxychloroquine and/or antiviral therapies were added to treatment regimens in 7 (25.9%) cases. In regard to overall outcome, 16 (59.3%) patients showed clinical improvement or achieved full or near full recovery, 9 (33.3%) did not show significant improvement or had a worsening clinical status. Of the 16 patients who improved, all but 2 were treated with IVIG. For 2 (7.4%) patient outcomes were not reported.

Table 1: A list of published cases of Guillain-Barré syndrome associated with COVID-19

Author	Case #	Age/ Sex	Onset neurologic syndrome	Neurologic signs and symptoms	Cerebrospinal fluid	Antiganglioside antibody	Imaging	Electrodiagnostic test	Treatment	Outcome
Alberti[7]	1	71M	10 days after fever	Flaccid areflexic tetraparesis, respiratory failure	Protein 54 mg/dL; WBC: 9 cells/μL; negative SARS-COV-2 PCR	Not tested	CT brain normal	Demyelinating features	IVIG (0.4g/kg/day 5 days), LPV/r, HCQ	Died
Assini[8]	2*	55M	>20 days after anosmia, ageusia, fever, cough	Ptosis, dysphagia, dysphonia, hyporeflexia, respiratory failure	Protein normal, positive ologoclonal bands, negative SARS-COV-2 PCR	Negative	MRI spine normal	Demyelinating features	IVIG (0.4g/kg 5 days)	Complete remission
Assini[8]	3	60M	>20 days after fever, cough	Leg weakness, areflexia, dysautonomia, respiratory failure	Protein normal, positive ologoclonal bands negative SARS-COV-2 PCR	Negative	None	Axonal polyneuropathy	IVIG (0.4g/kg 5 days)	Remission of gastroparesis, improved leg strength
Camdessanche[9]	4	64M	11 days after fever, cough	Paresthesia, flaccid areflexic tetraparesis, respiratory failure	Protein:166 mg/dL; normal cell count	Negative	None	Demyelinating features	IVIG (0.4g/kg 5 days)	Unknown
Coen[10]	5	70M	10 days after cough, myalgia	Paresthesia, allodynia, flaccid areflexic tetraparesis, difficulty voiding, constipation	Albuminocytologic dissociation, normal IgG synthesis	Negative	MRI spine normal	Demyelinating features	IVIG (0.4g/kg 5 days)	Remission 5 days after treatment
Gutierrez-Ortiz[24]	6*	55M	5 days after cough, malaise, fever	diplopia, paresthesia, areflexia, ataxic gait, anosmia, ageusia	Protein 80 mg/dL, WBC normal, negative SARS-COV-2 PCR	GD1b-IgG (+)	None	Not done	IVIG (0.4g/kg 5 days)	Resolution of neurologic symptoms except anosmia, ageusia
Gutierrez-Ortiz[24]	7*	50M	3 days after diarrhea, fever	Diplopia, areflexia, ageusia	Protein 62 mg/dL, WBC 2 /μl	Not tested	None	Not done	No immunotherapy	Complete recovery in 2 weeks
Helbok[11]	8	68M	14 days after cough, myalgia, fever	Paresthesia, weakness, areflexia, respiratory difficulty	Protein 64 mg/dL; WBC normal; negative SARS-COV-2 PCR	Not tested	None	Demyelinating features	IVIG 30 g total followed by PLEX x 4	Remission in 4 weeks
Lascano[12]	9	52F	15 days after cough, fever, arthralgia	flaccid areflexic tetraplegia, dysautonomia	Protein 60 mg/dL; WBC 3 /μL; negative SARS-COV-2 PCR	Negative	MRI spine normal	Demyelinating features	IVIG (0.4g/kg for 5 days)	Walking with assistance at 5 weeks post treatment
Lascano[12]	10	63F	7 days after cough, odynophagia	Paresthesia, flaccid areflexic tetraparesis, respiratory failure	Protein 40 mg/dL; WBC 2 /μL	Not tested	None	Demyelinating features	IVIG (0.4g/kg for 5 days)	Remission of tetraparesis, persistent paresthesia 5 weeks post treatment
Lascano[12]	11	61F	22 days after cough, fever, odynophagia	Paresthesia, flaccid areflexic tetraparesis, facial and bulbar weakness, dysautonomia,	Protein 140 mg/dL; WBC 4 cells/μL; negative SARS-COV-2 PCR	Not tested	MRI revealing lumbosacral root enhancement	Demyelinating features	IVIG (0.4g/kg for 5 days)	Walking with assistance at 5 weeks post treatment
Oguz-Akarsu[13]	12	53F	no preceding illness	Paresthesia, dysarthria, areflexia, leg weakness	Protein 32.6 mg/dL; negative SARS-COV-2 PCR	Not tested	MRI showing thickening and hyperintensity of nerve roots	Demyelinating features	PLEX x 5 days; HCQ, AZM	Improved leg weakness in 2 weeks
Ottaviani[14]	13	66F	10 days after cough, fever	Tetraparesis, areflexia	Protein 108 mg/dL; WBC normal	Not tested	None	Mixed demyelinating/axonal	IVIG (0.4g/kg for 5 days); HCQ, LPV/r	Persistent respiratory and multi-organ failure
Padroni[16]	14	70F	24 days after cough, fever	Paresthesia, weakness, gait difficulty	Protein 48 mg/dL; WBC normal	Not tested	None	Demyelinating features	IVIG (0.4g/kg 5 days)	Worsening weakness, required mechanical ventilation
Rana[15]	15	54M	14 days after odynophagia, fever, chill	ophthalmoparesis, facial diplegia, tetraparesis, areflexia,	Not done	Not tested	MRI thoracic & lumbar spine normal	Demyelinating features	IVIG (0.4g/kg 5 days); HCQ, AZM	Improved partially

Table 1: A list of published cases of Guillain-Barré syndrome associated with COVID-19 (continued)

Author	Case #	Age/ Sex	Onset neurologic syndrome	Neurologic signs and symptoms	Cerebrospinal fluid	Antiganglioside antibody	Imaging	Electrodiagnostic test	Treatment	Outcome
				dysautonomia, respiratory failure						
Reyes Bueno[25]	16	51M	15 days after diarrhea, odynophagia, cough	Limb and back pain, leg weakness, areflexia	Protein 70 mg/dL, WBC 5 /µl	Negative	None	Demyelinating features,	IVIG (0.4g/kg 5 days)	Improvement in facial and limb paresis, diplopia, pain
Scheidl[17]	17	54F	14 days after anosmia, ageusia	Paresthesia, proximal weakness, areflexia	Protein 140 mg/dL; WBC normal	Not tested	MRI cervical spine normal	Demyelinating features	IVIG (0.4g/kg 5 days)	Near complete resolution
Sedaghat[18]	18	65M	14 days after cough, fever, dyspnea	Tetraparesis, areflexia	Not done	Not tested	MRI cervical spine unremarkable	Axonal polyneuropathy	IVIG (0.4g/kg 5 days); HCQ, LPV/r, AZM	Unknown
Su[19]	19	72M	7 days after diarrhea, anorexia, chill	Paresthesia, weakness, dysautonomia, respiratory failure	Protein 313 mg/dL; WBC 1 /µL; negative SARS-COV-2 PCR	Negative	CT brain normal	Demyelinating features	Unknown	No improvement. Required tracheostomy and gastrostomy
Otmani[20]	20	70F	3 days after cough, fever, dyspnea	Tetraparesis, areflexia	Protein100 mg/dl; negative SARS-CoV-2 PCR	Not tested	None	Axonal polyneuropathy	IVIG (2g/kg 5 days); HCQ, AZM	no significant improvement one week after treatment
Toscano[21]	21	77F	7 days after fever, cough, ageusia	Paresthesia, facial weakness, flaccid areflexic tetraplegia, respiratory failure	protein 101 mg/dl; WBC 4/µl; negative SARS-CoV-2 PCR	Negative	MRI lumbar spine reveal caudal nerve root enhancement	Axonal polyneuropathy	IVIG 2 cycles	persistence limb weakness, and dysphagia
Toscano[21]	22	23M	10 days after fever and pharyngitis	Facial diplegia, leg paresthesia, ataxia areflexia	protein 123 mg/dl; WBC normal; negative SARS-CoV-2 PCR	Not tested	MRI brain bilateral facial nerve enhancement; MRI spine normal	Axonal polyneuropathy	IVIG 1 cycle	Partial improvement
Toscano[21]	23	55M	10 days after fever, cough	Flaccid tetraparesis, facial weakness, areflexia, respiratory failure	protein 193 mg/dl; WBC normal; negative SARS-CoV-2 PCR	Negative	MRI brain normal; MRI lumbar spine reveal caudal nerve root enhancement	Axonal polyneuropathy	IVIG 2 cycles	Persistent respiratory failure and flaccid tetraplegia
Toscano[21]	24	76M	5 days after cough, hyposmia	Flaccid areflexic tetraparesis, ataxia	protein and WBC normal; negative SARS-CoV-2 PCR	Not tested	MRI brain and spine normal	Not done	IVIG 1 cycle	mild improvement
Toscano[21]	25	61M	7 days after cough, ageusia, anosmia	Facial weakness, flaccid areflexic paraplegia, respiratory failure	protein 40 mg/dl; WBC 3/µl; negative SARS-CoV-2 PCR	Negative	MRI spine normal	Demyelinating features	IVIG, PLEX	Remained tetraplegic and ventilated 4 weeks after neurologic onset,
Virani[22]	26	54M	10 days after fever, cough	Paresthesia, leg weakness, areflexia, respiratory failure	Not done	Not tested	MRI spine normal	Not done	IVIG (0.4g/kg 5 days); HCQ	Arm weakness resolved but leg weakness persisted
Zhao[23]	27	61F	No preceding illness	Decreased distal sensation, limb weakness, areflexia	protein 124 mg/dl; WBC normal	Not tested	None	Demyelinating features	IVIG 1 cycle; Arbidol, LPV/r	Resolved by day 30

***Cases classified as Miller Fisher syndrome.**
Abbreviations: WBC, white blood cell; IVIG, intravenous immunoglobulin; LPV/r, Lopinavir/Rotinavir; HCQ, hydroxychloroquine; PCR, polymerase chain reaction; PLEX, plasmapheresis; AZM, azithromycin.

Myopathy and hyperCKemia

Myopathy and hyperCKemia are frequently reported complications of COVID-19. A retrospective case series by Mao et al. [4] included 214 COVID-19 patients from Wuhan, China, and found 10.7% of patients had evidence of skeletal muscle injury, defined as muscle pain with creatine kinase (CK) levels of being >200 U/L. Of the 88 patients with severe infection, the incidence of skeletal muscle injury increased to 19.3%, compared to only 4.8% in 126 patients with mild infection. Zhang et al.[28] analyzed another group of 95 patients with COVID-19 in Wuhan and reported an incidence of 29.5% with hyperCKemia (defined as CK >200 U/L). Similarly, a higher incidence (43.8%) of hyperCKemia was observed in 32 patients with severe infection.[28] Romero-Sanchez et al.[29] analyzed a group of 841 patients hospitalized with COVID-19 in Spain. In their analysis, hyperCKemia was found in 73 (9.2%), and clinical evidence of myopathy was seen in 26 (3.1%) patients, 3 of which had EDX evidence of myopathy. Their patients may include cases of critical care myopathy, as a multivariate analysis reported longer ICU stay was the only independent predictor in the development of myopathy.[29] A few additional studies reported rhabdomyolysis in the setting of COVID-19. Jin et al.[30] described a 60-year-old man with CK of 11,842 U/L and elevated myoglobin of >12.00 mg/L. His clinical symptoms and CK improved with aggressive fluid therapy. Guan et al.[31] defined rhabdomyolysis as the presence of muscle pain, weakness and CK level that was 10 times the upper limit of normal and found a low incidence of 0.2% among 1099 patients.

Neuromuscular Junction Disorders

Patients with neuromuscular junction disorders such as myasthenia gravis (MG) are known to be vulnerable to infection leading to exacerbations.[32] Chronic immunosuppressive or immunomodulatory therapy and thymectomy also place these patients at increased risk for infections.[33] Concerns have been raised in that MG patients are at higher risk for contracting COVID-19 or developing exacerbations secondary to coronavirus infection.[34] To date, there are a total of 7 MG patients reported as having contracted COVID-19.[35,42,44] Table 2 outlines the clinical characteristics, treatment regimes, and outcomes of these patients. All 7 cases reside in the United States and all had generalized MG. Six were positive for acetylcholine receptor antibody, and one was positive for muscle specific tyrosine kinase antibody. Three patients required mechanical ventilation for respiratory failure, and one required significant supple-

Table 2: A list of myasthenia gravis patients with COVID-19.

Author	Age/sex	MGFA Class at COVID-19 diagnosis	Antibody status	Thymus status	MG treatment at time of infection	Signs and symptoms	MG and COVID-19 treatment	Outcome	MG course during COVID-19
Anand[35]	57M	1	AChR-Ab+	thymectomy	AZA 50 mg/day	sore throat, cough	AZA 50 mg daily, HCQ, AZM, TOZ	Required ventilation but extubated on day 7	No exacerbation
Anand[35]	64M	Remission	AChR-Ab+	thymectomy	MMF 1000 mg BID, Pred 5 mg QOD	cough, chill	Pred 10mg daily for 9 days then 5mg QOD, HCQ, AZM, CTX	Required ventilation then tracheostomy	No exacerbation
Anand[35]	90F	1	AChR-Ab+	No thymectomy	MMF 1000 mg BID, Pred 30 mg/day IVIG 0.8 g/kg monthly	shortness of breath, cough, fever	Pred 25mg daily for 6 days then 20mg daily, IVIG continued, HCQ, AZM, CTX	Required high flow oxygen therapy without need for ventilation	No exacerbation
Anand[35]	42F	2B	MuSK-Ab +	No thymectomy	Pred 5 mg alternating with 2.5 mg QOD	sore throat, myalgia, worsening dysphagia, neck weakness, diplopia	Pred 20mg daily, IVIG 2 g/kg	No respiratory support required	Exacerbation
Anand[35]	64F	1	AChR-Ab+	No thymectomy	MMF 750BID, Pred 15 mg/day	cough, night sweat, chill	Pred 15mg daily	No respiratory support required	No exacerbation
Delly[42]	56F	2B	AChR-Ab+	No thymectomy	Pyridostigmine 60mg QID, Pred 40mg/day, IVIG 1.3 g/kg every 2 weeks), HCQ 200mg BID for CTD	dyspnea, fever, myalgia, proximal limb weakness, respiratory failure	Pred 80mg daily, IVIG at 0.4 g/kg for 5 days then 0.65 g/kg for 2 days	Required ventilation then extubated on day 13	Exacerbation with crisis
Ramaswamy[44]	42F	2B	AChR-Ab+	Thymoma without thymectomy	MMF 1000 BID, pyridostigmine 60mg QID, Pred 30mg/day, PLEX q4week	fever, chill, cough, anosmia, ageusia	PLEX was held, home regime continued	No respiratory support required	No exacerbation

Abbreviations: MGFA, Myasthenia Gravis Foundation of America; MG, myasthenia gravis; AChR-Ab, acetylcholine receptor antibody; AZA, azathioprine; HCQ: hydroxychloroquine; AZM, azithromycin; TOZ, tocilizumab; MMF, mycophenolate mofetil; Pred, Prednisone; CTX, ceftriaxone; IVIG, intravenous immunoglobulin; MuSK-Ab, muscle specific tyrosine kinase antibody; CTD, connective tissue disease; PLEX, plasmapheresis.

mental oxygen. Two patients showed definite signs of MG exacerbation on examination, however, such an impression could have been hindered by the need for ventilation and sedation in COVID-19 patients with severe pulmonary dysfunction. Outcomes were fairly good in six patients, with only one patient remaining intubated at day 35.[35]

Acute Myelitis

So far there has been no case reports of a motor neuron disorder associated with COVID-19 infection. Two cases of myelitis have been reported [36,37]. Zhao et al.[36] described a 66-year-old man who developed lower extremity weakness with bowel and bladder incontinence followed by flaccid lower extremity paralysis, hyporeflexia, and a thoracic sensory level. Spinal cord imaging and CSF studies were not performed on this patient. He was treated empirically with IVIG and methylprednisolone, which led to some clinical improvement. Munz et al.[37] described a 60 year-old-man who presented with lower extremity weakness and bladder dysfunction 8 days after developing respiratory symptoms. CSF studies revealed a lymphocytic pleocytosis and negative SARS-CoV-2 PCR testing. MRI spine imaging revealed T2 hyperintensity in the thoracic spinal cord. He was treated with methylprednisolone which led to clinical improvement.

Management Considerations in Neuromuscular Patients Receiving Immunotherapy

Neuromuscular patients who are on immunosuppressive and immunomodulatory agents as well as those with respiratory and/or bulbar dysfunction secondary to neuromuscular disease should be considered high risk for severe COVID-19 infection and complications.[5,38] Patients should be encouraged to notify their healthcare provider immediately if there are signs suspicious for COVID-19 infection. Although there are currently no evidence-based guidelines for the management of neuromuscular disease in the current COVID-19 pandemic, there have been recommendations made by the French Rare Health Care for Neuromuscular disease Network (FILNEMUS) as well as recommendations made in a recent review article in Neurology by Guidon and Amato.[5,39] Proposed treatment strategies for initiating and managing immunosuppressants in neuromuscular patients are summarized in Table 3.

An MG expert panel has made recommendations for the management of MG patients during COVID-19, stating that therapy decisions should be individualized and made jointly with the patient's overall healthcare team.[34] The general recommendation for MG patients who contract COVID-19 is to continue current treatment, but cortico-

Table 3: Recommended adjustment of immunotherapy in neuromuscular patients.

Medication Class	Examples	Patients initiating treatment	Patients already on treatment
Corticosteroids	Prednisone, Methylprednisolone, Deflazacort	Treat at lowest effective dose	Continue therapy regimen If treated with intravenous corticosteroids, consider home infusion, intramuscular or oral dosing.
Immunosuppressive Therapy	Azathioprine, Mycophenolate mofetil, Methotrexate, Tacrolimus, Cyclosporine	Consider delaying initiation in stable patients with mild disease. Consider spacing-out lab monitoring	Continue therapy regimen
Immunomodulatory Therapy	IVIG/SCIG, Plasmapheresis	Consider initiating home infusions for immunoglobulin	Consider home infusions, reducing frequency in stable patients.
Cell depleting Therapy	Rituximab, Cyclophosphamide	Avoid initiating unless no alternative	Consider postponing infusions, spacing out dosing or switching to subcutaneous therapy
Complement Inhibitors	Eculizumab	Consider need for immunizations, exposure to facilities during infusions	Likely does not increase COVID-19 risk
Non-immunomodulatory infusions, gene therapy	Edaravone, Nusinersen/zolgensma, Patisiran/Inotersen, Lumizyme/myozyme	Consider initiating home infusions. SMA1&2 should not delay initiation of Nusinersen/Zolgensma. SMA3&4 could consider delay	Consider home infusions, risk of exposure in facilities versus risk of treatment interruption. Recommend not delaying Nusinersen/Zolgensma infusions in children, could consider delay in adolescent or adult patients.

Modified from Guido & Amato.[5]

steroid dosage may need to be increased as in stress-dose protocols.[34] If patients are hospitalized it is recommended that immune depleting agents be held, especially those that deplete B-cell lines that would directly impair development of antibody-mediated immunity to the novel coronavirus, but standard immunosuppressive agents such as azathioprine or mycophenolate mofetil may be continued, given their long wash-out period.[34] Additionally, it is important to be cautious with investigational treatments for COVID-19 in MG patients such as hydroxychloroquine and azithromycin as these have been associated with myasthenic worsening.[5,35]

Discussion

There is rapidly growing evidence that COVID-19 infection can be associated with neuromuscular complications, and thus neurologists and clinicians should be vigilant of these manifestations. The precise mechanism of coronavirus induced neurological and neuromuscular complications are not completely understood. Several theories have been postulated including neurotropic mechanisms of direct viral invasion of the peripheral nervous system versus immune mediated injury.[5,40] Both SARS-CoV-1 and SARS-CoV-2 use the angiotensin converting enzyme 2 (ACE2) to gain entry into the cells.[43] ACE2, which plays a critical role in the renin-angiotensin-aldosterone system, has been identified on a variety of human organs particularly lung epithelium and small intestine enterocytes, providing an entry point for the virus.[43] ACE2 receptors are also expressed in the nervous system including membranes of spinal cord neurons, as well as skeletal muscle.[4,36,43] There is speculation that ACE2 may serve as a mechanism for neurologic complications seen in COVID-19 leading to central nervous system involvement including acute myelitis.[4,36,37] However, it is unclear whether muscle symptoms described in COVID-19 are related to viral invasion via ACE2 located on skeletal muscle or due to the immune response causing up-regulation of cytokines leading to inflammation and muscle damage.[4] Future investigation as well as long-term follow up of patients with neuromuscular complications associated with COVID-19 will likely clarify our understanding and improve management strategies for these patients.

Apart from hyperCKemia and myalgia, GBS appears to be the most commonly described neuromuscular complication associated with COVID-19. It is speculated that there is an autoimmune reaction in which SARS-CoV-2 elicits an immune response targeting self-epitopes leading to nervous system involvement described as "molecular mimicry."[11,13,18] Such mechanisms have been previously proposed in bacterial or viral infections that commonly precede GBS (e.g., Campylobacter, cytomegalovirus, Epstein-Barr virus and Zika virus).[5,22,41] COVID-19 could have a para-infectious association with GBS rather than the more recognized post-infectious pattern classically reported. All 15 GBS patients reported had negative CSF SARS-CoV-2 PCR testing, arguing against direct viral invasion or intrathecal viral replication. Improvement with immunotherapy and perhaps the discovery of GD1b antibodies in one patient favor an immune mediated mechanism.

It is important to realize that preceding COVID-19 symptoms may not be evident prior to the onset of GBS in some patients.[13,23] These patients could be asymptomatic carriers, or they could have an overlapping COVID-19/GBS course. COVID-19 should be considered in the differential diagnosis for patients presenting with acute neurologic symptoms suggestive of GBS, even in cases without preceding respiratory distress.

A significant portion of patients with COVID-19 develop respiratory failure in need of long ICU stay. It will also be important to study an association of COVID-19 with the possible occurrence of critical illness myopathy and critical illness neuropathy common to patients who require intensive care management.

Finally, neuromuscular patients that are on immunosuppression or those with respiratory or bulbar dysfunction who should be considered as high risk for severe complications of COVID-19 should be judiciously monitored. At this time, recommendations for immunotherapy adjustment are mostly speculative. Data collection via large case series collection or disease registry is needed before evidence-based recommendations can be made.

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