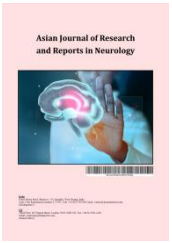

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Neuromuscular Complications of Covid 19: A Review of Literature

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Authors' contributions

This work was carried out in collaboration among all authors. All authors have contributed equally in the production of this manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: There is growing evidence that Covid 19 is associated with a myriad of neurological complications. There is still a paucity of understanding of the various biological underpinnings directing this association.
Results: This was a review of the literature on various neuromuscular complications associated with Covid 19 infection and vaccination. The literature extensively discusses conditions such as Guillain Barre Syndrome (GBS) and Myasthenia Gravis (MG), and the role of Covid 19 in various aspects of the disease process associated with these conditions. Cranial neuropathies have been reported in case studies and series.
Conclusion: Further studies are needed to deepen the understanding of this association and monitor the long-term implications of Covid 19 infection as well as vaccination on the neuromuscular system. This understanding can potentially translate into the determination of effective preventive and treatment strategies for various neuromuscular complications associated with Covid 19.

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ABBREVIATIONS

ACE : *Angiotensin Converting Enzyme*
Anti MDA 5 : *Anti-Melanoma Differentiation-Associated gene 5 Antibody*
Anti SAE 1 : *Anti Small Ubiquitin-like Modifier 1-activating Enzyme Antibody.*
CK : *Creatine Kinase*
CNS : *Central Nervous System*
GalNAc : *N-Acetylgalactosamine*
GBS : *Guillain Barre Syndrome*
GM1 : *Mono Sialotetrahexosyl Ganglioside Antibody*
IVIG : *Intravenous Immunoglobulin*
LRP-4 : *Lipoprotein- Related Protein 4*
MERS : *Middle East Respiratory Syndrome*
MG : *Myasthenia Gravis*
Mi 2 : *Anti Myositis-specific Autoantibody*
NA : *Neuralgic Amyotrophy*
PLEX : *Plasma Exchange*
SARS-CoV : *Severe Acute Respiratory Syndrome associated Coronavirus*
VAERS : *Vaccine Adverse Event Reporting System*

1. INTRODUCTION

Coronaviruses are a group of RNA viruses that cause various diseases in mammals and birds. The first case of coronavirus was reported in the 1920s in animals, and in the 1960s in humans. There are four coronaviruses, OC43, HKU1, 229E, and NL63, that usually produce mild symptoms. Three forms of coronavirus, SARS-COV in 2003, MERS in 2012, and SARS-COV 2 in 2019, have caused severe disease outbreaks. Pathogenesis of coronavirus is mediated by its high affinity for ACE receptors. ACE 2 receptors are expressed in several organs and tissues, including the CNS and PNS. Neuronal entry can occur either directly through ACE receptors [1] or indirectly through vascular endothelial cells [2]. Potential pathogenic mechanisms include hypoxia-mediated injury, immune-mediated injury, and direct neuronal pathways [3]. The neurological complications of Covid 19 infection can be specific and non-specific [4]. Non-specific complications such as headache, anosmia, ageusia, and altered mentation have been extensively described in the literature [5,6]. Specific neurological complications include ischemic and hemorrhagic stroke, seizures, meningoencephalitis, myelitis, demyelinating conditions, and neuromuscular disorders [4]. Although neurological manifestations have been studied extensively in Covid 19 infection, only a handful of studies are available regarding neuromuscular aspects and related complications. There is also a growing body of evidence linking these complications with Covid 19 vaccination [7]. In our article, we review the available literature focused on Neuromuscular correlates and complications of Covid 19 infection and Covid 19 vaccination. Neuromuscular complications can be broadly divided into three categories: nerve, muscle, and neuromuscular junction-related disorders (Table 1). Mechanisms mediating the association of Covid 19 infection with various neuromuscular manifestations include direct viral invasion, triggering of autoimmune responses due to molecular mimicry and activation of inflammatory cascade, although these hypotheses need further studies to be established (Fig 1). Both mRNA and virus vector vaccines against Covid 19 can potentially trigger autoimmunity that could manifest as GBS, MG, plexopathies and immune mediated myositis (Fig 1).

Table 1. Neuromuscular complications associated with covid 19 infection

Nerve	Muscle	Neuro-muscular junction
Guillain Barre Syndrome	Myalgia	Myasthenia Gravis
Cranial Neuropathies	Rhabdomyolysis	
Neuralgic amyotrophy	Myositis	
Critical illness Neuropathy	Critical illness myopathy	

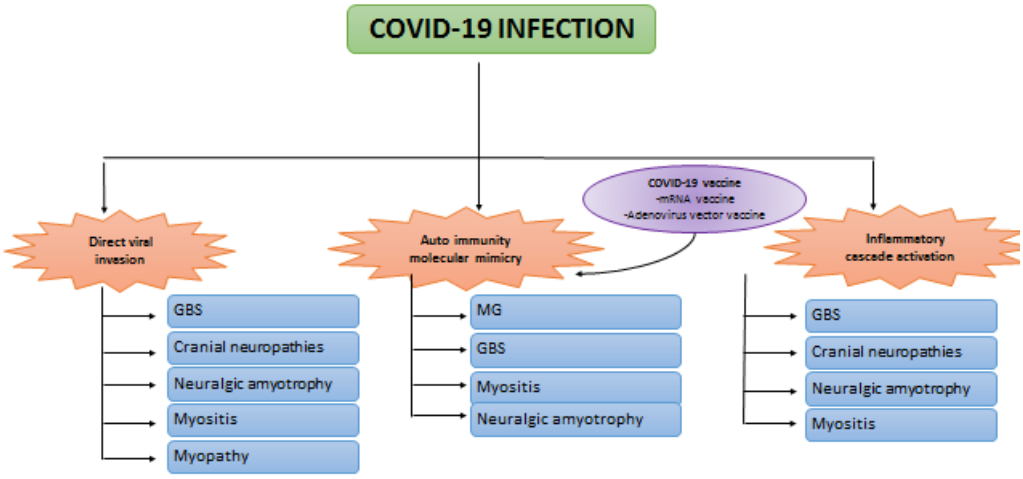

Fig. 1. Pathological mechanisms suggesting neuromuscular manifestation in Covid 19 infection as well as vaccinations against Covid 19

2. REVIEW

Aim of this review article is to highlight various neuromuscular complications associated with Covid 19 infection and vaccination. There is a growing body of evidence suggesting various neuromuscular conditions that share association with Covid 19 infection as well as vaccination. We aim to summarize various conditions in one review article. We are moving towards an era of Post Covid 19 long term sequelae and knowing the association and understanding the biological underpinnings of Covid 19 on the Neuromuscular system is helpful for early identification and monitoring these complications in Post Covid 19 era.

2.1 Nerve related Neuro-muscular Complications

2.1.1 Guillain-barre syndrome

This syndrome has been studied the most in association with Covid 19 infection so far. Although some of the initial studies showed a positive association between GBS and Covid 19 [8], debate regarding the role of Covid 19 infection in increasing the risk of GBS is ongoing [8]. In studies that showed positive association, the majority of GBS cases are post infectious [8]. Older males were at increased risk, with a mean age of 56.07 years [9]. A recently published systematic review suggested majority of Covid 19 infection associated GBS cases were sensory motor type and had acute demyelination pattern on electromyography [10]. Although the mean latency period of the onset of neurological symptoms from the initial symptom onset was 14 days [8,11], some cases were reported with neurological symptoms as early as 2-3 days. The pathology in most patients was found to be demyelinating, although some had axonal damage [8]. A retrospective study from Italy suggested a higher mortality rate in GBS associated with Covid 19, as compared to other virus related GBS [12]. Several hypotheses have been linked to the etiological association between Covid 19 and GBS, most likely the infection-mediated B-cell response. However, alternate hypotheses linking T cell-mediated responses to inflammatory mediator release and subsequent nerve damage have also been postulated. At Least 12 percent of patients with GBS were positive for antibodies to GALNAC and GM1 in previous studies [8,11]. Interestingly, the incidence of Miller Fisher Syndrome was higher in this cohort. A study showed that 5 of 39 patients with Covid-19 infection-associated GBS had Miller Fischer Syndrome and showed clinical improvement with IVIG and PLEX [8]. Another interesting association of bifacial paralysis was found in 46 percent of patients [8]. In another international cohort study, out of the 11 GBS patients with confirmed/ probable Covid 19 infection, 73% had a sensorimotor variant and 64% had facial palsy [13]. It was also noted that 33-45% of patients needed steroids, at a slightly higher rate than the general population, which

could be due to underlying lung involvement [8,11].

No specific consensus exists so far for the management of Covid 19 associated GBS, although the most sought treatment strategies are IVIG and PLEX. Although there was a theoretical concern of increased risk of thromboembolism in the setting of Covid 19 infection, patients who were treated with IVIG were not known to have developed these complications at a rate higher than that in the general population. In most of the published data, IVIG was the most administered treatment; however, 26 % of the patients had persistent neurological symptoms [14]. A mortality rate of 3.5% was observed despite aggressive treatment measures [14]. This points to poorer outcomes in patients who develop GBS in the setting of Covid 19 infection and warrants further studies to understand the mechanisms of nerve injury and appropriate treatment strategies.

As a momentum towards the next era of Covid 19, severity of illness has shifted towards milder subtypes. With such a trend, Covid 19 vaccination associated GBS is gaining attention. The risk of vaccine associated GBS varied with the type of vaccine. A retrospective study conducted using the data from VAERS found the incidence of post vaccination GBS was higher with Adenovirus vector vaccines, with risk being lower overall with mRNA Covid 19 vaccines [15]. Six out of seven cases reported in a case series of GBS after ChAdOx1-S vaccine progressed to areflexic quadriplegia, suggesting the possibility of severe form of GBS associated with the aforementioned vaccine [16]. Another series of eight cases with diverse neuromuscular manifestations following Covid 19 Vaccine showed four out of eight with GBS and its variants [17]. Interestingly these cases were associated with BNT162b2 (Pfizer-BioNTech) and ChAdOx1 nCoV-19 (AstraZeneca) vaccinations [17]. mRNA vaccine associated GBS, although with a lower incidence, has shorter interval between vaccination to symptom onset, as compared to vector vaccines [18]. The same systematic review reassuringly concludes that the vaccine related GBS did not differ significantly from GBS in the pre Covid era and treatment response of these patients was largely similar to those from pre Covid era [18]. Despite adequate number of epidemiological studies showing association of GBS with both Covid 19 infection and Covid 19 vaccination, exact biological underpinnings mediating this association continue to be investigational.

2.1.2 Facial palsy

Facial palsy in association with Covid 19 has been reported quite often, be it with infection, or post vaccination. One study found a stronger association with Covid infection than Covid vaccination when comparing matched vaccinated and infected individuals who developed facial palsy [19]. The mechanism of facial palsy associated with Covid 19 has been hypothesized to be secondary to molecular mimicry between viral and neuronal antigens. Vasculitis, which leads to ischemic injury, is another well-known phenomenon. Unlike GBS, facial palsy had an earlier onset of 2-10 days of the average interval from the onset of Covid symptoms [20]; and in about 20% of the patients it was the presenting symptom of Covid 19 [20,21]. Some studies have reported bilateral facial involvement [20], while others have reported co-involvement of other cranial nerves, such as sixth nerve palsy [22]. According to a recent systematic review, a significant proportion of patients with Covid 19 related facial nerve palsy was accompanied with GBS [23]. Those with concomitant GBS had a delayed onset of facial palsy, longer course and poorer outcome [23]. A higher prevalence of bilateral facial palsy was noted in those presenting with isolated facial palsy [23]. The majority of the patients were treated with steroids, antiviral regimens, and supportive care [20], with more than 70% recovering completely and up to 25% with partial recovery. Apart from concurrent treatment of Covid-related symptoms, no additional treatment was administered to these patients. Although some initially published studies strongly highlight the association of Covid 19 with facial palsy [24], subsequent systemic reviews that studied this association [25] have not been able to establish this association leaving the causative role of Covid 19 in facial palsy controversial.

Vaccination against Covid 19 has been studied to be well associated with facial palsy. Literature suggests no significant difference in presentation and outcome in Covid 19 vaccine associated facial palsy [26]. Interval between the vaccination and onset of symptoms varied across the studies and reports and was anywhere between 1 to 48 days [27]. Interestingly, left sided facial palsy was more common than right [27], although bifacial involvement was not uncommon as reported by some other studies [28]. The same study has

reported a concomitant diagnosis of GBS in utpo 68% of the patients [28]. There is no clear consensus on what type of vaccine has a higher risk. While some studies found higher risk with mRNA vaccines [29], others have found vector vaccines are more closely linked to this particular adverse effect [26]. Mechanism of facial palsy remains unclear, while autoimmune processes remain hypothetical. Some authors postulate Type 1 interferon response following mRNA based Covid 19 vaccines has a mediating role in facial palsy by affecting myelin sheath [29]. There could be an innate immunity activation from combined effect of mRNA and lipids, which includes interferon production that transiently impairs peripheral tolerance and development of neuropathies. For non mRNA virus vector vaccines, activation of T cells with subsequent raise in inflammatory mediators that affect the components of nervous system and disease manifestation [30]. Overall, evidence suggests that the facial palsy associated with Covid 19 vaccination had reasonably good outcome with most individuals achieving complete recovery over 6-9 months period [28].

2.1.3 Neuralgic amyotrophy

Neuralgic amyotrophy, which is synonymous with Parsonage Turner syndrome or idiopathic brachial plexopathy, commonly presents with unilateral upper extremity pain and patchy muscular weakness due to the involvement of the brachial plexus, especially the upper and middle trunks. Certainly, a rare condition in itself, neuralgic amyotrophy, was found to be associated with Covid 19 infection, with few case reports published in the literature [31-35]. Interestingly, none of these case reports have associated prolonged prone positioning, with Covid 19 infection and treatment. Infection- and immune-related mechanisms are most likely involved in this process. The age group was wide, with the youngest and oldest being 17 and 52 years, respectively. Two patients developed neurological symptoms as early as 1-2 weeks after the onset of Covid 19 symptoms. While one patient had pure sensory symptoms [33], the rest had both motor and sensory symptoms. Oral steroids were found to be beneficial in improving symptoms.

Neuralgic amyotrophy has also been associated with Covid 19 vaccination through rare case reports and case series. mRNA vaccines have shown some association so far. Patients who developed this condition following vaccination had predominant involvement of lower trunk compared to those of post Covid infection who had an involvement of upper and middle trunk [36]. Although there is a paucity of data through systematic reviews, based on case reports there was no significant difference in the outcomes of both the groups and majority of the patients responded corticosteroids [36].

2.1.4 Multiple cranial neuropathies

The involvement of cranial nerves in Covid 19 has been a well-recognized association. Cranial nerve palsy is accompanied by GBS in up to 50% of the reported cases [37]. According to a recent systematic review, there was a female preponderance in patients presenting with isolated cranial nerve palsy, and males had a higher incidence of GBS in comorbid cranial nerve involvement [37]. This presentation was observed across all ages, ranging from 6 to 63 years [37,38]. While the facial nerve is the most commonly involved nerve, cranial nerves 2, 3, 5, 6, and 10 have been frequently reported [38,39,40]. The involvement of multiple cranial nerves, although rare, has also been reported [22]. Poly cranial neuropathies involving 3, 6,7 and 12 cranial nerves have been associated with Covid 19 vaccination [41]. Poor outcomes were associated with concomitant GBS on presentation due to respiratory failure [37,38]. Most of the patients were treated conservatively or with steroids, although very few patients also received IVIG [37,38]. Novel treatment modalities such as transcutaneous non-invasive vagal nerve stimulation in patients receiving mechanical ventilation with Covid 19 have proven some benefits in improving respiratory function [42]. Although several studies identifying this association have been published, the pathological mechanisms remain unclear and debated between direct CNS involvement and immunological injury to the cranial nerves. Autopsy studies have identified viral particles in the cranial nerves and brain stem cells [42], and in the axons of cranial nerves [43], suggesting a hypothesis of retrograde transport of virus particles to the brain [44]. Identifying the exact mechanism of pathogenesis can help in the treatment of these patients and improve the overall outcomes.

2.2 Neuro-muscular Junction Related Complications

2.2.1 Myasthenia gravis

Covid 19 has a complex relationship with the MG. Studies have shown Covid 19 is associated

with an increased risk of new-onset MG, myasthenic crisis, respiratory failure, and worse outcomes in patients presenting with this comorbidity [45]. Patients with MG were also subjected to psychological stress and anxiety, affecting their quality of life during the pandemic time [46]. Studies examining the outcomes of Covid 19 in patients with pre-existing myasthenia gravis found around 25% incidence of severe Covid illness with a mortality of 15% [47]. Patients with MG had a higher incidence of severe Covid infection needing mechanical ventilation at > 70%) and a mortality of approximately 30% [48]. Severe Covid-19 illness was associated with immunosuppressive agents and severe MG at baseline [47], older age, and long-term use of steroids before Covid-19 infection [49].

MG crisis in Covid 19 infection has not been as common as it sounds to be, with an incidence ranging from 10-15% [50]. Certain factors such as cytokine storm and molecular mimicry between SARS CoV2 and acetylcholine receptors have proven to be potential mechanisms for MG exacerbation and crisis [45]. The MG crisis in this scenario can be a diagnostic challenge, as respiratory failure could be due to neuromuscular weakness (Type 2) or hypoxemia secondary to pulmonary damage (Type 1). Accurate diagnosis can direct physicians toward appropriate treatment measures. Treatments such as IVIG and plasmapheresis need to be tailored based on individual patients due to the inherent risks and potential side effects associated with these treatments [44]. Despite aggressive treatment, the outcomes seem to be poor [51].

A few cases of new-onset MG in patients with Covid 19 have been reported. While the majority of these were positive for acetylcholine receptor antibody [52], only one case has been reported so far with a negative Ach receptor ab [53]. The reported cases had manifestations of both ocular and generalized MG [53]. Some recently published case reports of new onset MG following Covid 19 had negative Ach receptor and muscle specific kinase antibody, but had positive antibodies against lipoprotein- related protein 4 (LRP-4). [54]. Infection triggering autoimmunity through molecular mimicry is a well-known pathogenic mechanism, which applies to Covid 19 infection as well. Studies are needed to further understand the exact mediating role of Covid 19 infection in new onset MG. [55].

Post-vaccination MG has been reported initially in few cases following Covid 19 vaccination [56,57]. New onset MG following Covid 19 vaccination, although rare, has been reported through case reports after receiving mRNA vaccines [58]. There was no evidence of severe MG symptomatology in post Covid 19 new onset MG [59]. As per the recent data published based on the Vaccine Adverse Event Reporting System (VAERS), there was no overall increase in the reporting rate of MG significantly after Covid 19 vaccination [60]. A recently published nested case control study from Israel supports the existing evidence that vaccines, especially mRNA vaccines against Covid 19 are not associated with significant increase in the risk of new onset MG as well as exacerbation of MG [61].

2.3 Muscle- related Neuromuscular Complications

Myalgia is a well-known and common manifestation of Covid 19, although myositis and rhabdomyolysis are less common [62]. Rhabdomyolysis often presents as acute severe proximal lower extremity predominant pain and weakness with myoglobinuria and acute kidney injury [63]. This was also an initial presentation of Covid 19 infection [64]. Rhabdomyolysis was also associated with higher mortality, and patients tended to have higher CK levels and negative serology for myositis-specific autoantibodies [65]. Dermatomyositis has rarely been associated with Covid 19. It usually presents with a skin rash, muscle involvement, and interstitial lung disease. Although the latter two are non-specific features and can be associated with Covid 19 infection, a pattern of skin involvement with heliotrope rash, periorbital edema, and malar or diffuse body rash can help suspect this entity. Bulbar involvement, although rare, has also been reported [65]. Some myositis-specific autoantibodies (anti-Mi 2, anti-MDA5, anti-SAE1, and anti-nuclear autoantibodies) are positive in patients diagnosed with this condition [66]. Isolated paraspinal myositis involving the bilateral lumbar paraspinal musculature with evidence of muscle edema and enhancement on imaging has also been reported [67]. Covid infection has also been associated with a flare-up of pre-existing myositis and dermatomyositis, although the relative role of the direct effect of Covid versus treatment non-compliance is unknown [68]. Similar to other neuromuscular complications, the proposed mechanisms of muscle involvement include

direct viral invasion, immune-mediated muscle damage, and the activation of inflammatory cascades.

Vaccination associated myositis is also known in the literature. A few cases of myositis following mRNA vaccines with positive serology for Anti-Mi2a, Anti-Mi2b and Anti MDA5have been reported [69,70]. A case series published from Yorkshire region of United Kingdom [71] suggested a high rate of new onset immune mediated myositis and dermatomyositis following RNA and DNA vaccination against Covid 19 in the setting of mass vaccination campaign. While concomitant skin involvement was reportedly more common with mRNA vaccines, concomitant interstitial lung disease was found in association with both mRNA and adenovirus vector vaccinations [72].

There are certain limitations for this review. This review is focused only on the most common Neuromuscular conditions that are extensively and exclusively studied in the setting of Covid 19. Some other conditions like peripheral neuropathies have not been covered in this review. Despite an extensive description of association of Covid 19 and various neuromuscular complications, the causative role of Covid 19 remains unclear.

3. CONCLUSION

Despite Covid 19 is a predominant respiratory pathogen, systemic involvement of infection has been a norm rather than an exception. Neuromuscular complications associated with Covid 19 are not common. So far, evidence suggests a strong association of Covid 19 with conditions such as GBS and MG. Immunological cross-reactivity and inflammatory responses have been the most consistent pathophysiological phenomena postulated to date. Isolated and multiple cranial neuropathies have been discussed in case reports and series. Muscle involvement has been noted in the forms of myalgia, rhabdomyolysis, and myositis. Further studies are needed to deepen the understanding of this association and monitor the long-term implications of Covid 19 on the neuromuscular system. Systematic reviews and meta-analysis could potentially address these aspects and possibly answer the causal role of Covid 19 on various neurological complications including Neuromuscular disorders. This understanding can potentially translate into determining effective preventive and treatment strategies for various neuromuscular complications associated with Covid 19 infection.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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