



A Narrative Review of Neurological Complications of SARS-CoV-2 Vaccination

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Abstract

Adverse reactions to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine depict a tropism for neural structures. This narrative review was aimed to discuss published data on the spectrum of neurological side effects of SARS-CoV-2 vaccines, which were accorded emergency use authorization. The majority of the neurological manifestations of SARS-CoV-2 vaccination are usually mild, brief, self-limiting, and easily manageable. Rarely, these side effects can be of serious nature and require hospitalization. High vigilance helps in early identification and treatment of these complications leading to good outcomes. The reported incidence of neurological complications in vaccinated population is a miniscule, and the overall benefits of the vaccine outweigh the risks of side effects. However, it is crucial to conduct larger collaborative multicenter studies to prove or reject the causal association between the SARS-CoV-2 vaccines and the postvaccination neurological side effects. Herein, we have tried to summarize the various neurological manifestations related to SARS-CoV-2 vaccines published in the literature from 2021 to mid-2023.

Keywords

- ▶ COVID-19
- ▶ SARS-CoV-2 vaccine
- ▶ Postvaccination neurological complications

Introduction

As of June 28, 2023, globally nearly 7.0 million patients have died from COVID-19 and approximately 13.5 billion doses of various vaccines against COVID-19 have been administered worldwide.¹ Currently, the most common vaccines against COVID-19 include mRNA-based vaccines (Moderna, and Pfizer's BioNTech162b2), vector-based vaccine (Astra-Zeneca's ChAdOx1nCoV-19 [AZV], and Janssen/Johnson & Johnson's Ad 26.CoV2.S [J&J]), and inactivated whole virus vaccine (Sinovac-CoronaVac, Covaxin, and Sinopharm).

Several vaccines such as for influenza, hepatitis A/B, papilloma virus, rabies, rubella, tetanus, etc., are temporally associated with various neurological adverse events.² Although common side effects of vaccines generally echo

their effectiveness and active immune response, serious debilitating neurological reactions may also arise, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is no exception. Neurological symptoms following this vaccination are usually mild, self-limiting, and easily manageable.³ However, infrequent serious complications that require hospitalization or even intensive care unit (ICU) care, which occasionally prove fatal, may also occur.

Females have higher incidence of neurological complications because immune-mediated diseases affect women more frequently.⁴ This has been attributed to a stronger immune response against foreign antigens, and self-antigen in them, compared to males and results in autoimmune disorders.⁵ Adverse reactions after the first dose of AZV are more frequent than the Pfizer or Sinopharm vaccine.⁶

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Methods

Articles, case reports, reviews, and research related to neurological manifestations of SARS-CoV-2 vaccination published in the literature from 2021 to mid-2023 were researched and reviewed in Google Scholar, PubMed, and NCBI databases. Keywords used for this search were COVID-19, SARS-CoV-2 vaccination, adverse effects, neurological manifestations, complications, cerebrovascular events, thrombosis, thrombocytopenia, myelitis, demyelination, mRNA-based vaccines (Moderna, and Pfizer's BioNTech162b2), vector-based vaccine (Astra-Zeneca's ChAdOx1nCoV-19 [AZV] and Janssen/Johnson & Johnson's Ad 26.CoV2.S [J&J]), and inactivated whole virus vaccine (Sinovac-CoronaVac, Covaxin, and Sinopharm). The spectrum of neurological manifestations reported following COVID-19 vaccination are tabulated in **Table 1**.

The minor and major complications seen post SARS-CoV-2 vaccination are discussed in the following sections.

Functional Neurological Disorders

Functional neurological disorders (FNDs) are disorders without any positive neurological abnormalities, frequently triggered by

emotional stress. Numerous FNDs have been reported following SARS-CoV-2 vaccination. Nonepileptic seizures characterized by bizarre hyperkinetic movements, without electroencephalogram (EEG) correlates may occur, others may present as limb weakness mimicking as cerebral vascular event.⁷

Videos depicting bizarre, asynchronous limb/trunk movements appeared on social sites purported to be vaccine complications. Kim et al clarified that these disordered movements were functional.⁸

Headache

It is the most common side effect of all SARS-CoV-2 vaccines. It starts within few hours of vaccination, resolving within 48 hours.⁹ However, headache occurring on an average 8 days later is frequently associated with cerebral venous sinus thrombosis (CVST).¹⁰ It is mostly a pressing or dull ache, but it can be throbbing pain in a few cases. The common accompanying symptoms are fatigue, exhaustion, and myalgia.

Headache can be a tension type or due to intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), reversible cerebral vasoconstriction syndrome (RCVS), or CVST.¹¹

Table 1 The spectrum of neurological manifestations reported following COVID-19 vaccination

Category	Complication
Cerebrovascular	Cerebral venous sinus thrombosis Hemorrhagic stroke: intracerebral hemorrhage, subarachnoid hemorrhage Acute ischemic stroke Transient ischemic attacks
Central nervous system neuroinflammatory disease	Acute transverse myelitis Multiple sclerosis Idiopathic neurologic amyotrophy (INA) aka Parsonage–Turner syndrome Optic neuritis Acute disseminated encephalomyelitis Guillain–Barre syndrome Small fiber neuropathy Postvaccination meningitis Postvaccination encephalitis
Cranial neuropathy	Bell's palsy Trigeminal neuralgia Sensorineural hearing loss Dysgeusia Olfactory dysfunction
Seizure disorder	Seizures Epilepsy Status epilepticus
Movement disorders	Tremors Dystonia Myoclonus
Cognitive dysfunction	Encephalopathy/delirium/confusion Acute psychosis Acute global amnesia
General	Headache Vertigo/dizziness Syncope Fatigue Sleep disturbances

Cerebrovascular Diseases

The cerebrovascular diseases (CVD) associated with SARS-CoV-2 vaccines are discussed in the following sections.

Cerebral Venous Sinus Syndrome

It is the most common and serious complication with incidence varying among different studies. Its most prominent manifestation is treatment-resistant headache with onset few days after vaccination. Seizures, altered sensorium, and focal deficit may also accompany. The median time to its occurrence is 9 days (range: 2–45 days).¹² Most cases are reported after the first dose of AZV; however, it is also seen after J&J vaccine. Partial or complete occlusion of cerebral venous sinus (CVS) or its draining veins leads to venous hypertension, localized edema, seizures, raised intracranial pressure (ICP), infarction, and rarely ICH. Messenger ribonucleic acid (mRNA) vaccines have also occasionally produced CVST.¹³

Affected patients are without any preexisting conditions predisposing them to thrombosis.¹² The peculiarities of CVST is its association with thrombosis and thrombocytopenia, which led to coining of the term vaccine-induced immune thrombotic thrombocytopenia (VITT).¹⁴ Incidence of VITT appears to be lower among the elderly,¹⁵ with a slight female predominance (2.25 females to 1 male for AZV).¹²

Victims of postvaccination CVST may have poor outcome from refractory raised ICP with high mortality (39–50%).^{14,16}

Pathophysiology of VITT

VITT is similar to heparin-induced thrombocytopenia (HIT), with elevated antibodies against platelet factor 4 (PF4) akin to HIT.¹⁷ Therefore, current guidelines suggest non heparin anticoagulants to manage VITT.¹⁸

VITT is a consumption coagulopathy that can present as CVST and/or splanchnic thrombosis.^{14,19} AZV triggers it by synthesizing immunoglobulin G (IgG) antibodies against PF4. Moreover, adenovirus-based vaccines lead to leakage of genetic material from transfer of the nucleic acids coding of the viral spike (S) protein, and their binding to PF4 results in onset of autoimmunity with autoantibodies to PF4.²⁰

PF4, being a positively charged chemokine, binds negatively charged patient's heparin, forming large PF4 heparin complexes that have antigenic characters.²¹ As a result, IgG autoantibodies against this complex can be formed, which directly activate platelets and promote cross-linking of platelets to FcγRIIA receptors.²² It is likely that the negatively charged components of vaccines such as glycoprotein of adenovirus, adjuvants components, and/or adenovirus deoxyribonucleic acid (DNA) are also able to bind PF4 similar to heparin.²³

Furthermore, vaccine viral antigens indirectly cause blood clotting by activating complement pathways and increasing thrombin production.²⁴

Acute Ischemic Stroke

Thrombosis in a cerebral artery results from VITT. Appearance of persistent or unusual neurological symptoms following SARS-CoV-2 vaccine should be urgently investigated for

VITT.²⁵ In meta-analytic studies, acute ischemic stroke (AIS) was reported in 4.7 cases per 100,000 vaccinations,^{26,27} which is comparable to its prevalence in the general population.

Most of the AIS patients after SARS-CoV-2 vaccination are women aged 26 to 60 years who got AIS 1 to 21 days after vaccination with AZV and J&J vaccines.^{19,25} It is also reported with J&J and mRNA vaccines.^{19,25,28}

The pathophysiology of AIS following SARS-CoV-2 vaccination is thought to be from vasculopathy (arterial hypertension, endotheliitis, vasculitis, vasospasm, dissection, VITT, CVST), coagulopathy (cardioembolism, dysfunctional thrombocytes, e.g., VITT), or endocarditis, myocarditis, atrial fibrillation, etc.²⁹ Treatment of vaccination-related AIS is similar to stroke from other etiology, except in that from VITT.

Recently, Ihle-Hansen et al concluded that currently they have no reason to believe that mRNA vaccines against SARS-CoV-2 disease, regardless of age, sex, or number of doses, lead to increased risk of stroke (either ischemic or hemorrhagic).²⁸

Hemorrhagic Stroke

Hemorrhagic stroke (HS) results from either ICH or SAH, or both, after SARS-CoV-2 vaccination. The condition could be primary or secondary to venous thrombosis. Even HS following the first dose of AZV in a patient without any prevalent risk factors has been reported.³⁰

A great majority of HS cases resulted following the first dose of Pfizer vaccine.^{31,32} Dissection of vertebral artery was reported following the first dose of mRNA vaccines in two cases.³³ Fatality from ICH following SARS-CoV-2 vaccine has been reported as 0.11 per 1,000,000 doses with 21.4% fatality.³⁴ Hypertension and diabetes are the most common risk factors.³⁴

There are various mechanisms of ICH following SARS-CoV-2 vaccines: immune thrombocytopenia or vasculitis following mRNA vaccines^{35,36} and VITT complicated by CVST from AZV.³⁷

There is no systematic study on aneurysmal SAH following anti-SARS-CoV-2 vaccination barring anecdotal case reports of aneurysm rupture following either the first or the second dose of mRNA vaccines.^{38,39} Since inflammatory responses in saccular aneurysm wall (mainly in the form of T-cells and macrophage infiltration) are known to be associated with aneurysm rupture, a relationship between stronger immune response in women and aneurysm rupture cannot be ruled out.⁴⁰

Guillain–Barre Syndrome

Guillain–Barre syndrome (GBS) has been reported following SARS-CoV-2 vaccine like any other vaccine. In the vast majority of patients, GBS followed the first jab of vaccine. It occurred mostly within 14 days of vaccination. Most frequently its cause was immunization with AZV vaccines, followed by J&J and Pfizer vaccines.⁴¹ J&J vaccines may be associated with very high incidence compared with mRNA-based vaccines.⁴² In fact, GBS after mRNA vaccines may represent the background incidence of the syndrome.⁴²

Pathogenesis

Many speculative factors are behind GBS from SARS-CoV-2 vaccine, but the only possible risk factor seems to be a history of a previous GBS.⁴³ The higher rate of facial palsy and lower rate of antiganglioside antibodies may be the characteristic feature of GBS following SARS-CoV-2 vaccination.⁴⁴ Therefore, in at least some cases, it is believed to involve anti-ganglioside (anti-GM₁) antibodies and molecular mimicry (MM), similar to following influenza vaccine. Nelson, while commenting on GBS following influenza vaccine, postulated that contaminating proteins or other vaccine components may elicit an antiganglioside antibody production and that the increased purification steps (used in recent preparation of influenza vaccines) could significantly reduce the pathogenic potential to produce GBS.⁴⁵ Thus, extra purification of SARS-CoV-2 vaccines might also decrease the incidence of GBS, even though it may not eliminate GBS completely. Specifically, the vaccine contains the same structure as ganglioside and thus a vaccinated person produces antiganglioside antibodies.⁴⁶

It is also theoretically possible that antibodies induced by J&J vaccines may cross-react with glycoproteins on the axonal myelin sheath of peripheral nerves, resulting in GBS.⁴⁷ Given the higher risk of GBS following adenovirus vector vaccines, it is more likely that the immune response to adenovirus vector rather than spike protein of SARS-CoV-2 may be involved in the pathogenesis of GBS postvaccination.

Recently, Rzymiski hypothesized that the administration of selected adenoviruses employed in vector vaccines triggers the adaptive response to the viral vector that can eventually lead to autoimmunity against proteins of the peripheral nervous system and induce GBS. He also presented an alternative hypothesis that implies the neuro-invasion of selected adenoviral vectors, their interaction with peripheral neurons, and the induction of subsequent inflammation and neuropathies are associated with GBS.⁴⁸

Facial Nerve Palsy

Isolated unilateral facial nerve palsy/Bell's palsy (BP) has been noted with almost all vaccines against viruses (including SARS-CoV-2). The first dose of SARS-CoV-2 vaccination (mRNA and vector based) has shown significant odds of developing BP versus placebo, with an almost similar incidence rate with both vaccines.⁴⁹ BP was also reported following the first dose of Covaxin.⁵⁰

Albakri et al reported the incidence of BP after SARS-CoV-2 vaccination to be 25.3 per million vaccinations and was higher after the first dose compared to the second and was higher with Pfizer or AZV compared to other vaccines. It occurs more frequently in males and is mostly unilateral. The average time of onset is 11.6 days.⁵¹ Its incidence following mRNA vaccine is up to three times higher than expected in the general population.⁵²

BP can occur in isolation or as a part of the autoimmune disease developed following the vaccine, as GBS, polyneuritis, or other forms of autoimmune neuropathy.⁵³ BP as a part of the Ramsay Hunt syndrome can also occur following the

first dose of the Pfizer vaccine.⁵⁴ The condition is self-limiting. It is advisable to monitor for BP 60 days following vaccination.

Pathogenesis

The exact mechanism is unknown. There is possibility of the involvement of autoimmune processes via either multiple myeloma (MM) by vaccine antigens or by bystander activation of autoreactive dormant T cells or it might be the result of the combined effect of lipids and mRNA, leading to interferon production and subsequently impairment of peripheral tolerance.⁵² Stimulation of the immune system might also contribute to BP.⁵⁵

Small Fiber Neuropathy

The rate of post-SARS-CoV-2 vaccine small fiber neuropathy (SFN) is roughly 0.01 to 0.13%.⁵⁶ SFN has been reported following various vaccines, including SARS-CoV-2 vaccine. Sukockienė et al reported 11 patients (including 3 with BP) with either Pfizer, Moderna, or J&J vaccine, 1 to 40 days postvaccination (none after AZV).⁵⁷ Nine of them showed symptoms after the first dose. Neuropathy develops at least 20 days following vaccination. Their clinical presentation is not different from other causes of SFN. Nerve conduction velocities confirmed small fiber axonal neuropathy. Symptoms resolve completely over a period of time spontaneously.

SFN is probably immune mediated from hypersensitivity either to the vaccine solvent or to the component of the vaccine itself.^{58,59} Other proposed mechanism (though questioned) is through MM. It is also hypothesized that COVID-19 vaccination may also create autoantibodies.⁶⁰

Idiopathic Neuralgic Amyotrophy (INA)

Idiopathic neuralgic amyotrophy (INA), also known as Parsonage–Turner syndrome (PTS) or brachial neuritis or neuralgic amyotrophy, is a rare brachial plexopathy of unknown etiology characterized by unilateral, acute self-limiting shoulder and upper limb pain, followed by upper extremity weakness with sensory changes.

It can result after the first and second dose of mRNA-based SARS-CoV-2 vaccines.⁶¹ Symptoms appear between 13 and 25 days postvaccination. INA, painless, may develop with a similar disease course.⁶² Physical examination and electrodiagnostic (EDX) studies show abnormalities localized to a part of the brachial plexus or to one or more of its branches. An immune-mediated inflammatory reaction against the brachial plexus in a genetically predisposed individual is the currently accepted cause, but the exact etiology is unclear. With the passage of time, some patients may show variable improvement.

Herpes Zoster

There has been an excess of 5 and 7 cases of hospitalization from herpes zoster (HZ) after every 1,000,000 doses of CoronaVac and Pfizer vaccination, respectively.⁶³ However,

the absolute incidence of HZ following these two vaccines is low, being 7.9 per 1 million doses of Pfizer and 7.1 per 1 million doses after CoronaVac vaccine.⁶³ This increased risk of HZ after the second dose of mRNA vaccines is potentially driven by increased risk in females older than 50 years.^{64,65}

Pathogenesis

A brief lymphopenia has been observed following either the first or the second dose of Pfizer vaccination.⁶⁶ Therefore, it is possible that reactivation of the varicella zoster virus (VZV) occurs following immunization during this period of lymphopenia. In addition, mRNA-based vaccines could potentially trigger zoster infection, as these vaccines stimulate toll-like receptor 3 (TLR3) and TLR7 signaling, a pathway involved in latency and reactivation of VZV.⁶⁷ Most cases of VZV activation after Pfizer vaccine occurred among those with immune-compromised conditions, including advanced age and autoimmune diseases and immunosuppressants.⁶⁸

Inflammatory Diseases of Central Nervous System

SARS-CoV-2 vaccines produced various inflammatory conditions, which are predominantly immunogenic. Either new onset of immunologic disease or flare of previously diagnosed disease (e.g., multiple sclerosis [MS]) has been reported as complications of SARS-CoV-2 vaccines.⁶⁹

Acute Disseminating Encephalomyelitis

Acute disseminating encephalomyelitis (ADEM) is an autoimmune disease involving white matter of the brain and spinal cord and/or optic nerve. Numerous case reports and case series have suggested its potential association with all the presently available SARS-CoV-2 vaccines. Nearly 85% individuals developed ADEM following the first dose.⁷⁰ Its most common cause is adenovirus-based SARS-CoV-2 vaccines.⁷¹ Recovery is complete in most cases without any residue. Current evidence of association of ADEM with SARS-CoV-2 vaccines is weak and more studies are needed in this regard.⁷⁰ The pathogenesis is suspected to be related to autoimmune response to myelin triggered by immunization via MM.

Acute Transverse Myelitis

SARS-CoV-2 vaccine related acute transverse myelitis (ATM) can occur in isolation or along with encephalitis or optic neuritis or both. Adenovirus vaccines cause 46% ATM cases, followed by 42% from mRNA vaccines and 12% from inactivated vaccines.⁷¹ The affected patients may have other immune-mediated diseases. The proposed mechanism of ATM is the concept of MM between infectious antigen and self-antigens. Viral antigens present in AZV or its chimpanzee adenovirus adjuvant may induce immune mechanism leading to ATM.⁷² For nonadenovirus vaccines, a hypothesis is that immune dysregulation secondary to vaccination might trigger ATM.³ Although the exact mechanism warrants further studies, an inflammatory cascade can lead to widespread axonal degeneration of both white and gray matter. In

most cases, it responds satisfactorily to treatment when recognized early.

Encephalitis

Many cases of SARS-CoV-2 vaccination related encephalitis have been reported. One study reported encephalitis to be more common in middle-aged males and AZV vaccines to be the most frequent offender, followed by mRNA vaccines, and most cases (66%) follow the first dose.⁷³ Although the underlying mechanism is uncertain, it could be attributed to different potential mechanisms of vaccine-induced autoimmune diseases. SARS-CoV-2 vaccine was shown to trigger proinflammatory cytokine expression and response of T cells.⁷⁴ These cytokines may enter the brain and activate microglial cells, leading to neuroinflammation.⁷⁵ MM has also been implicated. Some authors suggest spike protein produced by mRNA vaccine may act as a catalyst for the inflammatory process that ensues, particularly in autoimmune encephalitis.⁷⁶

Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder

These two neuroinflammatory disorders of the CNS have been reported following both inactivated and mRNA SARS-CoV-2 vaccines.⁷⁷ In an analysis, Mirmosayyeb et al reported that 76.3% patients were females, with the mean (standard deviation [SD]) time interval between vaccination and the first symptom of MS or neuromyelitis optica spectrum disorder (NMOSD) in the first and second doses of 7.5 (4.8) and 15.1 (12.8) days, respectively.⁷⁷

A significant correlation between Pfizer vaccines, low vitamin D levels, positive Epstein–Barr nuclear antigen IgG, family history of MS, and development of post-SARS-CoV-2 vaccine has been observed,⁷⁸ although genetic and environmental factors could not be ruled out in its causation.⁷⁸

TLRs, which play a crucial role in the innate immune system by recognizing pathogen-associated molecular patterns derived from various pathogens, also play a role in the pathogenesis of MS and NMOSD.⁷⁹ However, the exact pathogenesis of these two diseases from vaccines remains elusive.

Hypophysitis

Following SARS-CoV-2 vaccines, Taieb and Mounira reported eight cases of hypophysitis (50% each with Pfizer and AZV vaccines) until September 2022, more commonly in females.⁸⁰ In 50% of patients, pituitary disorder developed after the first dose of the corresponding vaccine. AZV also produces pituitary apoplexy (PA). Apoplexy resolves completely over a period of time, but hypophysitis can result in persistent central diabetes insipidus (CDI). The time interval between vaccination and pituitary disorder ranged from 1 to 7 days. However, CDI from Pfizer vaccine may take 8 weeks to develop.⁸¹ Improvement in pituitary function follows hormonal replacement.

The pathology of hypophysitis is unclear; however, autoimmune and inflammatory syndromes induced by vaccine adjuvants are the suspected factors. Hyperstimulation of the

immune system and MM of the vaccine components has been hypothesized.⁸²

The hypotheses explaining PA are inflammatory or immune reactions, leading to endothelial dysfunction. The latter produces hyperpermeability, which increases the risk of hemorrhages.⁸³ Both the immensity and fragility of the vessels of pituitary make it vulnerable to apoplexy.

Olfactory Dysfunctions

Olfactory dysfunctions (hyposmia, anosmia, parosmia, and phantosmia) have resulted after the first and second dose of AZV and after the second dose of Pfizer vaccine. The disorder may last up to 6 weeks.^{84,85} Its pathophysiology is unknown. Postvaccination inflammation of the neuroepithelium may be a mechanism. Another hypothesis is the presence of virus in neuroepithelium or olfactory bulb without causing symptoms.

Conclusion

All the currently available SARS-CoV-2 vaccines have more common but harmless, as well as rare but critical, neurological side effects. Therefore, a postvaccination surveillance must be performed to detect serious complications early. Within our limited search, we found that the complications are more frequent among females. The mechanism of most complications remains unclear, but autoimmunization and MM play a great role in the development of these complications. This understanding is important because adverse effects are the primary cause of vaccine hesitancy.

Conflict of Interest

None declared.

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