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Review

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Neurological complications of COVID-19 and SARS-CoV-2 vaccination: an update

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Abstract

The respiratory infectious disease COVID-19, which emerged in 2019, has affected the world population over a brief period. In 2020, the disease was declared a pandemic by the World Health Organization. Although most COVID-19 patients primarily develop respiratory symptoms, neurological symptoms have been observed. Neurological symptoms are usually mild and non-specific. However, some patients could experience life-threatening neurological symptoms. With the increase in the incidence of COVID-19, the disease spectrum of patients with central and peripheral nervous system involvement has expanded significantly compared to the previous period. Lack of awareness has caused delays in diagnosis and treatment; therefore, updating the disease spectrum of neurological complications of COVID-19 is necessary. After COVID-19 claimed millions of lives, researchers found that some vaccines may induce autoimmune inflammatory responses in the nervous system via molecular mimicry, leading to SARS-CoV-2 vaccine-related neurological deficits. These neurological complications are often ignored by clinicians, delaying diagnosis and treatment; it is essential to study cases of vaccine-associated neurological complications. Therefore, we summarize the neurological complications of COVID-19 and nervous system adverse reactions caused by SARS-CoV-2 vaccines to help clinicians and public health service personnel understand these rare complications. Avoiding delays in diagnosis and treatment would ensure the safety of COVID-19 patients and SARS-CoV-2 vaccine recipients.

Keywords: COVID-19, SARS-CoV-2, neurological complications, vaccine

INTRODUCTION

In March 2020, the World Health Organization announced that 2019 coronavirus disease 2019 (COVID-19) was a worldwide epidemic[1]. Since then, several studies have sought to understand acute respiratory syndrome and its treatment. As of August 21, 2022, there were more than 600 million confirmed cases of COVID-19 and over 6.47 million reported deaths globally (https://www.worldometers.info/coronavirus/)[1].

Although most COVID-19 patients develop respiratory symptoms (e.g., chest tightness and dyspnea), neurological symptoms have also been observed[2]. Reports from China revealed that 36% of patients had neurological manifestations[3]. SARS-CoV-2 may invade through the cribriform plate, olfactory nerve, thalamus, and brainstem[1,4]. Over 90% of patients with COVID-19 have at least one subjective neurological symptom[1].

COVID-19 patients with neurological complications have been susceptible to non-specific neurological symptoms. Headache, ageusia, myalgia, dizziness, and anosmia are the most common neurological symptoms in patients with COVID-19[5]. However, based on the diagnosis of specific neurological diseases, neuromuscular disorders (33.7%), cerebrovascular diseases (27.3%), and acute encephalopathy (19.4%), seizures (7.8%) were the most common[6]. Peripheral nervous system complications, including Guillain-Barr é syndrome (GBS), have been reported.

With the increase in cases, the spectrum of neurological complications of COVID-19 has also expanded significantly. Some new complications have been reported in addition to common non-specific neurological symptoms. With the increase in infections, the use of vaccines has also increased. Although vaccines have saved millions of lives, researchers observed that the SARS-CoV-2 vaccine itself could cause adverse vaccine-related neurological effects. The spectrum of vaccine-related neurological adverse reactions is similar to the neurological complications due to SARS-CoV-2 infection. However, there is a tendency for this disease spectrum to expand over time. This update will help clinicians identify and treat neurological complications of COVID-19 or SARS-CoV-2 vaccination to facilitate timely and effective treatment [Table 1].

CENTRAL NERVOUS SYSTEM COMPLICATIONS OF COVID-19

Ischemic stroke

Hematologic disorders and endothelial dysfunction are significant SARS-CoV-2 complications of infection[7]. Among COVID-19 patients, the proportion of having a cerebrovascular disease is substantial. Ghannam *et al.* reported cerebrovascular incidents in 48.8% of COVID-19 patients with neurological involvement, while most (87.5%) were ischemic strokes[8,9]. Ischemic stroke is a severe threat to patient safety and is a significant central nervous system complication of COVID-19[9-11].

Owing to the large population of COVID-19 patients with ischemic cerebrovascular disease, its mechanism has been thoroughly studied. Enhanced thrombus formation under conditions of hypoxia, coagulation abnormalities due to a viral infection, viral infection-induced activation of procoagulant factors, elevated platelet counts, D-dimer, and fibrinogen levels, rupture of atherosclerotic plaques, production of antiphospholipid antibodies, and direct destruction of blood vessels by SARS-CoV-2 (viral-induced central nervous system vasculitis) may lead to ischemic cerebrovascular disease[1,2,5,7,9].

Table 1. The symptoms, incidence, pathogenesis, and treatments of neurological complications in COVID-19 patients and SARS-CoV-2 vaccinated recipients

Disease	Symptoms	Incidence	Pathogenesis	Treatments
Ischemic stroke	Identical to COVID-19 and SARS-CoV-2 vaccine-unrelated ischemic stroke	42.7% (COVID-19-related)	Enhanced thrombus formation, coagulation abnormalities, activation of procoagulant factors, elevated platelet counts, D-Dimer, and fibrinogen levels, rupture of atherosclerotic plaques, production of antiphospholipid antibodies, and direct destruction of blood vessels	Identical to COVID-19 and SARS-CoV-2 vaccine-unrelated ischemic stroke
Cerebral venous thrombosis	Headache, papilledema, visual problems, reduced consciousness, seizures, and focal neurologic deficits	5%-15% (COVID-19-related)	Increase of D-dimers, elevated fibrinogen levels, a rise of antiphospholipid antibodies, and cytokine storm	Heparin and LMWH
Epilepsy and seizures	Identical to COVID-19 and SARS-CoV-2 vaccine-unrelated epilepsy and seizures	1.6% (COVID-19-related)	Fever, hypoperfusion, hypoxia, coagulation dysfunction, septic encephalopathy, cytokine storm, metabolic derangement, multiorgan failure, and cardiovascular disturbance	Drug interactions between drugs treating COVID-19 and treating seizures must be considered
Meningitis, encephalitis, and meningoencephalitis	Fever, headache, convulsions, seizure, and impaired senses	Less than 1% (COVID-19-related), 0.23 to 0.4 per 100,000 children, and 0.26 per 100,000 adults (SARS-CoV-2 vaccination-related ADEM)	Virus direct penetration and molecular mimicry	Corticosteroids, intravenous plasmapheresis, IVIg, and monoclonal antibodies like rituximab
Multiple sclerosis	Identical to COVID-19 and SARS-CoV-2 vaccine-unrelated multiple sclerosis	Unknown	Induced pro-inflammatory signals from brain cells to recruit blood-derived inflammatory cells	Identical to COVID-19 and SARS-CoV-2 vaccine multiple sclerosis
Acute myelitis	Identical to COVID-19 and SARS-CoV-2 vaccine acute myelitis	Unknown	Secondary immunogenic overreaction	Identical to COVID-19 and SARS-CoV-2 vaccine acute myelitis
Acute necrotizing encephalopathy	Consciousness change, epilepsy, and local nerve function deficiency	Unknown	Cytokine storm	Identical to COVID-19 and SARS-CoV-2 vaccine acute necrotizing encephalopathy
PRES	Acute impairment in the consciousness level and headache	Unknown	Increased inflammatory markers and cytokines, SARS-CoV-2 spike protein binds to the ACE2 receptor could also initiate cell entry	Same to COVID-19 and SARS-CoV-2 vaccine PRES
GBS	Paresthesia, ascending weakness, and areflexia cause respiratory failure	Unknown	Molecular mimicry	Same to COVID-19 and SARS-CoV-2 vaccine GBS
Neuromuscular disorders	Muscle atrophy and weakness	Unknown	The virus invades the muscle cell through the ACE2 receptor, inflammation, and cytokine storms	Same to COVID-19 and SARS-CoV-2 vaccine neuromuscular disorders

ADEM: Acute dissemiinated encephalomyelitis; GBS: Guillain-Barré syndrome; IVIg: immunoglobulin; LMWH: low molecular weight heparin; PRES: posterior reversible encephalopathy syndrome.

Traditional antithrombotic treatments, including anticoagulant and thrombolytic therapy, are also helpful for COVID-19 with ischemic stroke. Heparin has been used to treat the hypercoagulable state associated with COVID-19. Tang *et al.* reported that heparin could reduce COVID-19-induced mortality[12,13].

Cerebral venous thrombosis

Cerebral venous thrombosis is another COVID-19-related cerebrovascular disease[2,10]; 5%-15% of patients with COVID-19 were diagnosed with venous cerebral venous thrombosis[2,10]. Initial symptoms may include

progressive headache, papilledema, visual problems, reduced consciousness, seizures, and focal neurologic deficits[1]. Cranial magnetic resonance imaging or computed tomography may reveal cerebral venous sinus thrombosis-related intracranial hemorrhage. The most involved venous sinuses include the transverse (75%), sigmoid (50%), and deep venous sinuses (33%)[10].

Similar to ischemic stroke, the pathogenesis of cerebral venous thrombosis is more thoroughly investigated than other central nervous system diseases complicated by COVID-19 due to the larger patient population and higher mortality. Increased D-dimers, elevated fibrinogen levels, and a transient rise of antiphospholipid antibodies mark the hypercoagulable state of COVID-19. Cytokine storm in critically ill COVID-19 patients could be another mechanism; it is associated with the von Willebrand factor and inhibits the anticoagulant pathways leading to thrombosis[2].

Heparin has been recommended for treating COVID-19 complicated with cerebral venous thrombosis. Low-molecular-weight heparin (LMWH) appears to have an association with better outcomes than unfractionated heparin; LMWH treatment was associated with lower mortality rates. Hence, LMWH is the first-line treatment for cerebral venous thrombosis[3].

Intracranial hemorrhage

In a large population study, intracranial hemorrhage was observed in about 0.5% of the patients with COVID-19[2]. However, the pathogenesis of hemorrhagic strokes in patients with COVID-19 has not been fully elucidated. In patients in the intensive care unit, COVID-19 was associated with prolonged prothrombin time, causing hemorrhage. Another potential mechanism is that SARS-CoV-2-induced angiotensin-converting enzyme-2 (ACE2) downregulation could lead to vascular contraction and blood pressure increases that eventually cause cerebral hemorrhage[2,14]. The cytokine storm caused by the inflammation of COVID-19 could also cause hemorrhagic strokes[14].

Epilepsy and seizures

Seizures in COVID-19 patients were first reported by Moriguchi *et al.*, and they could be the presenting symptom of COVID-19[11,15,16]. COVID-19 can reduce the epileptic seizure threshold in patients with existing epilepsy; moreover, COVID-19 can induce new-onset seizures among patients without any history of seizures[1,2]. A study of COVID-19-related neurological disorders showed that seizures might occur in 1.6% of patients with COVID-19.[17]. Several indirect mechanisms, including fever, hypoperfusion, hypoxia, coagulation dysfunction, septic encephalopathy, cytokine storm, metabolic derangement, multiorgan failure, and cardiovascular disturbance, could also be related to the development of seizures in COVID-19 patients[1,2,17].

Diagnosing seizures in COVID-19 patients is crucial to treat them better and avoid seizure complications. Studies found no differences in treating and managing seizures and epilepsy between patients with and without COVID-19. However, when treating this patient population, we must consider drug interactions between drugs treating COVID-19 and treating new or existing seizures. Lopinavir/ritonavir are protease inhibitors used to treat COVID-19. These drugs may induce several CYP450 enzymes (CYP2C9, 2C19, 1A2, and 2B6) and glucuronyl transferase and could reduce the plasma concentration of lamotrigine and possibly phenytoin and valproate (through CYP enzymes)[11].

Meningitis, encephalitis, and meningoencephalitis

Several case report findings of COVID-19 patients indicate meningitis and encephalitis. Patients with COVID-19-related encephalitis initially complain of fever, headache, convulsions, seizure, and impaired senses. Encephalitis is reported in less than 1% of patients with COVID-19; however, it increases to 6.7%

among severely ill patients. COVID-19-related meningitis and encephalitis could have severe consequences[18]. The mortality rate of COVID-19 patients with an encephalitis complication is 13.4%[18].

SARS-CoV-2 was found in the cerebrospinal fluid (CSF) of COVID-19 patients with encephalitis[1,2]. Two potential pathways of virus penetration have been suggested; the first was through the trigeminal and olfactory nerve endings. The second could be increased blood-brain barrier permeability due to the inflammation induced by increased pro-inflammatory cytokines[2]. However, studies found no virus detected in the CSF in COVID-19 patients with acute meningoencephalitis[1,2]. Other induced meningoencephalitis in COVID-19[2,18]. Many case reports have revealed that molecular mimicry of SARS-CoV-2 may cause comorbidities such as anti-N-methyl-d-aspartate receptor encephalitis[18,19].

Many treatments for encephalitis in COVID-19 have been studied. Corticosteroids, intravenous plasmapheresis, immunoglobulin, and monoclonal antibodies like rituximab may be associated with positive outcomes[18].

Multiple sclerosis

Of around 8.5 million inhabitants in Austria, over 27,000 were diagnosed with SARS-COV-2 infections, and nearly 14,500 were diagnosed with multiple sclerosis; over 700 deaths from COVID-19[20]. At the autopsy of multiple sclerosis patients, antibodies for SARS-COV-2 in the brain were identified. The presence of coronavirus antigen and RNA in active demyelinating plaques indicates that SARS-COV-2 may be associated with the pathogenesis of multiple sclerosis. The neurovirulence of SARS-COV-2 depends on its ability to induce pro-inflammatory signals from brain cells to recruit blood-derived inflammatory cells[7,21]. No difference between the treatment of COVID-19-related and unrelated multiple sclerosis was reported.

Acute myelitis

Several COVID-19 patients were observed with acute transverse myelitis (ATM)[1]. The incidence of acute myelitis associated with COVID-19 infection is unknown. Three similar case reports were published linking COVID-19 to acute myelitis as a neurological complication. The first was by Zhao *et al.* in Wuhan, China[22]. The second was in Boston, where Sarma *et al.* reported a patient with acute myelitis seven days after contracting an upper respiratory tract infection[23,24]. It is debated whether the myelitis is due to direct viral infection or an autoimmune sequela[23]. However, secondary immunogenic overreaction was an underlying cause of myelitis after COVID-19[2]. No difference between the treatment of COVID-19-related and unrelated acute myelitis was reported.

Acute necrotizing encephalopathy

Acute necrotizing encephalopathy is a rare form of rapidly progressing encephalopathy characterized by consciousness change, epilepsy, and local nerve function deficiency. The imaging features of this disease are multiple bilaterally distributed lesions inside the thalamus, basal ganglia, brainstem, and subcortical white matter[25]. The cytokine storm associated with SARS-CoV-2 can lead to acute necrotizing encephalopathy, particularly in severely ill patients[2,10]. No difference between the treatment of COVID-19-related and unrelated acute necrotizing encephalopathy was reported.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) was reported in ten COVID-19 patients over eight studies. The initial symptoms are acute impairment in the consciousness level and headache. Although a definitive etiology is unclear, there are various proposed underlying mechanisms. In COVID-19, PRES may be caused by the changes in the endothelial morphology due to increased inflammatory markers and cytokines impairing the blood-brain barrier and resulting in enhanced vascular permeability[1,2]. Another

hypothesis holds that the SARS-CoV-2 spike protein binds to the ACE2 receptor to initiate cell entry. Hydroxychloroquine and tocilizumab, critical for COVID-19 treatment, may also be related to PRES[26]. No difference between the treatment of COVID-19-related and unrelated PRES was reported.

PERIPHERAL NERVOUS SYSTEM COMPLICATIONS OF COVID-19-RELATED GBS

GBS is a demyelinating autoimmune disease of the peripheral nervous system that follows an antecedent infection. It is characterized by paresthesia, ascending weakness, and areflexia, causing respiratory failure[10,27]. In a previous study, there was a significant dispute about whether COVID-19 was associated with subsequent GBS. We reported a GBS case secondary to COVID-19 in May 2020[28]. Keddie *et al.* published a study in Great Britain in 2020. GBS and COVID-19 incidences varied between regions, and there was no correlation between GBS and COVID-19 incidences ($r = 0.06$, $P = 0.86$). There was a drop in GBS incidence between March and May 2020 compared to the same months in 2016-19[29]. However, new research demonstrates a connection between COVID-19 and GBS. Another study in Italy population found that the GBS incidence in March and April 2020 was 0.202/100 000/month *vs.* 0.077/100 000/month in the same months of 2019, a 2.6-fold increase[30]. Approximately 33% of the patients needed mechanical ventilation, while about 20% to 30% of non-COVID-19 GBS patients required invasive ventilation[31].

Many syndrome variants could occur in COVID-19-induced sequelae or during the initial presentation[27]. However, a study on the clinical characteristics of COVID-19 combined with GBS suggested that COVID-19 induces different clinical manifestations from GBS causes, including difficulty in breathing due to COVID-19 combined with lung injury and the increase in the proportion of patients requiring intensive care unit treatment[29].

Gadolinium-enhanced magnetic resonance imaging reveals enhancement of the cauda equina nerve roots with asymmetrical thickening and hyperintensity of postganglionic roots from the brachial and lumbar plexuses. Moreover, cytoalbuminologic dissociation of the CSF was found in GBS with COVID-19, indicating nerve root involvement. Electrophysiological studies are frequently consistent with demyelination or axonal damage[1]. The predicted mechanism is molecular mimicry in which SARS-CoV-2 may share epitopes similar to the peripheral nerve components; these findings suggest that the immune system may attack peripheral nerve components and result in GBS[2].

It was reported that 11.70% of the patients responded to intravenous plasmapheresis. This result supports the proposed mechanism of COVID-19-induced demyelination in the peripheral nervous system[1,27]. Investigators found no differences between COVID-19 patients with GBS and other GBS patients regarding outcomes of immunosuppressive therapy.

NEUROMUSCULAR DISORDERS RELATED TO COVID-19

Skeletal muscle injury and myopathy have been reported among COVID-19 patients. Among 214 COVID-19 patients in Wuhan with neurological manifestations, 10.7% suffered skeletal muscle injuries[32]. The most common diagnosis of COVID-19-related muscle injuries was critical illness myopathy, seen in 12 patients (46.1%)[6,10]. Mao *et al.* reported that COVID-19 patients in the ICU had more severe muscle atrophy and weakness than patients within the critical care setting[32,33]. Due to the growing number of COVID-19 patients, myopathy could cause significantly more cases of long-term physical disability[2]. The possibility that the virus invades the muscle cell through the ACE2 receptor should also be considered because ACE2 is expressed in the muscle cells. In addition, excessive inflammation and cytokine storms in COVID-19 could lead to immune-mediated muscle damage[2]. No difference between the treatment of COVID-19-related and unrelated neuromuscular disorders was reported.

SARS-COV-2 VACCINES AND NEUROLOGICAL COMPLICATIONS

Since the global COVID-19 pandemic started in 2020, many SARS-CoV-2 vaccines have been developed. The vaccination has saved millions of lives; however, researchers also observed that it might lead to unpredictable adverse reactions. Nervous system complications are among the most common adverse reactions to SARS-CoV-2 vaccines. Neurological adverse events, including headache and fatigue, are generally mild and transient. However, some adverse reactions are life-threatening. The most severe neurological complication is cerebral venous sinus thrombosis[34,35]. Acute disseminated encephalomyelitis (ADEM), macrophagic myofasciitis, GBS, aseptic meningitis, transverse myelitis, and myositis have been reported in patients receiving vaccines[34]. After vaccination, several cerebrovascular accidents have been reported, including arterial thrombosis, transient global amnesia, intracerebral hemorrhage, and spinal artery ischemia[34]. As of April 28, 2021, the US Vaccine Adverse Event Reporting System suggested around 9000 reports of adverse vaccine reactions[36].

Since the SARS-CoV-2 vaccines were used in phase III clinical trials, several vaccines were associated with intracranial venous thrombosis. Thrombotic complications have been associated with BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), and ChAdOx1 nCov-19 (Oxford/AstraZeneca) vaccines. The total rate was 0.21 cases of venous or arterial thrombotic events per 1 million vaccinated people[35,37]. Since March 2021, cases of cerebral venous thrombosis in Europe started to be found in a large population after COVID-19 vaccination, particularly after receiving the AstraZeneca ChAdOx1 nCoV-19 and the Johnson and Johnson Ad26. COV2.S vaccines[34,36].

SARS-COV-2 vaccine-related cerebrovascular release

In addition to intracranial venous thrombosis, hemorrhagic stroke is a cerebrovascular complication of SARS-CoV-2 vaccines. The risk of hemorrhagic stroke with BNT162b2 was elevated[37]. Among those who received the BNT162b2 vaccine, 60 excess hemorrhagic strokes per ten million cases were reported after vaccination. In contrast, the ChAdOx1nCoV-19 vaccine was unrelated to an increased risk of hemorrhagic stroke[37]. Vaccine-induced hemorrhagic strokes are related to severe immune-mediated thrombotic thrombocytopenia. Thrombocytopenia may appear within five to 30 days after administration of the adenovirus vector-based vaccines. Microscopic examinations revealed that the vascular thrombotic occlusions appeared in the vessels of several body organs, accompanied by significant inflammatory infiltration[34].

SARS-COV-2 vaccine-related acute disseminated encephalomyelitis

ADEM is an immune-mediated central nervous system demyelination disease[38]. Many reports of possible ADEM after ChAdOx1 COVID-19 vaccination have been published. It is a rare entity, and the incidence is estimated to be 0.23 to 0.4 per 100,000 children and 0.26 per 100,000 adults[38]. The SARS-CoV-2 vaccines associated with ADEM include ChAdOx1 (AstraZeneca, Oxford, United Kingdom), Sinovac (Vero Cells, Beijing Institute of Biological Products Co., Ltd., Beijing, China), and Cominarty (Pfizer-BioMTech, New York, New York, USA)[38].

SARS-COV-2 vaccine-related central nervous system demyelinating disease

Central nervous system demyelinating disease has also been reported in SARS-CoV-2 vaccines. Garg *et al.* reported 29 cases of central nervous system demyelination occurring within six weeks of SARS-CoV-2 vaccination; 27 were temporally associated with the ChAdOx1-S vaccine, while the other two were associated with the BBV152 vaccine. Additionally, ten (34.5%) were positive for myelin oligodendrocyte glycoprotein (MOG) antibodies[34].

ATM is a rare clinical syndrome during which immune-mediated processes cause spinal cord neural injury, which may lead to motor, sensory, and autonomic dysfunction[39]. Vaccine-related ATMs are rare. Based on the US Vaccine Adverse Event Reporting System, 119 post-vaccination ATM cases were reported from 1985 to 2017. For COVID-19 vaccine-related events, 51,755,447 doses of COVID-19 vaccines were administered until March 2021, and nine cases of ATMs with COVID-19 were reported among 9442 adverse events for an incidence of 1.739 per million[39]. Vaccination-associated myelitis developed two weeks after vaccination, and symptoms rapidly improved with high dose-corticosteroid therapy[40].

SARS-COV-2 vaccine-related epilepsy

COVID-19 vaccine-related new-onset epilepsy has also been reported. The recurrent seizures occurred after vaccination and were difficult to control with conventional antiepileptic drug therapy; however, the seizures were significantly improved after steroid pulse therapy and plasma exchange[40].

SARS-COV-2 vaccine-related encephalitis

Post-vaccination encephalitis symptoms occur on day seven after vaccination. The first case of post-vaccination encephalitis was reported in Italy[40]. Case reports of COVID-19 vaccine-related encephalomyelitis were primarily associated with the Astra-Zeneca vaccine[40]. Patrick *et al.* suggested the patient may have developed anti-N-methyl-D-aspartate receptor encephalitis after a Pfizer BioNTech COVID-19 vaccination. This is considered one of the primary pathogenic antibodies that cause autoimmune encephalitis associated with the SARS-CoV-2 vaccine[41]. After eliminating other causes, autoimmune encephalitis associated with vaccination was suspected, and symptoms rapidly recovered after initiating immunosuppressive therapy[40].

SARS-COV-2 vaccine-related peripheral nervous system disease

There is an enhanced risk of GBS and Bell's palsy with ChAdOx1nCoV-19[37]. An elevated risk of hospital admission for GBS (15-21 days and 22-28 days) and Bell's palsy (15-21 days) was observed among those who received the ChAdOx1nCoV-19 vaccine[37,40]. Most patients recovered well after immunoglobulin therapy[40]. Bell's paralysis was reported after mRNA vaccine administration[34]. BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna), and CoronaVac (Sinovac Biotech) vaccines have been associated with vaccine-related facial nerve palsy. Colella *et al.* first described Bell's palsy following a Pfizer BioNTech vaccination. The pathogenesis of COVID-19-related facial nerve palsy might correlate with autoimmune events through molecular mimicry by the vaccine antigen, activating dormant autoreactive T cells, or immune-mediated segmental demyelination[35,42].

CONCLUSION

Since the beginning of the COVID-19 pandemic, neurological complications have garnered research attention. Most neurological complications are non-specific, including headache and fatigue, and ischemic stroke occurs rarely. However, these diseases lead to disability or death. The spectrum of neurological complications of COVID-19 is comprehensive; however, its pathogenesis is relatively uniform. Most complications are associated with the direct attack of the SARS-CoV-2 virus, inflammatory factor storm, and molecular mimicry. The virus penetrates the brain and interferes with the brain monoamine oxidase enzyme activity, as was recently demonstrated[43]. ACE2 downregulation induced by the SARS-CoV-2 infection might be associated with alterations in brain amine levels, strongly implicated in the etiology of Alzheimer's and Parkinson's diseases[44]. However, there are discrepancies concerning the pathogenesis of these diseases with or without COVID-19. The previous treatment options are adequate for neurological complications, and most patients respond to symptomatic treatment. Vaccines have protected millions from infection; however, molecular mimicry may induce vaccine-related autoimmune responses and neurological side effects. Fortunately, vaccine-related neurological adverse reactions are relatively rare. If neurological

symptoms are observed, the possibility of vaccine-related autoimmune reactions cannot be ruled out. The risk of adverse reactions to vaccination is very low. These vaccines have significantly contributed to preventing and treating COVID-19, and vaccination should be promoted.

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Authors' contributions

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