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REVIEW ARTICLE

A review of the potential neurological adverse events of COVID-19 vaccines

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Abstract
Despite the advantages of getting access to the coronavirus disease 2019 (COVID-19) vaccines, their potential ability to induce severe adverse events (AEs) has been a significant concern. Neurological complications are significant among the various adverse events following immunization (AEFI) due to their likely durability and debilitating sequelae. Neurological AEs following COVID-19 vaccination can either exacerbate or induce new-onset neuro-immunologic diseases, such as myasthenia gravis (MG) and Guillain–Barre syndrome (GBS). The more severe spectrum of AEs post-COVID19 vaccines has included seizures, reactivation of the varicella-zoster virus, strokes, GBS, Bell's palsy, transverse myelitis (TM), and acute disseminated encephalomyelitis (ADEM). Here, we discuss each of these neurological adverse effects separately.

Keywords COVID-19 · Vaccine · Adverse event · Neurologic · SARS-CoV-2

Introduction

Despite the advantages of getting access to the coronavirus disease 2019 (COVID-19) vaccines, their potential ability to induce severe adverse events (AEs) has been a significant concern. Neurological complications are significant among the various adverse events following immunization (AEFI) due to their likely durability and debilitating sequelae [1, 2]. Neurological AEs following COVID-19 vaccination can either exacerbate or induce new-onset neuro-immunologic diseases, such as myasthenia gravis (MG), and Guillain–Barre syndrome (GBS) [3–5]. In addition, after vaccination, hypercoagulability and a pro-thrombotic state may further increase cerebrovascular events [6, 7]. The Centers for Disease Control (CDC) Vaccine Adverse Event Reporting System (VAERS) has announced several neurological complications following COVID-19 vaccines [8]. The most common neurological symptoms following COVID-19 vaccines have included headache, anosmia, dysgeusia, myalgia, paresthesia, weakness, and dizziness [9]. Several rare side effects, including tremor, diplopia, tinnitus, dysphonia, delirium, and syncope, have also been observed

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that are significant to note [10, 11]. The more severe spectrum of AEs post-COVID19 vaccines has included seizures, reactivation of the varicella-zoster virus, strokes, GBS, Bell's palsy, transverse myelitis (TM), and acute disseminated encephalomyelitis (ADEM). Here, we discuss each of these neurological adverse effects separately.

Bells palsy

Bell'S palsy (BP), known as idiopathic facial paralysis, is an acute unilateral peripheral facial nerve palsy [12]. This condition is, in fact, an idiopathic facial palsy of spontaneous origin, although a causal association with the herpes simplex virus has been considered [13]. However, in the current pandemic, studies revealed abundant cases of BP following SARS-CoV-2 infection [14–16]. Several vaccines, including influenza, hepatitis B, and meningococcal conjugate vaccines, have been associated with BP [17–19]. With the development of COVID-19 vaccines, significant concerns have arisen about their potential to trigger the onset of Bell's palsy. Despite being less prevalent than expected, this complication has still been abundantly reported following these vaccines [12, 20, 21]. Nonetheless, the US Food and Drug Administration (FDA) announced that the frequency of Bell's palsy cases following vaccination is not more unusual than in the general population [22]. Despite the inability to confirm the causal relationship between the vaccines and this complication, the timing of onset following vaccination can suggest the association. Confirmation would need to be studied in larger populations [23]. This reaction could be either immune-mediated or induced by viral reactivation [24], but the latter does not seem valid for COVID-19 vaccines since no live attenuated COVID-19 vaccine platform has yet been introduced.

The immune-mediated mechanism for this complication is thought to be through host molecules' mimicry of the vaccine's antigens or by eliciting a type I interferons response [25, 26]. The timing of BP onset in relationship to vaccination is unclear, although most of the cases have occurred in an average 4-week interval after vaccination [27]. Moreover, there has been a case of sequential contralateral facial nerve palsies following each dose of COVID-19 vaccines reported recently [27]. Up to now, BP has been reported following various COVID-19 vaccine types, including Pfizer-BioNTech, Janssen, CoronaVac, Moderna, and Oxford-AstraZeneca vaccines [12, 23, 28–30]. Nonetheless, the risk of developing facial nerve palsy has been estimated to be higher with mRNA vaccines than with other vaccine platforms; this fact can help us decide the choice of COVID-19 vaccine in individuals with a history of BP [31]. It is vital to note that most cases of BP, regardless of etiology, are self-limiting and subside within a few months [32]. However, antiviral agents and steroids are frequently tried as a treatment and hasten recovery [32].

Guillain–Barré Syndrome

Guillain–Barré Syndrome (GBS) is defined as an inflammatory ascending polyradiculoneuropathy. The underlying triggers for this neurological disorder include infections and vaccines on an autoimmune basis [33] (Fig. 1). The introduction of COVID vaccines has arisen the concerns of developing GBS following vaccination [34] since GBS had been previously observed in individuals who received the meningococcal, tetanus-toxoid, human papillomavirus (HPV), and most prominently, the influenza vaccines [35–39]. This complication has been reported following Pfizer-BioNTech, Johnson & Johnson, and ChAdOx1 nCoV-19 COVID-19 vaccines [1, 40–42]. Moreover, one case of isolated bilateral facial diplegia with paresthesias (BFP), an uncommon variant of GBS, has been reported following the Janssen COVID-19 vaccination [43]. It is believed that vaccine-induced immune responses may trigger autoimmune reactions, resulting in autoantibody production against myelin, resulting in GBS [40]. The diagnosis of vaccine-induced GBS is the same as that of other causes, through clinical and paraclinical findings such as cerebrospinal fluid (CSF) analysis and electromyography and nerve conduction velocity (EMG/NCV) studies, in addition to considering the temporal relationship between the event and vaccination [44]. Intravenous immune globulin (IVIg) (0.4 g per kg body weight every day for 5 days) and plasma exchange (200–250 ml plasma kg body weight in 5 sessions) can be considered as efficient treatments for GBS [45].

Transverse myelitis

Transverse myelitis (TM) is a condition where spinal cord segments may become inflamed, resulting in significant motor, autonomic and sensory deficits. [46]. Since the beginning of the current pandemic, several cases of TM have been reported in SARS-CoV-2-infected patients [47, 48]. Apart from infections as a cause of TM, vaccines are of great importance in the evolution of this neurological condition [49]. TM following vaccination had previously been observed with various vaccines, including tetanus, measles–mumps–rubella, influenza (H1N1), hepatitis B, polio, and Japanese B encephalitis vaccines [50–54]. This neurological complication has also been reported following COVID-19 vaccination with viral vector-based and mRNA-based COVID-19 vaccines. However, their association has not been confirmed in a number of trials [2, 55–57]. Moreover, a rare subtype of TM, known as longitudinally extensive transverse myelitis (LETM), has been reported following COVID-19 vaccination [58]. The pathophysiology of TM

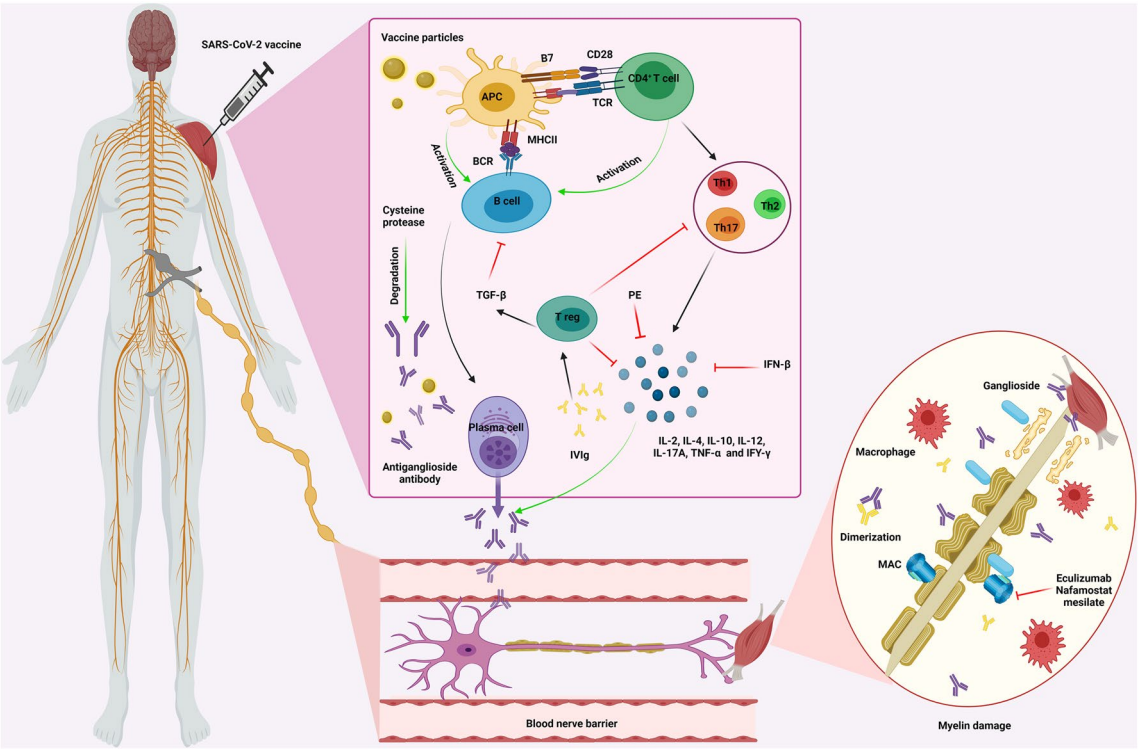

Fig. 1 COVID-19 vaccine-induced Guillain–Barré syndrome. After the administration of the COVID-19 vaccine, the vaccine particles enter the body and activate APCs, which could trigger B cells and $CD4^+$ T cells activation. Naïve $CD4^+$ T cells are then differentiated into three subgroups, Th_1, Th_2, and Th_{17}, producing cytokines, such as IL-2, IL-4, IL-10, IL-12, IL-17A, TNF-α, and IFY-γ. Moreover, B cells are converted to plasma cells, secreting antiganglioside antibodies. These antibodies are then gone through the blood-nerve barrier, binding to the ganglioside of the myelinated motor neurons or attaching to the neuromuscular junction. As a result of forming gangliosides-antiganglioside antibody complexes, MAC and macrophages are activated, attacking and destroying the myelin. Such demyelination would decrease the speed of action potential transmission through these nerves, causing an inflammatory ascending polyradiculoneuropathy. IVIg administration could reverse these mechanisms via 2 main pathways: triggering Treg cells, inhibiting B cells and inflammatory cytokines, and dimerizing with antiganglioside antibodies. Moreover, plasmapheresis could alleviate the symptoms via actively depleting inflammatory cytokines from patients' bloodstream. Furthermore, cysteine proteases can degrade antiganglioside antibodies, inhibiting this inflammatory neuropathy. Eculizumab and nafamostat mesylate would also inhibit MAC, alleviating the demyelination. Abbreviations: *APC* Antigen-presenting cell, *TCR* T cell receptor, *MHC II* Major histocompatibility complex II, *BCR* B cell receptor, *Th* T helper cell, *IL-2* Interleukin-2, *IL-4* Interleukin-4, *IL-10* Interleukin-10, *IL-12* Interleukin-12, *IL-17A* Interleukin-17A, *TNF-α* Tumor necrosis factor-α, *IFY-γ* Interferon-γ, *GBS* Guillain-Barré syndrome, *IVIg* Intravenous immune globulin, *Treg* regulatory T cell, *TGF-β* Transforming growth factor-β, *PP* Plasmapheresis, *IFN-β* Interferon-β, *MAC* Membrane attack complex

in the settings of SARS-CoV-2 infection is thought to be either via direct viral neuro-invasion or immune-mediated, while the mechanism by which COVID-19 vaccines might trigger TM may be immune and inflammatory reactions [59, 60]. The diagnosis is made by typical clinical evidence of bilateral sensory, motor, or autonomic dysfunction with an established spinal cord defect origin in magnetic resonance imaging (MRI) [61]. Unfortunately, TM is a neurological condition with unfavorable outcomes [62]. Although there is insufficient evidence, high-dose IV methylprednisolone (1 g per day for 3–7 days) has to be started immediately for all TM cases to improve neurological function and accelerate recovery [63, 64]. In a case report study, a COVID-19 patient with acute TM treated with high-dose IV methylprednisolone (1 g daily for 3 days) showed improved neurological symptoms immediately after receiving IV corticosteroid therapy [65].

Cerebrovascular events

Since the beginning of the COVID-19 pandemic, a significant increase in stroke rates was observed, later discovered to be due to SARS-CoV-2 infection [66–68]. Although not as common as SARS-CoV-2 infection, COVID-19 vaccination is also suspected to increase the risk of cerebrovascular events [69]. It is unknown whether the cerebrovascular events, including ischemic/hemorrhagic strokes and cerebral venous sinus thrombosis, are related to COVID-19 vaccination. If they are related, it also remains unclear how the vaccines may contribute–by causing arterial hypertension,

worsening thrombocytopenia, or exacerbating a hypercoagulable state [70, 71]. Previously, a stroke took place following vaccination with various other vaccines, including diphtheria, measles–mumps–rubella, and influenza vaccines [72–74]. The probability and reports of systemic thrombotic thrombocytopenic events following COVID-19 vaccination have caused a great deal of concern and hesitancy worldwide [71]. The Oxford-AstraZeneca (ChAdOx1 nCoV-19) vaccine had been the most notorious for this complication that many countries suspended its use [75]. However, thrombotic events have not been uncommon following the Johnson & Johnson COVID-19 vaccine [76, 77]. Cerebrovascular events, including hemorrhagic and ischemic strokes, from venous and arterial etiologies and an increased thrombotic and embolic risk, have been noted [78–81]. There have been reports of thrombosis in the cortical veins, transverse sinus, sigmoid sinus, inferior sagittal sinus, the vein of Galen, and the straight sinus that have all presented with intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH), shortly after COVID-19 vaccination [80–83].

However, we should take into account that individuals with risk factors of thromboembolic events, such as pregnancy, postpartum state, oral contraceptives use, surgery, trauma, immobilization, malignancies, and thrombophilic genetic or autoimmune conditions including anti-thrombin, protein C, and protein S deficiency, factor V Leiden mutation, antiphospholipid antibodies, and hyperhomocysteinemia, are more prone to vaccine-induced cerebrovascular complications [84–87]. It is important to note that anti-CXCL4 antibodies are responsible for most cases of vaccine-induced immune thrombotic thrombocytopenia (VITT); this is similar to what happens with heparin-induced thrombocytopenia (HIT) [71, 88]. Depending on which vessel is involved, clinical manifestations may range from a simple headache, nausea, vomiting, and diplopia to focal neurologic signs, altered consciousness, and coma. The diagnosis of cerebrovascular AEs is generally made with comprehensive imaging, including brain computed tomography (CT), venogram, angiography, and MRI [89]. Management of cerebrovascular events following vaccination is generally the same as with any other cause, with the goal being assessment and management of risk factors and secondary stroke prevention. Heparin and platelet transfusions should be avoided until VITT has been excluded [90, 91]. In cases of systemic thrombotic thrombocytopenic events, IVIg, high-dose glucocorticoids, and plasmapheresis are recommended when indicated to restore platelet counts and address the autoimmune phenomenon [79, 92].

Encephalopathy

Acute encephalopathy has been attributed to various etiologies, including toxins, infections, and vaccines. One of the most prevalent neurological sequelae of COVID-19 has been encephalopathy which presents with cognitive impairment, altered consciousness, and even seizures [93–96]. However, the condition has been observed much less frequently following COVID-19 vaccination [94, 97–100]. In the past, several cases of encephalopathy had been reported after various vaccines, including hepatitis B, rabies, pertussis, measles, influenza, and HPV vaccines [101–107]. The pathophysiologic mechanism for vaccine-induced acute disseminated encephalomyelitis (ADEM) seems to be the inflammatory cascade or the cytokine storm triggered by the production of spike protein from translated mRNA in the vaccines [108, 109]. The diagnosis of ADEM in the settings of COVID-19 vaccination is similar to that of other causes and is accomplished through clinical and cerebrospinal fluid (CSF) findings and imaging modalities such as brain MRI. The treatment consists of corticosteroids and sometimes IVIg and plasmapheresis [110]. Fortunately, ADEM has a favorable outcome if conservative support is satisfactory [111].

New-onset seizures

The pathophysiologic mechanisms of seizures during a SARS-CoV-2 infection differ significantly from those following COVID-19 vaccination. In the former, specific antibiotic therapies, cerebral hypoxemia, acute renal failure, and electrolyte impairment can be the underlying reasons [112–114]. The latter can happen in the settings of vaccine-induced encephalopathy or venous occlusion [97]. Before the current pandemic, HPV and H1N1 vaccinations had been related to functional (non-epileptic) seizures, which were believed to be psychogenic attacks [115, 116]. The association of febrile seizure with the measles–mumps–rubella–varicella vaccine has long been well established [117]. It is unknown whether non-motor seizures are related to COVID-19 vaccines or only a coincidence [118]. Patients with a known history of epilepsy or prior history of seizures may have a decreased threshold in the post-vaccine period due to the symptoms and illness. Rare attacks have included new-onset refractory status epilepticus that require further assessment and follow-up [119]. The diagnosis is based on clinical history, physical examinations, brain imaging (CT scan and MRI), electroencephalography, and serum prolactin level measurement. There are a variety of antiepileptic drugs (Table 1) that can be administered as first-line monotherapy in adults with epilepsy [120].

Varicella-zoster virus reactivation

Since the beginning of the COVID-19 pandemic, several cases of herpes zoster have been reported in SARS-CoV-2 infected patients, even in immunocompetent individuals

Table 1 Summary of the proposed diagnosis and management of neurological adverse events following COVID-19 vaccination

Neurological adverse event	Diagnosis	Management
Bell's palsy	History and physical examination: Rapid-onset (less than 72 h) unilateral paralysis of the facial nerve (weakness or complete loss of movement) with no defined reason	Oral corticosteroids (prednisolone) and antiviral agents (acyclovir and valacyclovir)
Guillain–Barré Syndrome	Clinical and paraclinical findings such as cerebrospinal fluid (CSF) analysis and electromyography and nerve conduction velocity (EMG/NCV) studies, in addition to considering the temporal relationship between the event and vaccination	IVIg (0.4 g per kg body weight every day for 5 days) and plasma exchange (200–250 mL plasma per kg body weight in 5 sessions) are similarly efficient remedies for GBS
Transverse myelitis	Typical clinical evidence of bilateral sensory, motor, or autonomic dysfunction with an established spinal cord defect origin in magnetic resonance imaging (MRI)	High-dose IV methylprednisolone (1 g daily for 3–7 days)
Cerebrovascular events	Brain computed tomography (CT), venogram, angiography, and MRI	IVIg High-dose glucocorticoids Plasmapheresis Non-heparin anticoagulants (like fondaparinux and argatroban)
Encephalopathy	Clinical and cerebrospinal fluid (CSF) findings and imaging modalities such as brain MRI	Corticosteroids and sometimes IVIg and plasmapheresis
New-onset seizures	Clinical history, physical examinations, brain imaging (CT scan and MRI), electroencephalography, and serum prolactin level measurement	Narrow-spectrum drugs (focal seizure) Carbamazepine Eslicarbazepine Gabapentin Lacosamide Oxcarbazepine Phenytoin Broad-spectrum drugs (focal and almost all generalized seizures) Lamotrigine Levetiracetam Topiramate Valproate Zonisamide
Myasthenia gravis exacerbation	Suspected through compatible signs and symptoms of fatigable muscle weakness and confirmed by EMG studies, pharmacologic testing, and serum Ab assay	Pyridostigmine (30 mg 3–4 times a day, then can be increased to 60 mg 4 times a day) Oral prednisone (0.75–1 mg per kg daily) Azathioprine Cyclosporine Tacrolimus Rituximab
Varicella-zoster virus reactivation	Clinical manifestations (dermatomal rash, pain, paresthesia, dysesthesia, allodynia, pruritus), IF test for VZV antigen, PCR test for VZV DNA	Acyclovir (800 mg orally 5 times a day for 7–10 days) Valacyclovir (1 g orally 3 times a day for 7 days) Famciclovir (500 mg orally 3 times a day for 7 days)

[121, 122]. The potential mechanism for this event is suggested to be COVID-19-induced lymphopenia and $CD4^+$ T cell dysfunction [123]. Nonetheless, immunomodulation, immune dysregulation, and attenuated alloreactivity are believed to be the underlying pathophysiology for vaccine-induced herpes zoster reactivation [124, 125]. Herpes zoster reactivation was previously reported following yellow fever, influenza, hepatitis A, and rabies vaccines [126, 127]. Up to the present time, this neurological complication has been reported following various COVID-19 vaccines, including mRNA-based (Pfizer-BioNTech, Moderna), viral vector (Oxford ChAdOx1-S or AZD1222), and inactivated vaccines (COVAXIN) [125, 128–133]. Moreover, a case of varicella-zoster virus-induced small vessel vasculitis following the first dose of the Pfizer-BioNTech COVID-19 vaccine has been reported [134]. It should be noted that in all suspected cases of vaccine-induced herpes zoster reactivation, a de novo SARS-CoV-2 infection should be ruled out. The diagnosis is made with clinical manifestations (dermatomal rash, pain, paresthesia, dysesthesia, allodynia, and pruritus), immunofluorescence (IF) test for VZV antigen, and PCR test for VZV DNA. acyclovir, valacyclovir, and famciclovir (guanosine analogs) are recommended for VZV treatment [135].

Table 2 Summary of the reported cases of neurological adverse events following SARS-CoV-2 infection vs post-COVID-19 vaccination

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
1	Afshar et al. [144]/2021	Bell's palsy	F/64	Iran	Left side facial nerve palsy	History and physical examination, brain CT scan and MRI, pulmonary CT scan, RT-PCR for SARS-CoV-2, and anti-SARS-CoV-2 IgM test	lopinavir/ritonavir (Kaletra) + dexamethasone	Associated with COVID-19 infection
2	Dahl et al. [145]/2021	Bell's palsy	M/37	Norway	Right side facial nerve palsy	History and physical examination, cerebral CT scan, spinal fluid examination, spinal fluid PCR, anti-SARS-CoV-2 IgG antibodies test	–	Associated with COVID-19 infection
3	Bastola et al. [146]/2021	Bell's palsy	M/48	India	Left side facial nerve palsy	History and physical examination, chest HRCT and PCR for SARS-CoV-2	Prednisolone	Associated with COVID-19 infection
4	Al-Mashdali et al. [147]/2021	Bell's palsy	M/21	Qatar	Right side facial nerve palsy	History and physical examination, chest CT scan and RT-PCR for SARS-CoV-2	Prednisolone and eye lubricant	Associated with COVID-19 infection
5	Hasibi et al. [148]/2021	Bell's palsy	M/52	Iran	Right side facial nerve palsy	History and physical examination, RT-PCR for SARS-CoV-2 and spiral chest CT scan	Prednisolone and favipiravir Then: remdesivir and IV dexamethasone	Associated with COVID-19 infection
6	Ferreira et al. [149]/2022	Bell's palsy	M/11	Portugal	Right side peripheral facial paralysis	History and physical examination, PCR for SARS-CoV-2, cranial CT, and MRI	Prednisolone	Associated with COVID-19 infection
7	Iacono et al. [150]/2022	Bell's palsy	M/5	Italy	Right side facial nerve palsy	History and physical examination, brain MRI and serological tests for SARS-CoV-2	Prednisolone and eye lubricant	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
8	Kaplan[151]/2021	Bell's palsy	F/48	USA	Left side facial nerve palsy	History and physical examination, PCR for SARS-CoV-2 and chest CT scan	Prednisone, valacyclovir, and doxycycline (the doxycycline was discontinued after Lyme disease titers became negative)	Associated with COVID-19 infection
9	Szewczyk et al. [152]/2021	Bilateral facial nerve palsy	M/70	Poland	Bilateral facial nerve palsy	History and physical examination, brain CT scan and MRI and serological tests for SARS-CoV-2	Intravenous immunoglobulins (IVIg)	Associated with COVID-19 infection
10	Kumar et al. [153]/2021	Bell's palsy	F/28	India	Right side lower motor neuron facial nerve palsy	History and physical examination, RT-PCR for SARS-CoV-2	Prednisone and valacyclovir	Associated with COVID-19 infection
11	Neo et al. [154]/2021	Bell's palsy	M/25	Singapore	Left side facial weakness/palsy	History and physical examination, RT-PCR for SARS-CoV-2, and serological tests for SARS-CoV-2	Oral corticosteroids, valacyclovir, and eye care advice	Associated with COVID-19 infection
12	Neo et al. [154]/2021	Bell's palsy	M/34	Singapore	Right side facial weakness	History and physical examination, RT-PCR for SARS-CoV-2, and serological tests for SARS-CoV-2	Oral corticosteroids, valacyclovir, and eye care advice	Associated with COVID-19 infection
13	Khaja et al. [155]/2020	Guillain-Barré Syndrome and Bell's Palsy	M,44	USA	Bilateral facial weakness	History and physical examination, RT-PCR for SARS-CoV-2, serological tests for SARS-CoV-2, and brain MRI	IVIg	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
14	Theophanous et al. [156]/2021	Bell's palsy	M/6	USA	Right side facial nerve palsy	History and physical examination, RT-PCR for SARS-CoV-2	IV acyclovir and IVIg infusion (because of agammaglobulinemia) Then discharged with prednisolone and acyclovir	Associated with COVID-19 infection
15	Wan et al. [157]/2020	Bell's palsy	F/65	China	Left side facial nerve palsy	History and physical examination, RT-PCR for SARS-CoV-2, and brain MRI	Arbidol and ribavirin	Associated with COVID-19 infection
16	Bohania et al. [158]/2021	Bell's palsy	F/18	–	Right side facial nerve palsy	History and physical examination, COVID-19 antigen testing	Steroids, eye taping during sleep, and methylcellulose eye drops	Associated with COVID-19 infection
17	Burrows et al. [159]/2021	Bell's palsy	M/61	UK	Right side lower motor neuron facial palsy	History and physical examination and head CT scan	Prednisolone	Associated with COVID-19 vaccination (Pfizer-BioNTech)
18	Cellina et al. [160]/2022	Bell's palsy	F/35	Italy	Left side facial nerve palsy	History and physical examination and brain MRI	Prednisone	Associated with COVID-19 vaccination (Moderna)
19	Iftikhar et al .[12]/2021	Bell's palsy	M/36	Qatar	Left side facial nerve palsy + left upper limb numbness and weakness	History and physical examination, brain CT scan, and MRI	Prednisolone and eye lubricant	Associated with COVID-19 vaccination (Moderna)
20	Mussatto et al. [161]/2022	Bell's palsy (he was also a 20-year-prior case of HIV)	M/60	USA	Left side facial nerve palsy	History and physical examination	Prednisone and valacyclovir	Associated with COVID-19 vaccination (Pfizer-BioNTech)
21	Repajic et al. [28]/2021	Bell's palsy	F/57	USA	Left side facial nerve palsy	History and physical examination	Prednisone and an antiviral agent	Associated with COVID-19 vaccination (Pfizer-BioNTech)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
22	Yu et al. [162]/2021	Bell's palsy	F/36	China	Right side facial nerve palsy	History and physical examination, serological tests for SARS-CoV-2, and brain CT scan	Prednisone and artificial tear	Associated with COVID-19 vaccination (Sinovac Life Sciences inactivated COVID-19 vaccine)
23	Mason et al. [163]/2021	Bell's palsy	F/35	USA	Bilateral facial nerve palsy	History and physical examination, brain MRI and CT angiography	Methylprednisolone (IV) and acyclovir	Associated with COVID-19 vaccination (Moderna)
24	Mirmosayyeb et al. [164]/2022	Bell's palsy	F/27	Iran	Left side facial nerve palsy	History and physical examination and brain MRI	Prednisone and valacyclovir	Associated with COVID-19 vaccination (Russian Sputnik V)
25	Mirmosayyeb et al. [164]/2022	Bell's palsy	M/58	Iran	Left side facial nerve palsy	History and physical examination	Prednisone and valacyclovir	Associated with COVID-19 vaccination (Russian Sputnik V)
26	Pothiawala[165]/2021	Bell's palsy	M/46	Singapore	Right side facial nerve palsy	History and physical examination	Prednisone and acyclovir	Associated with COVID-19 vaccination (Moderna)
27	Kundi et al. [166]/2022	Bell's palsy	F/66	USA	Right side facial nerve palsy	History and physical examination and brain CT	Prednisone, acyclovir, meclizine, and ondansetron	Associated with COVID-19 vaccination (Ad26.COV2.S vaccine)
28	Nishizawa et al. [167]/2021	Bell's palsy	F/62	Japan	Right side facial nerve palsy	History and physical examination, head CT and brain MRI	–	Associated with COVID-19 vaccination (Ad26.COV2.S vaccine)
29	Colella et al. [20]/2021	Bell's palsy	M/37	Italy	Left side facial nerve palsy	History and physical examination	Prednisone and artificial tear	Associated with COVID-19 vaccination (Pfizer-BioNTech)
30	Martin-Villares et al. [168]/2022	Bell's palsy	F/34	Spain	Right side facial nerve palsy	History and physical examination and brain MRI	–	Associated with COVID-19 vaccination (Moderna)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
31	Scheidl et al. [169]/2020	Guillain-Barré Syndrome	F/54	Germany	Acute, proximally pronounced, moderate, symmetric paraparesis, areflexia, numbness, and tingling of all extremities	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
32	Bueso et al. [170]/2021	Guillain-Barré Syndrome	F/60	USA	Symmetrical weakness of both the lower and upper extremities	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis)	IVIg (0.4 g per kg body weight every day for 5 days) + enoxaparin 30 mg twice a day	Associated with COVID-19 infection
33	Sedaghat and Karimi [171]/2020	Guillain-Barré Syndrome	M/65	Iran	Acute progressive weakness of distal lower extremities, quadriplegia, and bilateral facial paresis	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
34	Agosti et al. [172]/2021	Guillain-Barré Syndrome	M/68	Italy	Acute progressive symmetric ascending flaccid tetraparesis, bifacial nerve palsy, and muscular weakness	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
35	Paybast et al. [173]/2020	Guillain–Barré Syndrome	M/38	Iran	Acute symmetric progressive ascending paresthesia of both lower and upper extremities and bilateral facial droop	clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	Therapeutic plasma exchange for 5 sessions	Associated with COVID-19 infection
36	Paybast et al. [173]/2020	Guillain-Barré Syndrome	F/14	Iran	Progressive ascending quadripareshtesia and mild lower limb weakness	Clinical and paraclinical findings (such as CSF analysis)	IVIg (20 g daily for 5 d)	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
37	Dufour et al. [174]/2021	Guillain-Barré Syndrome	F/36	USA	Progressive ascending weakness	RT-PCR for SARS-CoV-2, history and physical examinations	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
38	Toscano et al. [175]/2020	Guillain-Barré Syndrome	–	Italy	Flaccid areflexic tetraplegia evolving to facial weakness, upper-limb paresthesia	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and head and spine MRI)	2 IVIg cycles	Associated with COVID-19 infection
39	Toscano et al. [175]/2020	Guillain-Barré Syndrome	–	Italy	Facial diplegia and generalized areflexia evolving to paresthesia of lower limbs with ataxia	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and head and spine MRI)	IVIg	Associated with COVID-19 infection
40	Toscano et al. [175]/2020	Guillain-Barré Syndrome	–	Italy	Flaccid tetraparesis and facial weakness evolving to areflexia	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and head and spine MRI)	2 IVIg cycles	Associated with COVID-19 infection
41	Toscano et al. [175]/2020	Guillain-Barré Syndrome	–	Italy	Flaccid areflexic tetraparesis and ataxia	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and head and spine MRI)	IVIg	Associated with COVID-19 infection
42	Toscano et al. [175]/2020	Guillain-Barré Syndrome	–	Italy	Facial weakness, flaccid areflexic paraplegia	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and head and spine MRI)	IVIg and plasma exchange	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
43	El Otmani et al. [176]/2020	A subtype of GBS: Acute Motor and Sensory Axonal Neuropathy (AMSAN)	F/70	Morocco	Bilateral weakness and paresthesia in all four extremities	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	IVIg (2 g/kg for 5 days), Hydroxychloroquine (600 mg/day), and Azithromycin (500 mg on the first day, then 250 mg/day)	Associated with COVID-19 infection
44	Khan et al. [177]/2021	Guillain-Barré Syndrome	M/27	India	Myalgia, weakness of the lower limb (then it involved the upper limb), and generalized hypotonia	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
45	Khan et al. [177]/2021	Guillain-Barré Syndrome	F/35	India	Paresthesia in both lower limbs followed by mild weakness	COVID-19 testing (she was positive for COVID-19), clinical and paraclinical findings (such as CSF analysis and NCV studies)	Managed as a case of COVID-19 (Supportive)	Associated with COVID-19 infection
46	Khan et al. [177]/2021	Guillain-Barré Syndrome	F/40	India	Lower-limb paresthesia is associated with weakness rapidly progressing from lower to upper limbs, respiratory muscles weakness	Clinical and paraclinical findings (such as CSF analysis and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
47	Khan et al. [177]/2021	Guillain-Barré Syndrome	F/48	India	Paresthesia in both lower limbs and weakness	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
48	Khan et al. [177]/2021	Guillain-Barré Syndrome	M/50	India	Paresthesia in both lower limbs (then it involved upper limbs) and weakness	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
49	Su et al. [178]/2020	Guillain-Barré Syndrome with dysautonomia	M/72	USA	Symmetric paresthesias and ascending appendicular weakness	SARS-CoV-2 PCR, clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	IVIg (2 g/kg between days 3 and 6)	Associated with COVID-19 infection
50	Darvishi et al. [179]/2021	Guillain-Barré Syndrome	M/56	Iran	Subacute progressive lower limbs weakness, paresthesia, and pain (then it progressed to severe, flaccid paraparesis)	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis)	IVIg (0.5 g/kg/d for 5 days)	Associated with COVID-19 infection
51	Zhao et al. [180]/2020	Guillain-Barré Syndrome	F/61	China	Symmetric weakness and areflexia in both lower limbs	RT-PCR for SARS-CoV-2, clinical and paraclinical findings (such as CSF analysis and NCV studies)	IVIg	Associated with COVID-19 infection
52	Mackenzie et al. [181]/2021	Guillain-Barré Syndrome	F/39	Colombia	Progressive generalized weakness of lower limbs	SARS-CoV-2 PCR, clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	Supportive care, enoxaparin, losartan, meperidine IV for muscle pain, hydroxychloroquine, and dexamethasone	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
53	Mostel et al. [182]/2021	Guillain-Barré Syndrome	F/69	USA	Progressive motor weakness and sensation loss in extremities, numbness and paresthesia in the right hand and leg, numbness and paresthesia in the left limb	SARS-COV-2 antibodies, clinical and paraclinical findings (such as EMG studies)	IVIg (2 g/kg for 5 days)	Associated with COVID-19 infection
54	Farzi et al. [183]/2020	Guillain-Barré Syndrome	M/41	Iran	Ascending paresthesia and paralysis	SARS-CoV-2 PCR, clinical and paraclinical findings (such as EMG and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 infection
55	Nejad et al. [184]/2021	Guillain-Barré Syndrome	M/70	Iran	Symmetric weakness and arefexia in both lower limbs	SARS-CoV-2 PCR, clinical and paraclinical findings (such as CSF analysis)	IVIg	Associated with COVID-19 infection
56	McKean et al. [185]/2021	Guillain-Barré Syndrome	M/48	Malta	Bilateral facial weakness, ascending paraesthesia, and bilateral progressive lower limb weakness	Clinical and paraclinical findings (such as CSF analysis and NCV studies),brain CT and MRI	IVIg (2 g/kg for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
57	Hasan et al. [186]/2021	Guillain-Barré Syndrome	F/62	UK	Paraesthesia and progressive weakness of both lower limbs	Clinical and paraclinical findings (such as CSF analysis and NCV studies),brain CT and MRI	IVIg (2 g/kg for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
58	Allen et al. [187]/2021	Guillain–Barré Syndrome	M/54	UK	Bilateral facial weakness and distal dysesthesia in hands and feet	Clinical and paraclinical findings (such as CSF analysis and NCV studies),brain MRI	Oral prednisolone (60mg for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
59	Allen et al. [187]/2021	Guillain–Barré Syndrome	M/20	UK	Bilateral facial weakness and distal dysesthesia in feet	Clinical and paraclinical findings (such as CSF analysis and NCV studies),brain MRI	Oral prednisolone (60 mg for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
60	Allen et al. [187]/2021	Guillain-Barré Syndrome	M/57	UK	Dysarthria and facial weakness, distal dysesthesia in feet, and proximal leg weakness	Clinical and paraclinical findings (such as CSF analysis and NCV studies), and brain MRI	IVIg	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
61	Allen et al. [187]/2021	Guillain–Barré Syndrome	M/55	UK	Bilateral thigh paresthesia, bilateral facial weakness	Clinical and paraclinical findings (such as CSF analysis) and brain MRI	No treatment	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
62	Min et al. [188]/2021	Sensory Guillain–Barré Syndrome	M/58	Republic of Korea	Severe paresthesia on both feet, mild hypoesthesia in vibration, temperature, and pain on both feet	SARS-CoV-2 PCR, Clinical and paraclinical findings (such as CSF analysis, NCV studies, and skin biopsy), and MRI	–	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
63	Min et al. [188]/2021	Sensory Guillain-Barré Syndrome	F/37	Republic of Korea	Paresthesia in both lower limbs	SARS-CoV-2 PCR, Clinical and paraclinical findings (such as CSF analysis, NCV studies, and skin biopsy), and MRI	–	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
64	Scendoni et al. [189]/2021	Guillain-Barré Syndrome	F/82	Italy	Progressively worsening of walking, weakness, lack of sensitivity in both lower limbs, and areflexia	Clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies)	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 vaccination (Pfizer-BioNTech)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
65	Maramattom et al. [190]/2021	Guillain–Barré Syndrome	F/43	India	Areflexic quadriparesis, facial diplegia, and respiratory failure	Clinical and paraclinical findings (such as CSF analysis and NCV studies)	IVIg	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
66	Maramattom et al. [190]/2021	Guillain-Barré Syndrome	F/67	India	Distal paraesthesia in all the extremities, bilateral facial weakness, dysphagia, and increasing limb weakness	–	IVIg and plasmapheresis	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
67	Maramattom et al. [190]/2021	Guillain-Barré Syndrome	F/53	India	Bilateral lower limb numbness and weakness, right-sided facial and tongue numbness (then it progressed to bilateral lower motor neuron facial palsy and Areflexic flaccid quadriplegia)	–	Mechanical ventilation	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
68	Introna et al. [191]/2021	Guillain-Barré Syndrome	M/62	Italy	Absent deep tendon reflexes, severe bilateral optic disk edema, progressively worsening sensory ataxia and ascending quadriparesis	Clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies), brain CT and MRI	IVIg (2 g/kg for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
69	Razok et al. [192]/2021	Guillain-Barré Syndrome	M/73	Qatar	Progressive bilateral lower limb weakness	Clinical and paraclinical findings (such as CSF analysis and EMG and NCV studies), brain CT and MRI	IVIg (0.4 g per kg body weight every day for 5 days)	Associated with COVID-19 vaccination (Pfizer-BioNTech)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
70	Rao et al. [193]/2021	Guillain-Barré Syndrome	F/42	USA	Progressive ascending weakness and paresthesias	Clinical and paraclinical findings (such as CSF analysis and NCV studies), brain and cervical MRI	IVIg (total of 2 g/kg in four divided doses)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
71	Moreno-Escobar et al. [194]	Transverse myelitis	M/41	–	Bilateral paresthesia in upper and lower limbs, along with urinary and fecal retention	Serological study and CSF analysis, imaging studies	IV methylprednisolone	Associated with COVID-19 infection
72	Qazi et al. [195]/2021	Transverse myelitis	F/35	Pakistan	Abrupt bilateral lower limb weakness, paresthesia, and urinary retention	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 7 days)	Associated with COVID-19 infection
73	Chow et al. [196]/2020	Transverse myelitis	M/60	Australia	Bilateral lower limb weakness, urinary retention, and constipation	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 3 days)	Associated with COVID-19 infection
74	Sarma et al. [197]/2020	Transverse myelitis	F/28	USA	Lower back pain, bilateral symmetric upper and lower extremity numbness, and urinary retention	Serological study and CSF analysis, imaging studies	Prednisolone and plasma exchange	Associated with COVID-19 infection
75	Ahmad et al. [198]/2021	Transverse myelitis	F/34	Iraq	Progressive intermittent leg pain, paresthesia, and weakness on both sides	Serological study and CSF analysis, imaging studies	IV methylprednisolone (500 mg 1 × 1 for 5 days)	Associated with COVID-19 infection
76	Nejad Biglari et al. [199]/2021	Transverse myelitis	F/11	Iran	Acute paresis in the lower limbs, urinary and fecal retention	Serological study and CSF analysis, imaging studies	IVIg (0.4 g per kg body weight every day for 5 days) + pulse of methylprednisolone 30 mg/ Kg for 3 days	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
77	Palahuta et al. [200]/2021	Transverse myelitis	M/23	Ukraine	Acute-onset non-compressive myelitis with bilateral paresthesia	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 5 days)	Associated with COVID-19 infection
78	Lingas [201]/2022	Transverse myelitis	M/70	USA	Numbness on both lower limbs	Serological study and CSF analysis, imaging studies	IV methylprednisolone (high dose), IVIg, ceftriaxone, ampicillin, and acyclovir	Associated with COVID-19 infection
79	Prete [202]/2022	Transverse myelitis	F/43	USA	Progressive numbness and tingling in lower limbs and complete quadriplegia	Serological study and CSF analysis, imaging studies	Long-term steroid regimen and plasmapheresis	Associated with COVID-19 infection
80	Shahali [203]/2021	Transverse myelitis	M/63	Iran	Weakness and immobility in lower extremities, constipation, and urinary retention	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 3 days)	Associated with COVID-19 infection
81	Hsiao et al. [204] /2021	Transverse myelitis	M/41	Taiwan	Progressive paresthesia below T4, lower-limb weakness	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1000 mg/day for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
82	Tan et al. [205]/ 2021	Transverse myelitis	F/25	Malaysia	Bilateral lower-limb weakness and impaired walking	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1000 mg/day for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
83	Notghi et al. [206]/2021	Transverse myelitis	M/58	UK	Progressive numbness in lower limbs, allodynia up to chest level, genital dysaesthesia, and an episode of urinary incontinence	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
84	Pagenkopf et al. [58]/2021	Transverse myelitis	M/45	Germany	Acute flaccid tetraparesis (especially in the lower limbs) and urinary retention	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 5 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
85	Eom et al. [207]/2022	Transverse myelitis	M/81	Republic of Korea	Bilateral hand weakness and numbness	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 5 days)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
86	Eom et al. [207]/2022	Transverse myelitis	F/23	Republic of Korea	Bilateral paresthesia and weakness in the lower limbs	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 5 days)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
87	Miyaue et al. [208]/2022	Transverse myelitis	M/75	Japan	Total sensory loss below the umbilicus and complete paralysis in both lower limbs	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 3 days), then oral prednisolone (initial dose of 1 mg/kg/day)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
88	Maroufi et al. [209]/2022	Transverse myelitis	F/31	Iran	Progressive lower limbs paraparesis and paresthesia, urinary retention, and fecal incontinence	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1 g/day for 7 days); Then, oral prednisolone 50 mg daily	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
89	Tahir et al. [210]/2021	Transverse myelitis	F/44	USA	Numbness and weakness in the lower extremities, urinary retention, and back pain	Serological study and CSF analysis, imaging studies	IV methylprednisolone and plasma exchange	Associated with COVID-19 vaccination (Johnson and Johnson COVID-19 vaccine)
90	Hirose et al. [211]/2021	Transverse myelitis	M/70	Japan	Progressive sensorimotor dysfunction of both lower limbs	Serological study and CSF analysis, imaging studies	IV methylprednisolone (1000 mg/day for 5 days); then oral prednisolone (30 mg/day with gradual tapering)	Associated with COVID-19 vaccination (Moderna)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
91	Rajae et al. [212]/2021	Cerebrovascular events (ischemic stroke)	M/68	Morocco	Left hemiparesis with dysarthria and left facial paralysis	Serological study and imaging studies (brain CT scan and MRI)	Thrombolysis	Associated with COVID-19 infection
92	Avvantaggiato et al. [213]/2021	Cerebrovascular events (ischemic stroke)	F/29	Italy	Left hemiplegia, left-sided central facial palsy, dysarthria, facial drop, and complete paralysis of the ipsilateral upper and lower limbs	Serological study and imaging studies (brain CT scan and MRI)	–	Associated with COVID-19 infection
93	Bigliardi et al. [214]/2020	Cerebrovascular events (ischemic stroke)	M/62	Italy	Left hemiplegia, left hemianopsia, and forced right deviation of gaze	Serological study and imaging studies (brain CT scan and chest CT angiography)	anticoagulant (LMWH)	Associated with COVID-19 infection
94	Zhai et al. [215]/2020	Cerebrovascular events (ischemic stroke)	M/79	China	Right limb weakness and non-fluent speech	Serological study and imaging studies (brain CT scan)	Clopidogrel (75 mg) and atorvastatin (20 mg)	Associated with COVID-19 infection
95	Farooque et al. [216]/2020	Cerebrovascular events (ischemic stroke)	M/70	Pakistan	Right-sided weakness and sensory loss in both upper and lower limbs	Serological study and imaging studies (brain CT scan and MRI)	Aspirin. (150 mg twice a day), LMWH (0.6 ml twice a day), and IV dexamethasone (1cc twice a day)	Associated with COVID-19 infection
96	Owolabi et al. [217]/2021	Cerebrovascular events (hemorrhagic stroke)	M/59	Saudi Arabia	Right-sided incoordination, weakness, facial deviation, and altered level of consciousness	Serological study and imaging studies (brain CT scan)	Hydroxychloroquine, dexamethasone, remdesivir, and antibiotics	Associated with COVID-19 infection
97	Owolabi et al. [217]/2021	Cerebrovascular events (hemorrhagic stroke)	M/51	Saudi Arabia	Left-sided limb and facial weakness	Serological study and imaging studies (brain CT scan)	Hydroxychloroquine, dexamethasone, and antibiotics	Associated with COVID-19 infection
98	Fraiman et al. [218]/2020	Cerebrovascular events (hemorrhagic stroke)	F/38	Brazil	Acute alteration in the level of consciousness	Serological study and imaging studies (brain CT scan and MRI)	–	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
99	Flores et al. [219]/2020	Cerebrovascular events (hemorrhagic stroke)	M/40	USA	Pinpoint, minimally reactive pupils, withdrawal to painful stimuli in the right side of the body, left hemiparesis	Serological study and imaging studies (brain CT scan and MRI)	–	Associated with COVID-19 infection
100	Dakay et al. [220]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	M/17	USA	Left-sided headaches and occasional emesis	Serological study and imaging studies (MRI brain with MR venography)	Anticoagulation	Associated with COVID-19 infection
101	Dakay et al. [220]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	F/72	USA	Dyspnea and generalized weakness	Serological study and imaging studies (CT angiogram)	–	Associated with COVID-19 infection
102	Dakay et al. [220]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	M/26	USA	Acute left-sided hemiparesis followed by severe headache, nausea, and dizziness	Serological study and imaging studies (MRI brain with MR venography, brain CT scan, cerebral angiography, and CT angiogram)	–	Associated with COVID-19 infection
103	Anipindi et al. [221]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	M/66	USA	Severe headaches, palpitations, dizziness, and diaphoresis	Serological study and imaging studies (MRI and CT brain along with CT venogram)	Rivaroxaban 20 mg (6 months)	Associated with COVID-19 infection
104	Tu et al. [222]/2020	Cerebrovascular events (cerebral venous sinus thrombosis)	M/ mid-thirties	Singapore	Generalized non-remitting headache	Serological study and imaging studies (MRI and CT brain along with CT venogram and MR venogram)	Dabigatran	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
105	Tu et al. [222]/2020	Cerebrovascular events (cerebral venous sinus thrombosis)	M/the late thirties	Singapore	First-onset seizure (generalized tonic–clonic convulsion)	Serological study and imaging studies (CT brain along with CT venogram)	IV heparin, IV levetiracetam, and cobalamin replacement	Associated with COVID-19 infection
106	Blauenfeldt et al. [78]/2021	Cerebrovascular events (ischemic stroke)	F/60	Denmark	Strong, persistent abdominal pain, headache	Serological study and imaging studies (CT brain)	Hemicraniectomy + postoperative dalteparin 5000 IU daily	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
107	Elaidouni et al. [223]/2022	Cerebrovascular events (ischemic stroke)	M/36	Morocco	Numbness in left hemibody, headaches (24 h after the vaccine injection),	Serological study and imaging studies (CT brain, MRI brain, MRI angiography of supra-aortic trunks)	Aspirin and Enoxaparin (100 UI/kg/12 h)	Associated with COVID-19 vaccination (Sinopharm)
108	Kenda et al. [224]/2021	Cerebrovascular events (ischemic stroke)	F/51	Slovenia	Acute-onset global aphasia, right-sided hemiplegia, and hemianopsia	Serological study and imaging studies (CT/MRI brain and CT angiography)	Mechanical thrombectomy + high-dose IVIg (1 g/kg for 2 consecutive days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
109	Al-Mayhani et al. [225]/2021	Cerebrovascular events (ischemic stroke)	F/35	UK	Right temporal and periorbital headache	Serological study and imaging studies (CT brain and CT angiography)	Urgent decompressive hemicraniectomy, IVIg, plasmapheresis, and fondaparinux	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
110	Al-Mayhani et al. [225]/2021	Cerebrovascular events (ischemic stroke)	F/37	UK	Diffused headache, left visual field loss, confusion, and left arm weakness	Serological study and imaging studies (diffusion-weighted MRI and CT angiography)	IVIg, IV methylprednisolone, plasmapheresis, and fondaparinux	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
111	de Mélo Silva et al. [226]/2021	Cerebrovascular events (hemorrhagic stroke)	F/57	Brazil	Acute-onset sweating and paleness, followed by left-sided hemiparesis, vomiting, and somnolence	Serological study and imaging studies (CT brain)	Hematoma drainage, external ventricular drain, and decompressive craniectomy	Associated with COVID-19 vaccination (Oxford/AstraZeneca)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
112	Takeyama et al. [227]/2022	Cerebrovascular events (hemorrhagic stroke)	F/48	Japan	Gradually progressing left-sided hemiparesis	Serological study and imaging studies (CT/MRI brain and CT angiography)	Right frontotemporal craniotomy	Associated with COVID-19 vaccination (Pfizer-BioNTech)
113	Dias et al. [228]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	F/47	Portugal	The sudden left-sided motor deficit, papilledema, left visual extinction, right gaze deviation, and left hemiparesis	Serological study and imaging studies (MRI brain, MRI venography)	Acetazolamide and enoxaparin 60 mg twice a day (later changed to warfarin)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
114	Dias et al. [228]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	F/67	Portugal	Sudden right-sided lower limb clonic movements, motor deficit, loss of consciousness, and headache	Serological study and imaging studies (MRI brain) and Electroencephalography	Levetiracetam (500 mg twice a day) and enoxaparin (80 mg twice a day); then switched to dabigatran (150 mg twice a day)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
115	Zakaria et al. [229]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	M/49	Malaysia	A new-onset headache and giddiness	Serological study and imaging studies (CT brain and CT cerebral venogram)	Subcutaneous Clexane (1 mg/kg twice a day) and clopidogrel (75 mg)	Associated with COVID-19 vaccination (Pfizer-BioNTech)
116	D'Agostino et al. [230]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	F/54	Italy	Left-sided signs	Serological study and imaging studies (CT/MRI brain and CT/MRI angiography)	–	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
117	Atta et al. [231]/2021	Cerebrovascular events (cerebral venous sinus thrombosis)	F/48	UK	Right-sided headache,	Serological study and imaging studies (CT cerebral venogram)	Fondaparinux (7.5 mg), IVIg (1 g/kg) and dexamethasone (20 mg/day)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
118	Delorme et al. [232]/2020	Encephalopathy	M/72	France	Acute psychomotor agitation, cognitive and behavioral frontal lobe syndrome, upper limbs myoclonus, and cerebellar ataxia	CSF analysis, electroencephalogram (EEG), brain MRI, and brain FDG-PET/CT imaging	IVIg (2 g/kg)	Associated with COVID-19 infection
119	Delorme et al. [232]/2020	Encephalopathy	F/66	France	Acute cognitive impairment, psychomotor slowing, cognitive and behavioral frontal lobe syndrome, and severe apraxia	CSF analysis, EEG, brain MRI, and brain FDG-PET/CT imaging	IVIg; then, due to persisting severe cognitive impairment, IV pulse corticosteroids (2 mg/kg/day 3 days then 1 g/day 3 days) started	Associated with COVID-19 infection
120	Delorme et al. [232]/2020	Encephalopathy	F/60	France	Acute anxiety, depressed mood, akathisia, gait imbalance, psychomotor agitation, dysexecutive syndrome, and cerebellar ataxia	CSF analysis, EEG, brain MRI, and brain FDG-PET/CT imaging	Pulse corticosteroids (2 mg/kg/day 3 days)	Associated with COVID-19 infection
122	Delorme et al. [232]/2020	Encephalopathy	M/69	France	Generalized convulsive status epilepticus, fever, fatigue, anosmia, and ageusia	CSF analysis, EEG, brain MRI, and brain FDG-PET/CT imaging	Pulse corticosteroids (1 g/day 5 days)	Associated with COVID-19 infection
123	Lazraq et al. [233]/2021	Encephalopathy	M/79	Morocco	Mental confusion, sudden-onset dysarthria	The serological study, CSF analysis, EEG, brain CT, MRI, and MR angiography	Sodium valproate	Associated with COVID-19 infection
124	Goodloe et al. [234]/2021	Encephalopathy	M/52	USA	Altered mental status, fever, and severe agitation	The serological study, CSF analysis, EEG, brain CT, and MRI	Vancomycin, ceftriaxone, azithromycin, acyclovir, and clevidipine	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
125	Teimouri-Jervekani et al. [235]/2021	Encephalopathy	M/53	Iran	Severe headache and bizarre behavior	The serological study, brain CT and MRI	Hydroxychloroquine (200 mg twice a day for 5 days)	Associated with COVID-19 infection
126	Al-Mashdali et al. [236]/ 2021	Encephalopathy	M/32	Qatar	Acute confusion, disturbed memory, and auditory hallucination	The serological study, CSF analysis, EEG, and brain MRI	Methylprednisolone	Associated with COVID-19 vaccination (Moderna)
127	Liu et al. [237]/2021	Encephalopathy	F/86	USA	Acute confusion with visual hallucinations and left frontal headache	The serological study, CSF analysis, EEG, brain CT, and MRI	Lorazepam, fosphenytoin, and discharged with levetiracetam	Associated with COVID-19 vaccination (Moderna)
128	Liu et al. [237]/2021	Encephalopathy	M/73	USA	Cognitive deficits, hallucinations, and periods of unresponsiveness	The serological study, CSF analysis, EEG, brain CT, and MRI	Lorazepam and levetiracetam	Associated with COVID-19 vaccination (Moderna)
129	Baldelli et al. [108]/2021	Encephalopathy	M/77	Italy	Confusion, agitation, and delirium	The serological study, CSF analysis, EEG, brain CT, and MRI	Oral prednisone (50 mg per day)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
130	Bensaidane et al. [238]/2022	Encephalopathy	M/56	Canada	Altered mental status	The serological study, CSF analysis, EEG, brain CT angiography, and MRI	High-dose IV methylprednisolone (1 g/day for 7 days)	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
131	Monti et al. [239]/2020	New-onset seizures	M/50	Italy	Acute onset of psychiatric symptoms (confabulations and delirious ideas), focal motor seizures, and impaired awareness	The serological study, CSF analysis, EEG, brain MRI, and total-body CT and PET	Diazepam, valproic acid, lacosamide, methylprednisolone, IVIg, plasma-exchange	Associated with COVID-19 infection
132	Bhatta et al. [240]/2020	New-onset seizures	M/11	USA	Acute-onset seizure for 2 min	The serological study, EEG, and brain CT	Levetiracetam (500 mg twice a day)	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
133	Park et al. [241]/2021	New-onset seizures	F/45	USA	Focal to bilateral tonic–clonic seizure, loss of consciousness, and urinary incontinence	The serological study, CSF analysis, EEG, brain MRI, and CT	Oxcarbazepine (600 mg twice a day); then lacosamide (200 mg twice a day)	Associated with COVID-19 infection
134	Dono et al. [242]/2021	New-onset seizuresa	M/81	Italy	Non-convulsive status epilepticus with coma	The serological study, CSF analysis, EEG, brain MRI, and CT	Lorazepam (4 mg two IV boluses), levetiracetam (2000 mg IV), methylprednisolone (1 g/daily IV for 5 days); then, oral prednisolone (60 mg/day for 10 days) and IVIg (160 g over 5 days)	Associated with COVID-19 infection
135	Cho et al. [243]/2022	New-onset seizures	M/84	Korea	Myoclonic seizures (Myoclonic status epilepticus)	The serological study, EEG, brain Diffusion-weighted MRI	Sedative medication: Midazolam Antiseizure medication: Lorazepam and Levetiracetam	Associated with COVID-19 infection
136	Cho et al. [243]/2022	New-onset seizures	M/45	Korea	Focal to bilateral tonic–clonic seizures (2 times)	Serological study and EEG	Sedative medication: Remifentanil and Dexmedetomidine Antiseizure medication: Lorazepam and Levetiracetam	Associated with COVID-19 infection
137	Cho et al. [243]/2022	New-onset seizures	M/63	Korea	Focal impaired aware seizures (several times)	Serological study and EEG	Sedative medication: Dexmedetomidine Antiseizure medication: Phenobarbital, Levetiracetam, Topiramate, and Perampanel	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
138	Cho et al. [243]/2022	New-onset seizures	M/72	Korea	Myoclonic seizure, generalized tonic–clonic seizures (several times)	Serological study and EEG	Sedative medication: Remifentanil and Dexmedetomidine Antiseizure medication: Levetiracetam and Topiramate	Associated with COVID-19 infection
139	Cho et al. [243]/2022	New-onset seizures	M/73	Korea	Myoclonic seizures (several times)	Serological study and EEG	Sedative medication: Remifentanil and Propofol Antiseizure medication: Levetiracetam and Valproic acid	Associated with COVID-19 infection
140	Cho et al. [243]/2022	New-onset seizures	F/39	Korea	Generalized tonic–clonic seizures (3 times)	The serological study, EEG, brain CT	Sedative medication:—Antiseizure medication: Levetiracetam	Associated with COVID-19 infection
141	Aladdin et al. [119]/2021	New-onset seizures	F/42	Saudi Arabia	Generalized tonic–clonic seizure	The serological study, CSF analysis, EEG, and brain MRI	Lorazepam, phenytoin, levetiracetam, and lacosamide	Associated with COVID-19 vaccination (Oxford/AstraZeneca)
142	Bauman et al. [244]	New-onset seizures	M/56	USA	New-onset refractory status epilepticus	The serological study, CSF analysis, EEG, and brain MRI	Corticosteroids, plasmapheresis, IVIg, rituximab, midazolam, propofol, ketamine, levetiracetam, lacosamide, phenobarbital, clobazam, zonisamide, oxcarbazepine, and perampanel	Associated with COVID-19 vaccination (Pfizer-BioNTech)
143	Desai et al. [245]/2021	Varicella-zoster virus reactivation	F/62	India	Painful blisters and fluid-filled bubble-form rashes	Serological studies	Oral and topical Acyclovir	Associated with COVID-19 infection

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
144	Saleh et al. [246]/2021	Varicella-zoster virus reactivation	F/49	Egypt	Unilateral fluid-filled vesicles and painful erythematous areas over the hard palate	Serological studies	Oral acyclovir, topical antiseptics, chlorhexidine, and paracetamol	Associated with COVID-19 infection
145	Saati et al. [122]/2020	Varicella-zoster virus reactivation	M/57	Saudi Arabia	Fluid-filled bubble-form rashes and vesicles with surrounding erythematous areas over the right nipple	Serological studies	Famciclovir	Associated with COVID-19 infection
146	Van Dam et al. [129]/2021	Varicella-zoster virus reactivation	F/29	The Netherlands	Painful multiple vesicles on the left side of the ox coccyges	Clinically diagnosed	–	Associated with COVID-19 vaccination (Pfizer-BioNTech)
147	Van Dam et al. [247]/2021	Varicella-zoster virus reactivation	M/34	The Netherlands	Swollen, painful inguinal lymph nodes and a rash on the right lower limb	Serological studies and PCR tests over vesical fluid for VZV	Valacyclovir	Associated with COVID-19 vaccination (Pfizer-BioNTech)
148	Rodríguez-Jiménez et al. [248]/2021	Varicella-zoster virus reactivation	M/58	Spain	Asymptomatic herpes-form umbilicated vesicles and lymphadenopathy in the cervical area	PCR	–	Associated with COVID-19 vaccination (Pfizer-BioNTech)
149	Rodríguez-Jiménez et al. [248]/2021	Varicella-zoster virus reactivation	F/47	Spain	Herpes-form umbilicated vesicles and dysesthesia	PCR	–	Associated with COVID-19 vaccination (Pfizer-BioNTech)
150	Rodríguez-Jiménez et al. [248]/2021	Varicella-zoster virus reactivation	M/39	Spain	Painful herpes-form umbilicated vesicles	–	–	Associated with COVID-19 vaccination (Pfizer-BioNTech)
151	Rodríguez-Jiménez et al. [248]/2021	Varicella-zoster virus reactivation	F/56	Spain	Herpes-form umbilicated vesicles	PCR	–	Associated with COVID-19 vaccination (Pfizer-BioNTech)

Table 2 (continued)

Case number	Reference	Neurological disorder	Sex/Age (years)	Country	Clinical manifestation	Diagnosis	Treatment	Associated with SARS-CoV-2 infection vs post-COVID-19 vaccination
152	Rodríguez-Jiménez et al. [248]/2021	Varicella-zoster virus reactivation	F/41	Spain	Herpes-form umbilicated vesicles and dysesthesia	–	–	Associated with COVID-19 vaccination (Pfizer-BioN-Tech)
153	Santovito et al. (249)/2021	Varicella-zoster virus reactivation	M/27	USA	Popular rashes over the left upper limb	–	–	Associated with COVID-19 vaccination (Pfizer-BioN-Tech)

Miscellaneous neurological adverse events

Apart from the aforementioned neurological side effects, some other AEs, including narcolepsy, small fiber neuropathy, neuroleptic malignant syndrome (NMS), and multiple sclerosis flare-ups, have been reported following COVID-19 vaccination, although their causal relationships are not confirmed [4, 136–139].

Relative risks of neurological adverse events in SARS-CoV-2 infection vs. post-COVID-19 vaccination

Many studies have reported various neurological disorders associated with COVID-19 infection and vaccines [80, 140–143]. However, given the shortage of comprehensive, prospective studies, it is still far too difficult to establish cause-effect relations between these factors. Therefore, future studies should determine the real risk of these adverse events following COVID-19 vaccination. Until then, it does not seem reasonable to limit vaccine administration. Nonetheless, considering the existing data, in this section, we have summarized some studies reporting cases of neurological adverse events associated with SARS-CoV-2 infection or vaccination (Table 2).

Conclusion

The present review can help healthcare workers and also the general population by emphasizing these points: any neurological symptom after COVID-19 vaccination can be potentially critical and needs to be cautiously evaluated; for any suspected adverse event following vaccination, we should initially exclude current or recent SARS-CoV-2 infection; and despite the current literature on serious complications imposed by COVID-19 vaccines, the benefits of vaccination outweigh the risks in ending the current pandemic since all of these complications can occur with the infection itself.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Terence T. Sio reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no relevant financial interests to be declared.

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