

INVITED REVIEW

Neuro-COVID-19

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Abstract

Neuromuscular manifestations of new coronavirus disease 2019 (COVID-19) infection are frequent, and include dizziness, headache, myopathy, and olfactory and gustatory disturbances. Patients with acute central nervous system disorders, such as delirium, impaired consciousness, stroke and convulsive seizures, have a high mortality rate. The encephalitis/encephalopathy that causes consciousness disturbance and seizures can be classified into three conditions, including direct infection with the SARS-CoV-2 virus, encephalopathy caused by central nervous system damage secondary to systemic hypercytokinemia (cytokine storm) and autoimmune-mediated encephalitis that occurs after infection. The sequelae, called post-acute COVID-19 syndrome or long COVID, include neuromuscular manifestations, such as anxiety, depression, sleep disturbance, muscle weakness, brain fog and cognitive impairment. It is desirable to establish diagnostic criteria and treatment for these symptoms. Vaccine-induced thrombotic thrombocytopenia, Guillain-Barré syndrome, bilateral facial paralysis, encephalitis and opsoclonus-myoclonus syndrome have been reported as adverse reactions after the COVID-19 vaccine, although these are rare.

KEYWORDS

COVID-19, neuromuscular manifestations, post-acute COVID-19 syndrome, vaccine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a SARS-CoV-2 infection that has spread rapidly since it was reported in Wuhan, China, in December 2019, and was declared a pandemic by the World Health Organization in March 2020. At the time of writing this manuscript, in August 2021, we are unfortunately facing the fifth wave of δ -mutant strains, and there are no prospects for containment. The purpose of this article is to introduce and share information on the acute neuromuscular manifestations and complications, sequelae, and adverse reactions after the COVID-19 vaccine that have been shown to date.

2 | FREQUENCY AND CHARACTERISTICS OF NEUROMUSCULAR MANIFESTATIONS

The most characteristic symptom of COVID-19 is respiratory symptoms, but neuromuscular manifestations also occur frequently and

might appear as the first symptom. The frequency of neuromuscular manifestations has been reported in China, Spain, Europe and the USA, ranging from 36.4% to 88.0%.¹⁻⁵ Although olfactory and gustatory disturbances are characteristic of this disease, it should be noted that non-specific symptoms, such as headache, dizziness and muscle symptoms, are frequently observed (Table 1), and consciousness disturbance is common in severe cases. Neurological evaluation is essential when impairment of consciousness or psychiatric symptoms occur in the absence of hypoxemia or metabolic abnormalities.

3 | NEUROMUSCULAR COMPLICATIONS

It has been reported that COVID-19 is associated with a variety of serious neuromuscular complications (Table 2), and that these complications worsen the prognosis.⁶ However, some of the evidence is based on a small number of case reports or case series, and the possibility that the complications occurred by chance at a time after

TABLE 1 Frequency of neuromuscular symptoms

	China (Ref.1)	Spain (Ref.2)	Europe (Ref.3)	Spain (Ref.4)	Chicago (Ref.5)
Total no. patients	214	841	Unknown (only patients with neurological symptoms were considered)	100 (inpatients seen by neurologist)	509
Proportion of patients presenting with neuromuscular symptoms (%)	36.4%	57.4%	Unknown	88%	42.2% at onset 62.7% at the time of hospitalization 82.3% at total course
Types of neuromuscular symptoms (%)	<ol style="list-style-type: none"> 1. Dizziness (16.8%) 2. Headache (13.1%) 3. Muscle symptoms (10.7%) 4. Consciousness disturbance (7.5%) 5. Taste disorder (5.6%) 6. Smell disorder (5.1%) 	<ol style="list-style-type: none"> 1. Muscle symptoms (20.3%) 2. Consciousness disturbance (19.6%) 3. Headache (14.1%) 4. Taste disorder (6.2%) 5. Dizziness (6.1%) 6. Smell disorder (4.9%) 7. Autonomic disturbance (2.5%) 8. Stroke (1.7%) 9. Convulsions (0.7%) 10. Movement disorders (0.7%) 	<ol style="list-style-type: none"> 1. Headache (61.9%) 2. muscle symptoms (50.4%) 3. Smell disorder (49.2%) 4. Taste disorder (39.8%) 5. Consciousness disturbance (29.3%) 6. Psychomotor symptoms (26.7%) 7. Encephalopathy (21.0%) 8. Stroke (21.0%) 	<ol style="list-style-type: none"> 1. Smell disorder (44%) 2. headache (44%) 3. Muscle symptoms (43%) 4. Dizziness (36%) 5. Encephalopathy (8%) 6. Syncope (7%) 7. Convulsions (2%) 8. Stroke (2%) 	<ol style="list-style-type: none"> 1. Muscle symptoms (44.8%) 2. headache (37.7%) 3. Encephalopathy (31.8%) 4. Dizziness (29.7%) 5. Taste disorder (15.9%) 6. Smell disorder (11.4%)

the onset of COVID-19 cannot be ruled out. A proof of causality is required to confirm the epidemiological increase in the incidence and/or to elucidate the pathogenic mechanism.

3.1 | Cerebrovascular disease

In the cerebrovascular diseases associated with COVID-19, cerebral infarct is frequent.⁷ In addition, critical-illness microbleeds might occur due to disruption of the blood–brain barrier.⁸ In a meta-analysis of hospitalized patients in the USA, Canada and Iran, it was shown that the frequency of cerebrovascular diseases was 1.8% and in-hospital mortality was as high as 34.4%; the risk factors for in-hospital mortality were advanced age, comorbidity and severity of respiratory symptoms.⁹ In addition to atherosclerotic factors, such as hypertension, diabetes mellitus, dyslipidemia and obesity, severe COVID-19 has been shown to be a risk factor for developing the cerebrovascular disease. Another meta-analysis showed that the complication rate of cerebrovascular disease increased 4.2-fold in patients with severe COVID-19 compared with those without severe disease.¹⁰

3.2 | Encephalitis and encephalopathy

There are at least three types of encephalitis/encephalopathy.¹¹ The first is considered to be viral encephalitis caused by direct viral infection of the central nervous system (CNS). The second is encephalopathy, in which systemic inflammation (hypercytokinemia/cytokine

storm) is followed by the rapid onset of neurological and psychiatric symptoms. The third is autoimmune encephalitis that develops after a certain period of time after COVID-19 infection and meets the diagnostic criteria for “possible autoimmune encephalitis” by Graus *et al.*¹² Evaluation of cytokines and chemokines might be distinguished by elevation in cerebrospinal fluid in encephalitis and in serum in encephalopathy.¹³ As encephalopathy and autoimmune encephalitis can be treated by immunotherapy, an appropriate diagnosis is required.

In addition, a number of encephalitis/encephalopathies with unique clinical and imaging findings have been reported. These include acute hemorrhagic necrotizing encephalitis,¹⁴ acute disseminated encephalomyelitis,¹⁵ mild encephalitis/encephalopathy with a reversible splenic lesion¹⁶ and posterior reversible encephalopathy syndrome.¹⁷

3.3 | Multiple sclerosis/anti-myelin oligodendrocyte glycoprotein antibody-associated disease

A small number of patients with multiple sclerosis¹⁸ and anti-myelin oligodendrocyte glycoprotein antibody-associated disease¹⁹ have been reported after COVID-19 infection.

3.4 | Movement disorders and cerebellar ataxia

There are many reports of patients with myoclonus²⁰ and opsoclonus-myoclonus syndrome²¹ after recovery from respiratory

TABLE 2 Neuromuscular complications

1. Cerebrovascular diseases	Cerebral infarct Cerebral hemorrhage Venous sinus thrombosis Critical illness-associated cerebral microbleeds
2. Meningoencephalitis/encephalopathy	meningoencephalitis Steroid-responsive encephalitis/encephalopathy
3. Other characteristic encephalopathies and encephalitis	Acute hemorrhagic necrotizing encephalopathy Acute disseminated encephalomyelitis Mild encephalitis and encephalopathy with reversible corpus callosum lesions Posterior reversible encephalopathy syndrome
4. Multiple sclerosis/anti-MOG antibody-related diseases	
5. Movement disorders/ataxia	Myoclonus Myoclonus-psychosomatic syndrome Parkinsonism Cerebellar syndrome
6. Peripheral neuropathy	Guillain-Barré syndrome, Miller Fisher syndrome isolated facial nerve palsy Sudden onset sensorineural hearing loss Pressure neuropathy due to supine position
7. Neuromuscular junction disease	Myasthenia gravis
8. Muscle diseases	Acute myositis Critical illness myopathy
9. Adverse effects associated with COVID-19 treatment (remdesivir, favipiravir)	Headache, seizures, myoclonus, delirium, abnormal behavior, hallucinations, consciousness disturbance

COVID-19, coronavirus disease 2019; MOG, myelin oligodendrocyte glycoprotein.

symptoms. In addition, acute onset of parkinsonism after infection²² and anti-amphiphysin antibody-positive cerebellar ataxia²³ have been reported. As there have been reports of an increase in functional movement disorders in both adults and children after the pandemic, an appropriate diagnosis is necessary.²⁴

3.5 | Peripheral neuropathy

In a systematic review of 18 cases of Guillain-Barré syndrome (GBS), the median time from COVID-19 onset to GBS onset was 10 days, and most patients presented with demyelinating GBS, with a prognosis of eight (44%) on artificial ventilators and two (11%) deaths.²⁵ In a study in northern Italy, the incidence of GBS in March and April 2020 was reported to have increased 2.6-fold compared with the same period a year earlier.²⁶

Miller Fisher syndrome,²⁷ isolated peripheral facial paralysis²⁸ and sudden sensorineural hearing loss²⁹ have also been reported. Furthermore, compression neuropathy caused by supine posture management, which is recommended for respiratory failure associated with acute respiratory distress syndrome, has also been reported.³⁰ The most commonly injured nerves are the ulnar, radial, sciatic, brachial plexus and median nerves, in that order. It is necessary to avoid prolonged compression and extension of the elbow, upper arm, and shoulder.

3.6 | Neuromuscular junction disease

A few patients with the anti-acetylcholine receptor antibody³¹ or anti-muscle-specific tyrosine kinase-positive³² systemic myasthenia gravis have been reported within 5–7 days of COVID-19 onset.

3.7 | Muscle disorders

Patients with COVID-19 might present with myalgia and flaccid tetraplegia, hyperCKemia and abnormal muscle magnetic resonance imaging signals. A patient with a positive anti-small ubiquitin-like modifier 1 activation enzyme antibody specific for dermatomyositis and myopathological findings consistent with dermatomyositis has been reported,³³ and the possibility that COVID-19-related myositis is dermatomyositis has been discussed.^{33,34} Although dermatomyositis is a type I interferonopathy in which type I interferon is involved in the pathogenesis, type I interferon, an antiviral cytokine induced by a viral infection, might cause dermatomyositis-like myositis. In severe cases, critical illness myopathy might be considered as a differential diagnosis.

3.8 | Neuromuscular manifestations associated with COVID-19 therapeutics

For remdesivir (Veklury), the adverse effects of headache, seizures, myoclonus, delirium and encephalopathy should be noted. For

favipiravir (Avigan), the adverse effects of abnormal behavior, delirium, hallucinations, delusions, seizures and consciousness disturbance should be noted.

4 | PATHOGENESIS OF NEUROMUSCULAR COMPLICATIONS

The pathogenesis of the neuromuscular manifestations has been suggested to be a result of: (i) direct infection of the CNS; (ii) direct infection of cerebral blood vessels; (iii) disruption of the blood-brain barrier; (iv) thrombus formation; and (v) indirect neurological damage. First, direct infection of the CNS is thought to be mediated by the angiotensin-converting enzyme 2 receptor³⁵ and the membrane protein, neuropilin-1.³⁶ It has also been speculated that the SARS-CoV-2 virus spreads from the lungs and lower respiratory tract to the medulla oblongata through mechanoreceptors and chemoreceptors in a trans-synaptic manner.³⁷ In fact, in human autopsy findings, viral proteins were found in the brainstem and lower cranial nerves, indicating that the virus can reach the brain.³⁸ The ability of the SARS-CoV-2 virus to infect the brain (neurotropism) has been confirmed by several methods, including infection experiments using transgenic mice expressing the human angiotensin-converting enzyme 2 receptor.³⁹ However, there are some criticisms of the hypothesis that direct infection of the CNS is the primary pathogenesis, based on the fact that animal models are artificial and overexpress the human angiotensin-converting enzyme 2 receptor, and that viral RNA levels in the brains of most human patients are much lower than those in the nasal cavity.⁴⁰ With regard to direct infection of cerebral blood vessels, it has been reported that the SARS-CoV-2 virus is replicated in pericytes and can infect astrocytes.⁴¹ The disruption of the blood-brain barrier has been confirmed by analysis of cerebrospinal fluid findings in patients with encephalopathy,⁴² and by experiments using infected animals in which viral proteins were transferred to the brain.⁴³

Regarding thrombus formation, it has been considered that coagulopathy in COVID-19 is similar to, but not identical to, sepsis-induced coagulopathy and disseminated intravascular coagulation syndrome, and that some features overlap with antiphospholipid antibody syndrome, hemophagocytic syndrome and thrombotic microangiopathy.⁴⁴ The release of neutrophil extracellular traps, which is a known mechanism of intravascular thrombus formation in the antiphospholipid antibody syndrome, has also been confirmed, suggesting its involvement in the pathogenesis of the disease.⁴⁵

Finally, indirect neurological damage might be associated with systemic conditions, such as hypoxia, multiple organ failure, sepsis and shock. In addition, systemic hypercytokinemia (cytokine storm) might cause secondary neuroinflammation by disruption of the blood-brain barrier.⁴⁶ It has also been shown that various autoantibodies, including an anti-hypocretin receptor antibody produced after infection may cause CNS disorders.⁴⁷

TABLE 3 Adverse reactions that may occur with various coronavirus disease 2019 vaccines

Adverse reactions	Vaccine
Anaphylactic shock	All vaccines
Vaccine-induced immune thrombocytopenia and cerebral venous thrombosis and cerebral hemorrhage	AstraZeneca
Myocarditis and pericarditis in young patients	Pfizer, Moderna
Bilateral facial nerve palsy	AstraZeneca
Guillain-Barré syndrome	Johnson & Johnson
Encephalitis, opsoclonus myoclonus syndrome	AstraZeneca
Arterial thromboembolism	AstraZeneca

5 | POST-ACUTE COVID-19 SYNDROME

Long-lasting symptoms in patients recovering from an acute phase are called post-acute COVID-19 syndrome or post-acute sequelae of SARS-CoV-2 infection or long COVID/long-haul COVID.^{48,49} These are also the first diseases in history to be defined by patients themselves using social networking services (SNS), such as Twitter and Facebook. COVID-19 is referred to as the acute phase from onset to 4 weeks, the subacute phase from 4 to 12 weeks and the chronic phase thereafter. It presents with various symptoms, including fatigue, exercise intolerance, persistent low-grade fever, lymphadenopathy, hair loss, muscle weakness, arthralgia, dyspnea, cough, palpitations, chest pain, anxiety, depression, sleep disturbance and post-traumatic stress disorder.⁵⁰ It also presents neuromuscular manifestations, including headache, brain fog, cognitive impairment and various autonomic disturbances (postural orthostatic tachycardia syndrome, temperature dysregulation, constipation and diarrhea).

Brain fog is a type of cognitive impairment that presents as a "foggy brain state", and includes a lack of intellectual clarity, poor concentration, mental fatigue and anxiety. Several studies on cognitive impairment have been carried out. First, it was reported that cognitive impairment with frontal and parietal lobe dysfunction, and frontal and parietal hypometabolism on fluorodeoxyglucose positron emission tomography occurred in the subacute phase of patients hospitalized with COVID-19.⁵¹ In a study of hospitalized patients, the frequency of cognitive impairment 4 months after onset was reported to be 61 out of 159 (38%).⁵² In addition, the frequency of cognitive impairment was 18% in all age groups and 11% in the 16–30 age group, suggesting that cognitive impairment as a sequela is an important problem, even in the younger generation.⁵³

The following hypotheses have been proposed for the mechanism of brain fog and cognitive impairment. First, although the SARS-CoV-2 virus does not directly infect the CNS, microglial activation and abnormal mitochondrial function occur.⁵⁴ Second, systemic inflammation crosses the blood–brain barrier and causes inflammation in the CNS, resulting in brain cell changes similar to those seen in neurodegenerative diseases, such as Alzheimer's disease. Third, neuroinflammation after viral infection leads to aggregation of tau protein, resulting in neurodegeneration.⁵⁵

A recent review proposed that chronic neurological sequelae can be classified into four categories, including: (i) cognitive, mood and sleep disorders; (ii) dysautonomia; (iii) diverse pain syndrome; as well as (iv) marked exercise intolerance and fatigue, although more long-term follow-up studies are required.⁵⁶ In any case, it is necessary to recognize that neuromuscular complications can occur even in mild cases and young people undergoing home treatment, and infection should be avoided as much as possible.

6 | POST-VACCINATION NEUROLOGICAL ADVERSE REACTIONS

Several mRNA vaccines and viral vector vaccines have been developed, and have shown remarkable efficacy in preventing infection and severe disease. However, adverse reactions after vaccines have been reported (Table 3). Specifically, vaccine-induced immune thrombocytopenia (VITT; AstraZeneca),⁵⁷ GBS and its subtype (Johnson & Johnson),⁵⁸ bilateral facial paralysis (AstraZeneca),⁵⁹ encephalitis, and opsoclonus-myoclonus syndrome (AstraZeneca)⁶⁰ have been reported. VITT is particularly important, because it is associated with cerebral venous thrombosis and cerebral hemorrhage, is difficult to treat, and has a severe outcome. The prognosis of VITT is worse than that of usual cerebral venous thrombosis, and the mortality rate is reported to be as high as 73% when the platelet count is <30 000 and intracranial hemorrhage is present.⁶¹ In addition, it has been shown that the causative VITT antibody has been shown to bind to the same platelet factor 4 region as heparin.⁶²

Although all of these adverse reactions are extremely rare, neurologists should be aware of the high incidence of adverse neurological reactions. However, the preventive effect of vaccines and their ability to reduce the severity of COVID-19 greatly outweigh the risk of adverse reactions, and it is important to inform the public that vaccination is recommended.

Importantly, as a very large number of people are vaccinated, it is natural that some people will develop neurological diseases after vaccination. If this is mistakenly diagnosed as an adverse reaction to the vaccine, and the information spreads through SNS and so on, it might lead to a decrease in the vaccination rate and, as a result, unnecessary infections and deaths.⁶³ Therefore, to determine

causality, an epidemiological increase in incidence and clarification of pathological mechanisms are required.

In addition, functional movement disorders after vaccines have also become a problem, as detailed on SNS. For example, "rapid-onset tic-like behavior" in young girls has been reported.⁶⁴ It is characterized by predominance in young, severity and inducibility by unusual stimuli, as well as its spread through SNS. As these functional movement disorders also increase vaccine anxiety, it is necessary for healthcare providers to communicate appropriately with the general public to prevent a decline in vaccination rates and unnecessary expansion of the pandemic.⁶⁵

7 | CONCLUSION

In this article, I have detailed that COVID-19 can cause neuromuscular manifestations during the course of the disease and that the disease can start with neuromuscular manifestations. I have also detailed that COVID-19 can cause brain fog and cognitive impairment in patients of all ages, showing that the disease should be avoided, even by young people. I hope that the COVID-19 pandemic resolves, and the knowledge described here will no longer be necessary.

DISCLOSURE

The author declares no conflict of interest.

1. Approval of the research protocol: N/A
2. Informed Consent: N/A
3. Registry and the Registration No. of the study/trial: N/A
4. Animal Studies: N/A

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