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A review of long-term neurological side sequalae Associated of COVID-19 vaccinated subjects

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مراجعة للآثار الجانبية العصبية طويلة المدى المرتبطة بالأشخاص الذين تلقوا لقاح كوفيد-19

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Abstract:
The neurological sequelae of COVID-19 vaccination have been the subject of investigations, due to cases of prolonged neurological symptoms in a fraction of vaccinated individuals. Although COVID-19 vaccines are highly efficacious in preventing severe disease and death, rare cases of adverse events including neurological symptoms have been reported. Objective: This review seeks to summarize existing evidence of potential chronic neurologic effects that vaccination could bring about such as chronic headaches, neuropathies, cognitive dysfunction or in rare cases autoimmune-mediated conditions such as Guillain–Barré syndrome or transverse myelitis. The pathophysiological mechanisms underlying these sequences of events are incompletely understood but may involve immune-mediated, molecular mimicry, or genetic and environmental susceptibility factors. A major methodologic challenge is to distinguish the temporal associations of vaccine-related effects versus background conditions unrelated to vaccination or neuro-complications from a prior SARS-CoV-2 infection. Recent findings Current data are limited owing to the rarity of these events, reliance on self-reported symptoms, and lack of long-term, population-based cohort studies. These potential sequelae warrant routine surveillance and external validation through rigorous epidemiological studies and mechanism-based research to more specifically characterize their incidence, risk factor associations and short and longer-term prognosis. These efforts are critical for public health planning and implementation, mitigation of vaccine adverse events and communication to reduce vaccine hesitance by allowing clear communication of the risks and benefits of vaccines.

Keywords: COVID-19, Ischemic Stroke, Delirium, Seizers, Tinnitus, COVID-19 vaccines.

الملخص
كانت العواقب العصبية للقاح كوفيد-19 موضوعًا للتحقيقات، بسبب حالات الأعراض العصبية المطولة في جزء من الأفراد الذين تم تطعيمهم. وعلى الرغم من فعالية لقاحات كوفيد-19 في الوقاية من المرض الشديد والوفاة، فقد تم الإبلاغ عن حالات نادرة من الأحداث السلبية بما في ذلك الأعراض العصبية. الهدف: تسعى هذه المراجعة إلى تلخيص الأدلة الموجودة على التأثيرات العصبية المزمنة المحتملة التي يمكن أن يسببها التطعيم مثل الصداع المزمن، أو الاعتلالات العصبية، أو الخلل الإدراكي، أو في حالات نادرة الحالات التي يسببها المناعة الذاتية مثل متلازمة غيلان باريه أو التهاب النخاع المستعرض. الآليات المرضية الفسيولوجية الكامنة وراء هذه التسلسلات من الأحداث غير مفهومة تمامًا ولكنها قد تنطوي على عوامل مناعية أو محاكاة جزيئية أو عوامل حساسية وراثية وبيئية. يتمثل التحدي المنهجي الرئيسي في التمييز بين الارتباطات الزمنية للتأثيرات المتعلقة باللقاح مقابل الظروف الخلفية غير المرتبطة بالتطعيم أو المضاعفات العصبية من عدوى سابقة بفيروس سارس-كوف-2. النتائج الأخيرة البيانات الحالية محدودة بسبب ندرة هذه الأحداث، والاعتماد على الأعراض المبلغ عنها ذاتيًا، والافتقار إلى دراسات طويلة الأجل قائمة على السكان. وتستدعي هذه المضاعفات المحتملة المراقبة الروتينية والتحقق الخارجي من خلال الدراسات الوبائية الدقيقة والبحوث القائمة على الآلية لتحديد حدوثها وارتباطات عوامل الخطر والتشخيص على المدى القصير والطويل بشكل أكثر تحديدًا. هذه الجهود حاسمة للتخطيط للصحة العامة وتنفيذها، والتخفيف من الآثار السلبية للقاح والتواصل للحد من التردد في التطعيم من خلال السماح بالتواصل الواضح بشأن مخاطر وفوائد اللقاحات.

الكلمات المفتاحية: كوفيد-19، السكتة الدماغية الإقفارية، الهذيان، النوبات، طنين الأذن، لقاحات كوفيد-19.

Introduction

This virus – SARS Covid-2 – we were to first experience in the wild in December 2019. It was a higher viral load virus with a short time in between outbreaks in several parts of the world. The World Health Organization had to declare a global health emergency after that situation in 2020. The virus is responsible for pulmonary pneumonitis and hypoxia [1]. WHO figures [2] show that 630.3 million people have been diagnosed with COVID-19 and 6.58 million deaths worldwide as of Nov. 2022.

The first vaccines to save the pandemic came way back in early 2021. Besides, this disease has reached nearly 68.2% fertile world citizens having been recommended and authorized for the permanent use of vaccines.

These four COVID-19 vaccine strategies include nucleic acid-based vaccines (DNA– mRNA), viral vector (replication–non-replication) vaccines, live inactivated (or attenuated) virus vaccines, and protein (spike protein or its subunits) vaccines. For nucleic acid and adenovirus vectored vaccines, pieces of the virus mRNA or genome enter the human cells and cause the human cells to produce viral antigens [3]. They are later recognized as antigens and promote the development of antibodies against those viral proteins. Inactivated or protein viruses and protein viruses can be used as antigens to induce immune responses in vaccines [4]. Since phase 3 of clinical studies, World Health Organization has approved 11 candidate vaccines for mass vaccination against COVID-19 as of November 2021. But to show whether it is effective for safety & side effects, we need phase 4 of clinical studies. That the phase 4 studies results are the appropriate gold standard of how well the vaccine works [5].

Although vaccines have been acknowledged as the safest and most efficient drugs ever known, specific side effects of vaccines have been reported, such as the association between demyelinating syndromes and influenza, hepatitis, and HPV vaccines 1, 2, 3, and the incident of narcolepsy in young people following influenza vaccine injection [4, 5].

The adverse effects of each vaccine should be tracked carefully because these COVID-19 vaccines are fast-tracked approved meaning they skip the normal clinical trials. We should pay attention because, in mass vaccination, incidence of adverse effects of vaccination is relatively high due to different races, disease histories, ages, lifestyles and other effective factors [7]. The medium- and long-term outcome of COVID-19 vaccination looks very good as regards the level of adverse effects, at least based on data from the CDC, VAERS and EMA databases, but for certain vaccines intermediate and long-term adverse effects had been noted, which in the long run might turn out as quite concerning. You should identify and treat VST as the most serious condition as soon as possible. So, physicians and medical center staff affiliated with animals in these patients must identify and respond to these complications as early as possible.

Neurological complications following COVID-19 vaccination

Based on various reports from VAERS database, Vaccines induce a range of local and systemic neurological complications associated with COVID-19 that can affect individuals from mild to severe, according to age, sex, history of disease and associated immunity. Complications

They typically manifest between 1 day to 1 month following injection and are characteristically acute, transient, and self-resolving; however, in severe cases, they require hospitalization and intensive care [8] in contrast, neurological complications are most common in women as they provoke a higher immune response towards foreign antigens [9]. We are more often talked about adverse reactions after the second dose of the vaccine than after the first one.

The neurological and mild effects include weakness, numbness, headache, dizziness, and imbalance, which are more common than independently reported melancholic fatigue, muscle spasms, joint pain, restless leg syndrome, and less common than tremor, tinnitus, and herpes zoster. On the other hand,

Bell's palsy, Guillain–Barre syndrome (GBS), strokes, seizures, anaphylaxis, and demyelinating syndromes, such as transverse myelitis and acute encephalomyelitis [10]. Among them, the most serious side effect of COVID-19 vaccines, in particular, the adenovirus-based, occurs in women of childbearing age: cerebral venous sinus thrombosis.

To facilitate the understanding of COVID-19 vaccination-related side effects, the systemic classification has presented in Fig. 1.; the mechanisms, ectopic immune reactions, molecular mimicry, have been

suggested for the potential pathogenicity of vaccines and the subsequent development of these complications.

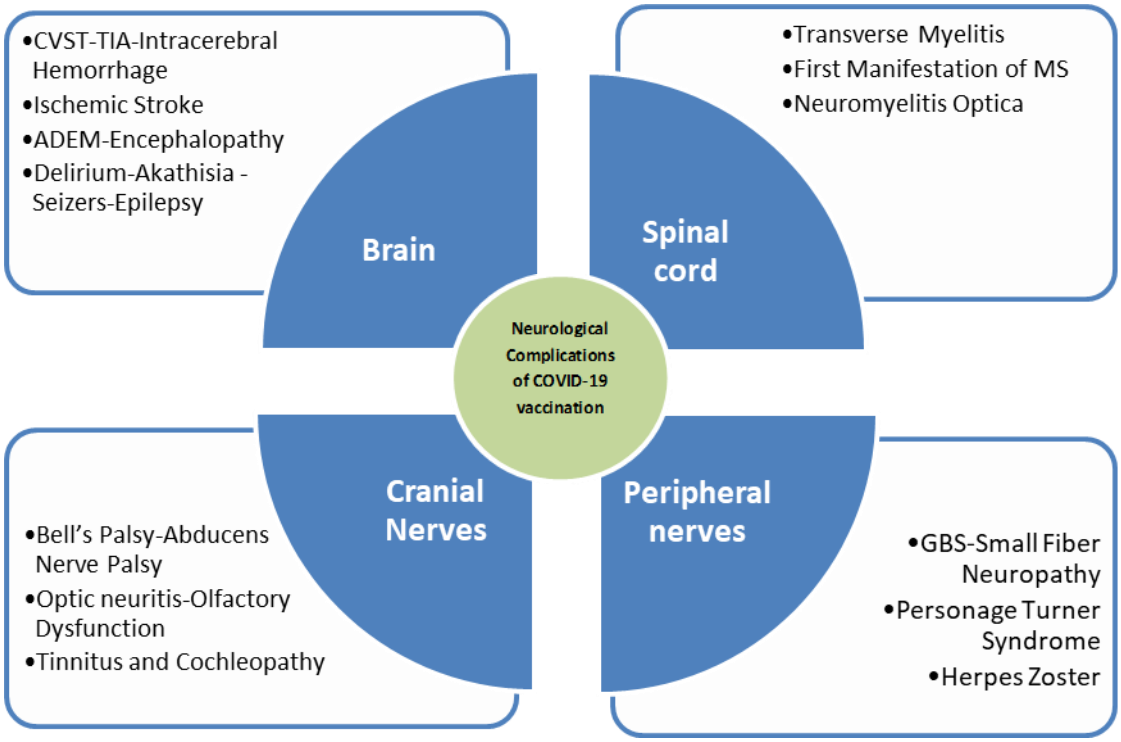

Figure 1: Classification of neurological problems following COVID-19 immunization.

Neurological complications involving the brain following COVID-19 vaccination

SARS-CoV-2 caused a global pandemic, but COVID-19 vaccines are helping end morbidity and mortality posed by it. Nevertheless, there are reports of adverse events, especially rare neurological complications following vaccination. Of these, CVST, TIA, and ICH may be of particular interest given their possible seriousness. Although the advantages of vaccination unquestionably exceed the risks, these events demand improved knowledge in relation to their pathophysiology, clinical presentation, and management. The current review discusses the cerebrovascular complications related to COVID-19 vaccination, with particular regard to the VITT-associated ones.

2. CVST-TIA-Intracerebral Hemorrhage

*** Cerebral Venous Sinus Thrombosis (CVST)**

Cerebral venous sinus thrombosis (CVST) is thrombosis in the dural venous sinuses with impaired venous drainage, increased intracranial pressure and possible hemorrhagic infarction. POSTVACCINATIONAL CVST IS PRIMARLY RELATED TOADI (CVST)–In the postvaccination phase, CVST has mostly been linked to adenoviral vector-based vaccines, such as those developed by AstraZeneca (ChAdOx1-S) and Johnson & Johnson (Ad26. COV2. S). This is due to the underlying mechanism often being associated with VITT, a rare immune-mediated disorder that is similar to heparin-induced thrombocytopenia (HIT) [11]. Platelet activation, thrombosis, and thrombocytopenia in the context of vaccine-induced immune thrombotic thrombocytopenia (VITT) possibly develop due to a mechanism in which vaccine components result in an antibody response to platelet factor 4 (PF4).

CVST after adenovirus-based vaccines likely happens at ~1–2 cases per 100,000 doses; it occurs more frequently in younger women. Risk factors include previous episodes of thrombophilia, use of hormonal contraceptives, and previous thromboembolic episodes.

Such patients with post-vaccination CVST commonly manifested with a severe headache, focal neurological deficit, seizure, or papilledema. Imaging that is used to confirm a diagnosis includes Magnetic Resonance Venography (MRV) or Computed Tomography Venography (CTV), which are the modalities of choice. Diagnosis of VITT is supported by laboratory findings with thrombocytopenia and elevated D-dimer levels [12].

Management consists of treating with non-heparin anticoagulants, for example, direct oral anticoagulants (DOACs) or fondaparinux, in order not to worsen the VITT. Intravenous immunoglobulin (IVIG) neutralizes PF4 antibodies and stops the immune-driven process. In extreme situations, endovascular interventions may be necessary [13].

*** Transient Ischemic Attack (TIA)**

Transient ischemic attack (TIA) as an episode of short-lived neurological dysfunction without infarction has seldom been mentioned following COVID-19 vaccination. The pathophysiology is less well characterized but may involve vaccine-induced hypercoagulability, endothelial dysfunction, or microvascular thrombosis. Although TIA is more frequently related to pre-existing cardiovascular risk factors, its presence following vaccination is important to explore [14].

TIA after vaccination has been extremely rare and usually occurs in those with relevant predisposing factors, such as atrial fibrillation or carotid artery stenosis. Clinical features comprise sudden weakness, speech disturbances, visual deficits, and in most of cases, symptoms get back to normal within a few minutes to a couple of hours [15].

Clinically based, imaging is used to rule out infarction or other structural abnormalities in the diagnosis of TIA. Management consists of secondary prevention (including antiplatelet therapy, anticoagulation for atrial fibrillation, and aggressive risk factor modification).

* **Intracerebral Hemorrhage (ICH)**

Intracerebral hemorrhage (ICH), which is bleeding into the brain parenchyma, has occurred very rarely after receiving a vaccine for COVID-19. The mechanism could be linked to either VITT, especially for adenovirus-based vaccines, [15], or coagulopathy from overdose anticoagulation in post-vaccination thrombosis patients [16].

The incidence of ICH following vaccination is rare, and usually occurs in patients with risk factors such as hypertension, cerebral amyloid angiopathy, and use of anticoagulants. The common presentation of ICH includes sudden focal neurological deficits, decreased level of consciousness, and increased intracranial pressure. Non-contrast CT is the diagnostic gold standard, allowing for rapid assessment of both hematoma location and volume.

The treatment consists of blood pressure management, the reversal of the anticoagulation and surgical treatment in some cases. In patients with ICH associated with VITT, IVIG and non-heparin anticoagulants are administered to treat the underlying immune-mediated process when VITT is suspected [17].

2. Ischemic Stroke

Over the past few months, rare cases of ischemic stroke, defined as the occlusion of cerebral arteries, following COVID-19 vaccination have been described. In the case for adenovirus-based vaccines, VITT may be implicated in the pathophysiology, or other mechanisms associated with vaccine-induced endothelial dysfunction or hypercoagulability may be responsible. Widespread platelet activation and generation of thrombin in VITT can also lead to arterial thrombosis in patients [18].

Ischemic stroke after vaccination is rare and most of the cases were reported to be among those patients who had a strong predisposition to develop stroke, including those with atrial fibrillation, atherosclerosis or previous stroke. Both adenovirus-based and mRNA vaccines have been described as being associated with ischemic stroke; however, the association with adenovirus-based vaccines is more robust.

Individuals with ischemic stroke typically develop focal neurological deficits — hemiparesis, aphasia, or visual field deficits — that come on suddenly. Imaging is also a means to confirm the diagnosis, with non-contrast CT or MRI being the primary modalities of diagnosis. Patients with VITT-related ischemic stroke can have laboratory evidence of thrombocytopenia and increased levels of D-dimer [18].

Reperfusion therapy (ie, intravenous thrombolysis with tissue plasminogen activator [tPA] or mechanical thrombectomy) is given according to the time of presentation and imaging findings in management of ischemic stroke. VITT-associated ischemic stroke is treated with non-heparin anticoagulation and IVIG to treat the underlying immune-mediated process [19].

3. ADEM-Encephalopathy

ADEM is a very rare vaccination complication, most vaccines have an incidence of 0.1–0.2 per 100000 vaccine doses. The cases of ADEM following COVID-19 vaccination are reported only as single case reports or small case series and consequently the real incidence of this complication is difficult to evaluate [20].

Vaccines based on mRNA: Several cases of ADEM have been documented after Pfizer-BioNTech and Moderna vaccines. In most of these cases, vaccination had occurred within the previous days to weeks.

Adenovirus – based vaccines: VITT has been associated with AstraZeneca (AZD1222) and Johnson & Johnson (JNJ – 78436735) vaccines, ADEM has been also reported.

ADEM following immunization against COVID-19 tends not to have well-defined risk factors [21], but may include a history of autoimmune disorder or preceding demyelinating events.

Clinical presentation ADEM usually manifests days to weeks after vaccination and is defined by:

- Encephalopathy: Change in mental state, disorientation, or diminished responsiveness.
- Focal neurological signs: Weakness, ataxia, visual disturbances, or sensory deficits.
- Seizures — occasionally in severe cases.
- Fever and malaise may associate with neurological symptoms.

The clinical presentation of ADEM may overlap with other post-vaccinated neurological syndromes including transverse myelitis, or Guillain-Barre syndrome, requiring a careful evaluation to exclude alternative diagnoses.

ADEM is diagnosed based on clinical presentation, imaging findings and the exclusion of other causes of CNS inflammation [22]. Key diagnostic tools include:

Magnetic Resonance Imaging (MRI) — ADEM is characterized by multiple, asymmetric lesions in the white matter which sometimes enhances with gadolinium. Lesions may also be located in the basal ganglia, thalamus, or at the level of the brain stem.

Cerebrospinal fluid (CSF) analysis may show mild pleocytosis and elevated protein levels, but oligoclonal bands are usually absent, helping to distinguish ADEM from multiple sclerosis.

Serological Testing: Testing in order to eliminate other diagnoses by checking for infectious or autoimmune causes.

Immunomodulatory therapies for the mitigation of CNS inflammation and the promotion of recovery are used in the management of ADEM [22]. Treatment options include:

- Intravenous methylprednisolone (1 g/day for 3–5 days) — High-dose corticosteroids are the first-line treatment for ADEM.
- Intravenous Immunoglobulin (IVIG): Reserved for steroid-resistant cases or cases affecting patients with contraindications to steroids.
- Depending on the severity and/or refractory nature of the condition, therapeutic plasmapheresis may also be considered to remove pathogenic antibodies.
- Supportive care: It includes seizure management, rehabilitation and preventing complications.

The majority of individuals with ADEM have a good response to treatment with marked neurological improvement over weeks to months. Nevertheless, in others, there may be some residual or rarely, progression to chronic demyelinating disorder.

ADEM Following COVID-19 Vaccination: A series of CASE REPORTS

There are multiple case reports of ADEM following COVID-19 vaccination:

- **Case 1:** A 56-year-old female with ADEM with onset 10 days after the AstraZeneca vaccine His clinical manifestations included confusion, ataxia, and visual disturbances. Neuromyelitis optica (NMO) was the diagnosis in one patient, who had multifocal white matter lesions by MRI and responded well to corticosteroid therapy.[23]

•**Case 2:** A 42-year-old male with ADEM 14 days after Pfizer-BioNTech vaccine He had encephalopathy and hemiparesis. MRI suggestive of ADEM was present, and the patient improved with IVIG.[24]

•**Case 3:** A 72-year-old female presented with ADEM after the Johnson & Johnson vaccine. Her initial presentation included seizures and an altered level of consciousness. MRI revealed diffuse demyelination, and she was treated with a combination of corticosteroids and plasmapheresis.[25]

These cases exemplify the different approaches in clinical presentation and treatment response; thus, we recommend individualized management.

4. Delirium, Akathisia, Seizers

*** Delirium**

Delirium is an acute neuropsychiatric syndrome associated with disturbances in attention, cognition, and consciousness. Pathophysiology of Delirium Following COVID-19 Vaccination The exact pathophysiology of post-COVID-19 vaccination delirium is unclear, but may include:

• **Cross talk via systemic inflammation:** Vaccination elicits a strong immune response as vaccines directly boost antibody production/activation in the peripheral system, specifically the blood circulation leading to enhanced release of pro-inflammatory cytokines such as IL-6, and TNF-α that have the capacity to breach blood-brain barrier integrity and to affect neurotransmitter system function.

• **Neurotransmitter derangement:** An imbalance of acetylcholine, dopamine, and serotonin maybe partake in the cause of delirium.

• **Existing susceptibility**: Older adults and those suffering with pre-existing cognitive impairment or systemic illness may be more at risk.

Post-COVID vaccination delirium is an uncommon phenomenon which has primarily described in elderly patients or those with underlying neurological or systemic diseases. Although the incidence of liver abscess is difficult to estimate because of lack of data, it is likely an uncommon event, based on existing case reports.[26]

Delirium has a clinical onset that occurs hours to days after vaccination and is described as follows:

• New confusion or altered mental status.
• Altered states of awareness.
• Dysfunction of cognitive process such as memory and attention.
• Change in behavior, such as agitation or lethargy.

Diagnosis is clinical and based on criteria such as the Confusion Assessment Method (CAM). To exclude other causes of delirium, laboratory and imaging studies may be necessary.[27]

Delirium management is mainly dependent on controlling the underlying causative agent and its supportive therapy:

•**Non-pharmacological:** Reorientation, hydration, nutrition, and environmental (i.e., noise and light).

• **Pharmacological:** Antipsychotics (e.g., haloperidol) may be used in severe case scenario but should be used sparingly, particularly in older adults [27].

*** Akathisia**

Akathisia is another movement dysfunction that is often described as an inner sensation of restlessness and an unmet need to remain still. Akathisia is most often associated with antipsychotic medications but also occurs rarely after COVID-19 vaccination.[28]

The mechanisms which they propose are:

•**Dysregulation of dopaminergic system (dopaminergic dysregulation**): The immune activation caused by the vaccine may interfere with dopamine system in the basal ganglia, causing akathisia.

•**Neuroinflammation:** Pro-inflammatory cytokines may get in the way of normal motor control pathways.

Akathisia is rare as a complication of COVID-19 vaccination, and only rare case reports are found in the literature. Risk factors include a previous history of movement disorders, psychiatric disorders or sensitivity to change in dopaminergic function.

Akathisia most often looks like:

- •Inner agitation which is a sense if feeling restless inside.
- •Overt motoric symptoms, such as walking back and forth, fiddling or inability to stay seated.
- •Emotional distress (anxiety, overreacting, being irritable, etc.)

Diagnosis is based on patient history and observation of motor symptoms. Assessment of severity may use the Barnes Akathisia Rating Scale (BARS).[28]

Treatment for akathisia includes:

•**Pharmacological treatment**: β-blockers (e.g., propranolol)، benzodiazepines (e.g., clonazepam) or anticholinergic agents (e.g., benztropine) may work.

• **Symptomatic relief:** Observation and reassurance for improvement of symptoms [29].

*** Seizures**

Seizures post Covid vaccination is uncommon and can happen in patients with or without chronic epilepsy [30]. These mechanisms have been proposed:

Burden of ill effects:

- **• Seizures related to fever:** Fever following vaccination may lower the seizure threshold, especially in small children or people with epilepsy.
- **• Neuroinflammation:** The release of cytokines following vaccination may alter neuronal excitability mechanisms, promoting seizure activity.
- **• immune effects (direct):** It is likely a mechanism of autoimmunity in rare cases — antibodies against neuronal antigens.

Vaccination against COVID-19 causes seizures at a rate of less than 1 in 100,000 doses, a rare phenomenon. Risk Factors for a Calamity include past medical history of epilepsy, febrile seizure, and any other neurological condition.

Seizures may present as:

- • Generalized tonic clonic seizure.
- • Focal seizures with/without impaired awareness.
- • In severe cases, status epilepticus.

Diagnosis is through clinical and EEG data, and imaging studies to rule out structural or metabolic causes [31].

Seizure management involves:

- **• Treatment of immediate symptoms:** Seizure Termination for Acute-Benzodiazepines (e. g., lorazepam)
- **• Chronic treatment:** Changes in the antiepileptic drugs in already existing epileptics.

• **Supportive care:** watch for recurrent illness and management of inciting factors, such as Fever [31].

Neurological complications involving the Spinal Cord following covid 19 vaccination

1. **Transverse Myelitis**

Transverse myelitis (TM) is an immune-mediated, inflammatory, rare disorder of the spinal cord with various degrees of motor, sensory, and autonomic dysfunction. Acute transverse myelitis (ATM) is a rare neurological disorder characterized by inflammation of the spinal cord which can be caused by a variety of causes such as infections, autoimmune disorders and vaccinations. Although COVID-19

vaccines have been widely deployed and have helped curb the pandemic, they have been linked to infrequent adverse events such as TM. This review summarizes the available evidence about the frequency, pathophysiology and treatment of TM after vaccination against COVID-19.[32]

The trigger-motivated or TM reporting of post-COVID vaccination continues to be extremely low. A total of 593 TM cases were reported globally after COVID-19 vaccination from more than 11.7 billion doses administered so far, according to the Vaccine Adverse Event Reporting System (VAERS)[5]. Another substantial study assessing 99 million vaccinated persons found TM described to the database as a possible AE, showing an estimated incidence of 1.82 cases/million doses [32]. Importantly, these findings highlight the rarity of TM post-vaccination, especially in relation to the substantial morbid and mortal benefit from COVID-19 vaccination.

The immunopathogenic mechanisms of TM after COVID-19 vaccination are suspected to be mediated by the immune response. The (Pfizer-BioNTech and Moderna) mRNA-based (AstraZeneca and Johnson & Johnson) and viral vector-based platforms vaccines may induce an abnormal immune response. This in turn can be through processes like molecular mimicry, where the antibodies created by the vaccine cross-react with spinal cord antigens, or it can be through direct activation of inflammatory pathways [33]. Although the spike protein precipitation are the vaccine-encoded proteins of SARS-CoV-2 and interactions with angiotensin-converting enzyme 2 (ACE2) receptors have been considered to promote neuroinflammation.[16]

Symptoms of TM usually appear suddenly or in a short span of time, and can include limb weakness, sensory deficits, or autonomic dysfunction with bowel or in bladder urgency, frequency, or incontinence. In cases with post-vaccination symptom onset, this has been reported days to weeks after immunization. One example is the report of longitudinally extensive transverse myelitis (LETM) that occurred six days after administration of the Moderna vaccine, manifested by paresthesia and gait disturbance (Gao et al., 2021). There is a report that 21% of patients with TM also experienced symptoms within 1 week of obtaining vaccination.[34]

Diagnosis of TM is made clinically, with imaging and CSF analysis. While patients with multiple sclerosis usually have multifocal lesions that are hyperintense in T2-weighted magnetic resonance imaging (MRI), LETM is characterized by hyperintense lesions that extend over multiple vertebral segments in the spinal cord. Cerebrospinal fluid (CSF) analysis can demonstrate pleocytosis, increased protein, and oligoclonal bands indicating an inflammatory process.[35]

TM is managed with immunosuppressive therapies, including high-dose corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIG). Although most improve, some remain with neurologic deficits. For instance, Medavarapu et al. indicated that 10% of TM patients needed further treatments like plasmapheresis or IVIG, in particular in children. Infrequently, paraplegia or death has been documented as an outcome [34].

2. First Manifestation of Multiple Sclerosis

Immediate post-vaccination first demyelinating event of MS is extremely uncommon. Between billions of doses of COVID-19 vaccines administered globally, a systematic review reported 23 cases of new-onset MS temporally associated with COVID-19 vaccination. Such cases are estimated to occur in less than 1 in a million doses, indicating this phenomenon is rare. The majority of reported cases were after delivery of mRNA-based vaccines (Pfizer-BioNTech and Moderna), but cases were also seen following viral vector vaccines (AstraZeneca and Johnson & Johnson).[36]

Although the pathogenesis of Covid-19 vaccine related MS is not entirely clear, it is likely to be immune-mediated. Vaccines provoke strong immune responses, which can, though rarely, lead to autoimmunity in people who are genetically predisposed. For instance, the mechanism of molecular mimicry, in which antibodies induced by the vaccine cross-react with CNS antigens, has been suggested as a possible explanation. Similarly, the pro-inflammatory cytokine response of the immune system to vaccination may act to worsen pre-existing subclinical autoimmunity, thus resulting in the clinical manifestation of MS [36]. These causal mechanisms are also still speculative and require further, detailed research .[36]

Manifestations may range from optic neuritis, transverse myelitis, events of isolated brainstem syndrome, or multifocal neurological deficits. A case series showed median time to symptom onset was 14 days following vaccination, and most patients presented with optic neuritis or transverse myelitis. In these patients, MRI findings were compatible with demyelinating lesions typical of MS, with

periventricular, juxtacortical, and infratentorial distribution often meeting the 2017 McDonald diagnostic criteria for MS.

In these instances, the diagnosis of MS is made according to clinical, radiological, and laboratory data. MRI is fundamental in diagnosing MS, where the characteristic lesions are hyperintense on T2-weighted images in the white matter of the CNS. Analysis of the cerebrospinal fluid (CSF) may show the presence of oligoclonal bands, a sign of intrathecal IgG synthesis. Of note, the temporal relationship with vaccination does not imply causation, and other conceivable triggers or predisposing factors should be carefully assessed.[37]

Management of post-COVID-19 MS is largely identical to that of idiopathic MS: acute relapses are often managed with high-dose corticosteroids, whereas DMTs are used for long-term prevention of relapses and progression. The vast majority of post-vaccination MS cases have had a good response to standard treatments, and there is no evidence of increased severity or atypical course of the disease. Nevertheless, long-term follow-up data are limited and need confirmation in a larger cohort to evaluate prognosis of these patients.

3. Neuromyelitis Optica

Neuromyelitis Optica spectrum disorder (NMOSD) is an uncommon, autoimmune demyelinating disease of the CNS mainly affecting the optic nerves and spinal cord. Characterized by dramatic relapses, including optic neuritis and longitudinally extensive transverse myelitis (LETM) Associated with aquaporin-4 IgG antibodies (AQP4-IgG) Although NMOSD according to its etiology is multifactorial and requires genetic predisposition with environmental factors, there have been case reports which suggest association of COVID-19 vaccination with development of NMOSD [38]. This review summarizes the available evidence about NMOSD after vaccination against COVID-19, in terms of epidemiology, pathophysiology, clinical presentation and implications for vaccination strategies.

NMOSD is extremely rare after COVID-19 vaccination. Results of the study: one in five million doses Earlier this year, a systematic review of NMOSD cases temporally related to COVID-19 vaccination included 15 cases from around the world, despite more than 2 billion doses delivered. The majority of reported cases have followed mRNA-based vaccines (Pfizer-BioNTech and Moderna), although cases have also been reported after viral vector vaccines (AstraZeneca and Johnson & Johnson) [39]. Finally, the rate of post-vaccination NMOSD has been put at less than 1 per million doses. Crucially, the odds of developing NMOSD after SARS-CoV-2 infection greatly exceed those associated with vaccination.

The mechanism of NMOSD after COVID-19 vaccination are incompletely understood, but post-vaccination NMOSD is possibly based on immune-mediated mechanisms. Vaccines induce strong immune responses, and in some rare individuals with genetic predisposition to autoimmunity, the responses may be exaggerated in a more disease-producing way. A potential mechanism has been proposed, namely, molecular mimicry resulting in cross-reactivity of antibodies induced by the vaccine with CNS antigens [36]. Furthermore, the response mediated by pro-inflammatory cytokines post-vaccination can aggravate pre-existing subclinical autoimmunity and trigger the clinical phenotype of NMOSD. In some of these cases, the role is somewhat more critical in that the finding of AQP4-IgG antibodies has confirmed a diagnosis of NMOSD and implied a specific autoimmune mechanism.

The clinical characteristics of NMOSD post-COVID-19 vaccination are in line with the natural history of NMOSD. They manifest as optic neuritis, severe and painful, resulting in loss of vision, and spinal cord lesions, with motor, sensory and autonomic dysfunction (longitudinally extensive transverse myelitis) [3]. The median time from vaccination to symptom onset was 10 days, and the majority of cases had LETM (61%) [2]. Spinal cord lesions were longitudinally extensive on MRI Positive serology for AQP4-IgG [40] .

In these instances, NMOSD diagnosis is established using clinical, radiological, and serological criteria. MRI usually reveals longitudinally extensive spinal cord lesions (at least three vertebral segments long) and optic nerve lesions in optic neuritis cases. AQP4-IgG antibodies are a specific feature of NMOSD, and serve to genetically and clinically differentiate the disorder from other demyelinating diseases including multiple sclerosis (MS). In seronegative cases the diagnosis depends on clinical and radiological features.

Overview of Management of NMOSD After COVID-19 Vaccination while information about the suggested EMSDA deal with the main suggested approach for managing NMOSD following COVID-19 vaccination. Acute relapses are managed with high-dose corticosteroids and, in severe relapses, by plasmapheresis or intravenous immunoglobulin (IVIG). Immunosuppressive therapies such as

rituximab, azathioprine, or mycophenolate mofetil are then given for longer-term management in order to prevent relapses. The clinical course after NMOSD following vaccination was responsive to standard therapies in most of the reported cases, but some patients developed residual neurological deficits [38]. This has limited data on follow-up data in the long term, and more cases are needed to investigate the prognosis of these patients.

Neurological complications involving the Cranial Nerves following covid 19 vaccination

1. Bell's Palsy, Abducens Nerve Palsy

Vaccines for COVID-19 and the swift global rollout of those vaccines has played a vital role in curbing the spread of SARS-CoV-2 and in lower morbidity and mortality related to infections. Nevertheless, there have been rare reports of neurological complications since every medical intervention induces adverse events. Amongst these, Bell's palsy (BP) and abducens nerve palsy (ANP) have gained significance owing to their purported link to COVID-19 vaccination [41]. This review summarizes the current data on the incidence, pathophysiology, and clinical outcomes of BP and ANP associated with COVID-19 vaccinations, and emphasizes the need for additional studies to better address causality and mechanisms.

Bell's Palsy and COVID-19 Vaccination

Bell's palsy, which is a rare cause of acute unilateral paralysis of the facial nerve, has been referred to among the adverse events of special interest after receiving COVID–19 vaccination. According to a systematic review that included 35 studies, the incidence rate is 25.3 cases per 1,000,000 doses of vaccines, with the majority of cases occurring after the first dose of mRNA vaccines (such as Pfizer-BioNTech and Moderna) and adenoviral vector vaccines (such as AstraZeneca and Sputnik V) [42]. Most patients had unilateral facial paralysis, with left-sided involvement predominant. Overall recovery was good with most cases resolving with corticosteroids and antiviral therapies.

The mechanism of BP post-vaccination is unclear. Suggested mechanisms are related to the immune-induced inflammation, molecular mimicry and reactivation of latent herpes simplex virus (HSV) triggered by the immune response to the vaccine [43]. However, only a small number of BP cases were observed in clinical trials of mRNA vaccines, and the incidence was similar to the background rate in the general population (Albakri et al., 2023). Follow-up monitoring without assigning a causal link has been advised by regulatory agencies including the U.S. Food and Drug Administration (FDA).

Abducens Nerve Palsy and COVID-19 Vaccination

Abducens nerve palsy (the second most common isolated ocular motor nerve palsy) has also been post-vaccination after Corona Virus Disease 2019 (COVID-19) vaccination, but less reported than BP. Illustrated a case of acute ANP occurring in a 59 -year-old female 2 days following her Pfizer-BioNTech vaccine [44]. The isotropic presented with binocular horizontal diplopia and complete abduction deficit of right eye. Thus, a presumptive diagnosis of vaccine-associated ANP after exclusion of other possible etiology were made based on MRI and laboratory investigations. It resolved on its own in weeks, typical for many cranial neuropathies after vaccination which did not require further management.

The exact mechanisms of ANP after vaccination remain unclear. Possible mechanisms include vaccine-driven immune-mediated demyelination, localized vasculitis, or microvascular ischemia. There have been similar cases with other vaccines like flu and measles-mumps-rubella [45], which points to a common underlying pathophysiological pathway.

Comparative Risk: Vaccination vs. SARS-CoV-2 Infection for Bell's Palsy, Abducens Nerve Palsy

Thus, the risk of BP and ANP after vaccination must be compared to the neurological complications associated with SARS-CoV-2 infection itself, which is essential for proper context." In addition, several cranial neuropathies have been associated with COVID-19, including bilateral peripheral (BP) [38,39] and acute neuropathic pain (ANP) [40] with incidence rates higher than that observed post-vaccine. A compelling example of this is SARS-CoV-2 infection that can either directly enter the nervous system through angiotensin-converting enzyme 2 (ACE2) receptors or induce damage via an immune-mediated mechanism resulting in cranial nerve dysfunction [45]. Therefore, the potential harms of rare adverse events pale in comparison to the benefits of vaccination in the prevention of severe COVID-19 and its associated neurological sequelae.

2. Optic neuritis, Olfactory Dysfunction

The fast development and fast immunization of COVID-19 vaccines as a cause of SARS-CoV-2. The striking safety and efficacy of these vaccines has been well-documented, although rare adverse events have been described, including neurological adverse events. Notably, optic neuritis (ON) and olfactory

dysfunction (OD) are considered as post-vaccination phenomenon [46]. This review discusses the currently available evidence on the incidence, pathophysiology and patient outcomes following both ON and OD post vaccination and highlights the importance of additional research to determine whether a causal relationship exists and whether a mechanism may underpin this association.

*** Optic Neuritis and COVID-19 Vaccination**

Optic neuritis is an inflammatory demyelinating condition of the optic nerve which presents with acute vision loss, ocular pain with movement, and visual field defects. Although ON is primarily seen in multiple sclerosis and other autoimmune diseases, it has infrequently occurred after COVID-19 vaccination.

Incidence and Clinical Presentation

There have been multiple case reports and several case series of ON in individuals who received the COVID-19 vaccine. A 35-year-old woman presented with unilateral vision loss and retro-orbital pain 3 days following the Pfizer-BioNTech vaccine [47]. MRI demonstrated enhancement of the optic nerves consistent with ON. Also, bilateral ON in a 21-year-old male after AstraZeneca vaccine [48]. The majority of cases followed the first dose, with the symptoms typically occurring within days to weeks after getting vaccinated.

Pathophysiology

The exact pathophysiological mechanisms of ON following vaccination remain a matter of speculation. Potential mechanisms include a molecular mimicry whereby the vaccine induced immune response targets myelin antigens, and/or immune-mediated inflammatory processes initiated by adjuvants contained in the vaccine formulation [47]. It has also been proposed that latent, and perhaps innocuous (at least until the lupus diagnosis), autoimmune mechanisms have been activated in genetically influenced individuals. Importantly, ON has also been described after other vaccines, including seasonal influenza and hepatitis B vaccines, suggesting a possible common immunological pathway [48].

Outcomes and Management

The general prognosis of ON after COVID-19 vaccination seems to be good, with most patients responding to high-dose corticosteroids. Nevertheless, long-term follow-up is required to keep an eye out for recurrence or development to other demyelinating diseases, such as several sclerosis or neuromyelitis Optica spectrum condition (NMOSD).

*** Olfactory Dysfunction and COVID-19 Vaccination**

Anosmia (loss of smell) and hyposmia (reduced sense of smell) as exploratory highlights of SARS-CoV-2 infection, olfactory dysfunction has been broadly perceived as typical symptom of SARS-CoV-2 contamination. But the report of OD after COVID-19 vaccination has been rare, with clinical significance and possible mechanisms being questioned [49].

Incidence and Clinical Presentation

Isolated case reports have described post-COVID-19 vaccination OD. For instance, a 42-years-old female patient with anosmia and dysgeusia two days following the Moderna vaccine [50]. All patients had mild, temporary symptoms, which disappeared spontaneously in less than 2 weeks. In the same way, a case series reported OD in three patients after mRNA-based vaccines with an interval of 24 hours to 7 days after vaccination [51].

Pathophysiology

However, the underlying mechanisms of OD post-vaccination are not yet clear. Potential hypotheses include immune-mediated inflammation of the olfactory epithelium or olfactory bulb and temporary perturbation of olfactory signaling pathways caused by release of cytokines. Alternatively, OD could reflect a non-specific inflammatory response not related to vaccine. Importantly, OD has been observed with other vaccines, including the flu vaccine, which implies a possible immunology explanation.

Outcomes and Management

OD after vaccination against COVID-19 is usually self-limited, and the majority of cases will resolve within days to weeks, providing no specific treatment is required. In cases of persistency, supportive measures such as olfactory training may help. Importantly, the prevalence of OD following vaccination is many folds lower than the incidence reported with sars-cov-2 infection, wherein anosmia is common and prolonged symptom [49].

Comparative Risk: Vaccination vs. SARS-CoV-2 Infection for Optic neuritis, Olfactory Dysfunction

This risk of ON and OD after vaccination should be put into perspective with the risk of these neurological complications after infection by SARS-CoV-2 itself. COVID-19 has been linked to the central and peripheral nervous system with possible involvement with various neurological manifestations, such as ON and OD—with much higher incidence and severity than those found post-vaccination [51]. SARS-CoV-2 could directly enter the central nervous system through the olfactory route or it can induce immune mediated damage resulting in cranial nerve involvement. Therefore, the advantage of vaccination in preventing serious COVID-19 and its complications far exceeds the risks of rare adverse events.

3. Tinnitus and Cochleopathy

The worldwide vaccination against coronavirus disease (Covid-19) was a significant factor in fighting the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and decreasing the considerable morbidity and mortality associated with it. Although longstanding security information exists for these vaccines and efficacy has been demonstrated in the current health crisis, some rare side effects, these may include auditory and vestibular symptoms. Tinnitus and cochleopathy (inner ear dysfunction) are now possible vaccine-associated phenomena among the above-mentioned [52]. Conclusions The current evidence pertaining to COVID-19 related tinnitus and/or cochleopathy is reviewed, in terms of incidence, pathophysiology and clinical outcomes, highlighting the need for further research, particularly longitudinal studies that could confirm causality and identify mechanisms of effect.

* Tinnitus and COVID-19 Vaccination

Tinnitus, the perception of sound in the absence of an external sound source, is a common and debilitating symptom associated with many conditions that can greatly impact quality of life. It has been reported as an uncommon side effect of COVID-19 vaccination.

Incidence and Clinical Presentation

Several case reports / observational studies have reported tinnitus after COVID-19 vaccination. For example, they studied the Vaccine Adverse Event Reporting System (VAERS) data and found 555 cases of tinnitus after mRNA-based vaccines (Pfizer-BioNTech and Moderna) and adenoviral vector vaccines (AstraZeneca and Johnson & Johnson) [53]. Symptoms usually occurred within a few to many hours of vaccination, and were typically on one side, but bilateral cases were also noted. Tinnitus varied in severity from mild to disabling, and was accompanied by symptoms including dizziness or fullness in the ear in some cases.

Pathophysiology

Speculations are ongoing regarding the mechanisms pertaining to tinnitus following vaccination. Proposed hypotheses include:

Immune-Mediated Cochlear Injury: There is a potential for inflammation of the cochlea or auditory nerve as a consequence of the immune responses to the vaccine that may disrupt the normal auditory process [53].

Microvascular Ischemia: Vaccination activates an immune response, potentially causing transient immune-mediated endothelial dysfunction and subsequent cytokine release leading to microvascular ischemia in the inner ear [54].

Stress and Anxiety: Psychological stress related to vaccination, and to the pandemic at large may worsen existing tinnitus or induce new-onset symptoms [54].

Outcomes and Management

Most of the time, tinnitus is spontaneously resolved or improves with symptomatic treatment, such as corticosteroids or vasodilators, and is usually good after COVID-19 vaccination [8]. But there have also been sporadic cases, leading to a need to learn more about the long-term consequences and how to address them.

* Cochleopathy and COVID-19 Vaccination

Cochleopathy is a pathological process resulting in cochlear dysfunction, which is the sensory organ of hearing, and may present with sensorineural hearing loss (SNHL), vertigo, or other auditory symptoms. Though cochleopathy is a rare adverse event, it has been observed after COVID-19 vaccination [55].

Incidence and Clinical Presentation
Single cases of sensorineural hearing loss (SNHL) following COVID-19 vaccination have been described. As such, one case is a 52-year-old male with new-onset sudden SNHL in left ear two days following Pfizer-BioNTech vaccination [56]. Audiometric testing confirmed interestingly, that her loss was moderate-to-severe, and MRI did not reveal another potential cause. Likewise, a bilateral SNHL case post Moderna vaccine with related tinnitus and vertigo.

Pathophysiology
There is little known about the pathophysiological mechanisms as to why cochleopathy occurs post-vaccination. Hypotheses include

Immune-mediated Damage: The damage cause here involves the breakdown that may cause inflammation of the auditory nerve or demyelinazation of cochlear structures due to immune response by vaccine [56].

Vascular Insufficiency: Vaccine-induced endothelial dysfunction or cytokine release causing microvascular ischemia of the cochlea could lead to SNHL [54].

Autoimmune Activation: Vaccination may reveal or worsen hidden autoimmune disorders, like autoimmune inner ear disease (AIED), leading to cochlear injury [53].

Outcomes and Management
Cochleopathy as a consequence of COVID-19 vaccination has an ambiguous prognosis. Sudden SNHL is an otologic emergency, and high-dose corticosteroids should be started as early as possible to improve the prognosis. In the majority of reported cases, with early administration and other therapeutic treatments hearing was partially or completely restored. Despite this, some instances of long-term hearing impairment have been reported, highlighting the necessity of extended follow-up and further studies.

Comparative Risk: Vaccination vs. SARS-CoV-2 Infection for Tinnitus and Cochleopathy
We must consider risk of tinnitus and cochleopathy after vaccination in relation to the auditory complications of SAR-CoV-2 infection itself. COVID-19 has been linked to a number of different auditory and vestibular symptoms such as tinnitus, SNHL and vertigo, at higher frequencies and severity than reported after vaccination [57]. There are two main mechanisms responsible for auditory dysfunction; direct invasion of the inner ear by SARS-CoV-2 through angiotensin-converting enzyme 2 (ACE2) receptors, or immune mediated damage to structures within the inner ear. However, the risks of rare adverse events from vaccines are vastly outweighed by the benefits of vaccination for preventing severe COVID-19 and complications of the disease.

Neurological complications involving the Peripheral Nerves following covid 19 vaccination

1. Guillain–Barré Syndrome and Small Fiber Neuropathy

International vaccination against COVID-19 has been a key component of the pandemic response to SARS-CoV-2, as it is known to lower the risk of severe disease and death. Although the safety profile for these vaccines is excellent, rare neurological adverse events have been reported including GBS and SFN. The subset of conditions involving immune-mediated damage to the peripheral nervous system have recently raised suspicions of associations with COVID-19 [58]. Objective To summarize the available data regarding the incidence, pathophysiology, and clinical impact of the few reported cases of GBS and SFN post-vaccination for COVID-19 and to explore the research gaps informing causality and mechanism.

* **Guillain–Barré Syndrome and COVID-19 Vaccination**

Guillain–Barré syndrome (GBS) is an acute, immune-mediated polyneuropathy associated with weakness, areflexia, and, less often, respiratory failure. Infections are most common, but they are also sometimes triggered by vaccinations [58].

Incidence and Clinical Presentation
Multiple reports have described cases of GBS following COVID-19 vaccination, especially with adenoviral vector vaccines such as AstraZeneca and Johnson & Johnson (Janssen). In a study that evaluated cases of GBS following COVID-19 vaccination reported to the Vaccine Adverse Event Reporting System (VAERS), a total of 130 cases of GBS were identified, with a higher incidence of GBS following an adenoviral vector vaccine than mRNA vaccine (59). The symptoms appeared 1–4 weeks after vaccination and included ascending weakness, paresthesia and cranial nerve involvement, consistent with the typical presentation of GBS.

Adenoviral vector vaccines have been associated with GBS, albeit rarely, and this potential causation has already been recognized by the European Medicines Agency (EMA), with an incidence of approximately 1–2 per 100,000 doses [60]. Still, the incidence is similar to background rates of GBS in the general population and the risk is much lower than the one associated with the SARS-CoV-2 infection itself.

Pathophysiology

Despite the unknown nature of GBS pathogenesis, it is possible that immune-mediated mechanisms can be attributed to several types of pathogens and immune response after vaccination-related triggering due to molecular mimicry or epitope spreading (5). Proposed hypotheses include:

Molecular mimicry: The vaccine antigen may share structural similarities with components in the peripheral nerve, resulting in cross-reactive immune responses [59].

Immune Dysregulation: A powerful immune activation caused by adenoviral vector vaccines may result in pathological immune responses in susceptible individuals [60].

Outcomes and Management

The overall outcome of GBS after COVID-19 vaccination is good with early treatment. Standard treatments, such as intravenous immunoglobulin (IVIG) and plasmapheresis, are effective in the majority of cases. Yet, there have been severe cases needing mechanical ventilation, emphasizing the need for early identification and treatment (61).

*** Small Fiber Neuropathy and COVID-19 Vaccination**

Damage to small-diameter sensory and autonomic nerve fibers resulting in burning pain, paresthesia, and autonomic dysfunction is known as small fiber neuropathy. SFN is usually linked to autoimmune disorders, diabetes, and other infections; nevertheless, few instances have been documented after COVID-19 vaccination [62].

Incidence and Clinical Presentation

Feedback on the occurrences of SFN after COVID-19 vaccination is scarce but increasing. In a case series, three patients who experienced symptoms of SFN (including burning pain, numbness, and autonomic dysfunction) days to weeks after mRNA-based vaccinations (i.e., Pfizer-BioNTech and Moderna) [63]. As is common for SFN, symptoms were primarily distal in nature and symmetric.

In one other instance report, post-vaccination SFN in a 45-year-old female who developed incapacitating burning pain and dysautonomia within days of the 2nd dose of the Moderna vaccines. Decreased density of intraepidermal nerve fibers, a cardinal diagnostic sign for SFN [64], was confirmed by skin biopsy.

Pathophysiology

The potential mechanisms of SFN after COVID-19 vaccination are largely speculative. Proposed mechanisms include:

2. **Possible Immune-Mediated Inflammation:** Activation of immune responses by the vaccine may promote inflammation and, thus, harm small nerve fibers [65].
3. **Uncontrolled Cytokine Release:** The potent cytokine response induced as a result of vaccination may harm nerve fibers that are already vulnerable in susceptible patients [64].
4. **Autoimmunity**: Vaccination can reveal or aggravate the underlying autoimmune conditions and thus cause SFN [65].

Outcomes and Management

The long-term outcome of SFN after COVID-19 vaccine is heterogeneous. In some patients, these symptoms spontaneously resolve while others need treatment with immunomodulatory therapies (steroids or intravenous immunoglobulin). Patients must be followed over the long term to check for symptom persistence or progression toward other neuropathic disorders.

Comparative Risk: Vaccination vs. SARS-CoV-2 Infection Guillain–Barré Syndrome and Small Fiber Neuropathy

Contextualizing the risk of GBS and SFN after vaccination with the neurological complications after the SARS-CoV-2 infection itself is crucial. There is a strong link between COVID-19 and GBS and SFN with a higher incidence and more severe symptoms compared to the post-vaccination [60]. These may

occur either through direct invasion of the peripheral nervous system by SARS-CoV-2 or as a result of immune-mediated damage. That said, the advantages of vaccination in safeguarding from serious COVID-19 and its sequelae greatly exceed the threats of uncommon unwanted side-effects.

2. Parsonage-Turner Syndrome

The worldwide roll out of COVID-19 vaccines has been a vital tool in the fight against the SARS-CoV-2 pandemic. Although the use of these vaccines and their safety and effectiveness has been proven, rare adverse events affecting peripheral nerve have been documented. Of these, Parsonage-Turner Syndrome (PTS) (also referred to as neuralgic amyotrophy or brachial plexopathy) have recently been described as a newly post-vaccination phenomenon. This review focuses on the current knowledge regarding the incidence, pathophysiology, and clinical consequences of PTS following COVID-19 vaccination and calls for further investigations to confirm causality and mechanisms [66].

Parsonage-Turner Syndrome and COVID-19 Vaccination

Parsonage–Turner syndrome (PTS) is a rare neurological disorder characterized by sudden-onset severe shoulder or upper arm pain, later followed by weakness and atrophy of muscle in the affected region, together with a sensory disturbance. Adams et al discuss typically in association with an immune-mediated inflammation of the brachial plexus or peripheral nerves, and although linked to infections and/or trauma, it has less rarely been associated with vaccinations [66].

Incidence and Clinical Presentation

Although rare, the literature does contain reports of PTS following COVID-19 vaccination. Such as a 42-year-old male, who experienced acute right shoulder pain and arm weakness three days post Pfizer-BioNTech vaccine. Motor conduction studies showed evidence of brachial plexopathy by electromyography (EMG), while imaging excluded structural causes. The same goes for PTS in a 55-year-old woman with symptoms occurring within seven days of AstraZeneca vaccine [67].

PTS symptoms usually start days to weeks after vaccination, with unilateral involvement being more frequent. Affected patients usually complain of severe burning pain in the shoulder or upper arm, and there is progressive weakness and muscle atrophy in the affected limb. Sensory symptoms, such as numbness or paresthesia, may also be present, but are usually less prominent than motor symptoms [68].

Pathophysiology

The mechanism of both pathophysiological events and the time at which they can be hazardous are not entirely established but are believed to result from an immune-mediated response following a COVID-19 booster vaccination. Proposed mechanisms include:

- Immune-mediated inflammation (Vaccination can cause dysregulation of the immune system, resulting in the inflammation and destruction of the brachial plexus or peripheral nerves) [67].
- Molecular mimicry: Vaccine antigens may be structurally similar to components of the nerve and trigger cross-reactive immune responses [25].
- Cytokine-Mediated Damage: A strong cytokine response evoked by vaccination can lead to localized nerve inflammation and damage [68].

Importantly, PTS had already been identified as a potential side effect following the vaccines against influenza, tetanus, and hepatitis B, pointing towards the possibility of a specific immunological mechanism.

Outcomes and Management

Pessimism is generally not indicated regarding the prognosis of PTS associated with COVID-19 vaccination, but the course of recovery may take months. The majority of patients improve gradually over months to years, and some achieve complete symptom resolution. Management is mainly supportive and includes:

- **Pain relief**: Nonsteroidal anti-inflammatory drugs NSAIDs (e.g., ibuprofen), corticosteroids, or neuropathic pain medications (e.g., gabapentin).
- **Assisted Care:** After surgery, rehabilitation is important to help you regain strength and function in the affected limb.
- **Immunomodulatory Therapies:** For severe or refractory disease, intravenous immunoglobulin (IVIG) or plasmapheresis may be considered although evidence for their efficacy in PTS is limited [66].

Comparative Risk: Vaccination vs. SARS-CoV-2 Infection

We must also place the risk of PTS post-vaccination into perspective with the neurological risks of SARS-CoV-2 infection itself. The neurological manifestations ascribed to COVID-19 such as brachial plexopathy may be a consequence of direct viral invasion, of immune-mediated damage, or of a post-infectious inflammatory response [69]. The rate of post-vaccination PTS is far lower than the rate of PTS associated with SARS-CoV-2 infection, highlighting the fact that vaccination against COVID-19 prevents severe disease and its sequelae.

3. Herpes Zoster

The vaccination against COVID-19 appeared as a global initiative for the SARS-CoV-2 pandemic response. Although the safety and efficacy of these vaccines have been well established, rare adverse events have been described, including reactivation of immune responses to endogenous pathogens, most notably herpes zoster (HZ). Following primary infection (chickenpox), the varicella-zoster virus (VZV) remains latent in sensory ganglia and can reactivate at a later time causing herpes zoster, also called shingles [70]. In this review, we summarize the existing data on the epidemiology, pathophysiology, and clinical significance of post-COVID-19 vaccination HZ and stress the need for additional studies to demonstrate a causal relationship and underlying mechanisms.

Herpes Zoster and COVID-19 Vaccination

Incidence and Clinical Presentation

Rare case of herpes zoster following COVID-19 vaccination/Superiorbrasil. Systematic review of 91 cases of HZ post-COVID-19 vaccination, predominance among mRNA-based vaccinees (Pfizer-BioNTech, Moderna), and adenoviral vector vaccines (AstraZeneca, Johnson & Johnson) HZ symptoms began within 1–14 days of the vaccination, although most HZ cases occurred after the first dose.[71]

Patients presented with the classic painful vesicular rash confined to a single dermatome. Some cases reported complications, most notably postherpetic neuralgia (PHN) or disseminated zoster, but these were seen in immunocompromised patients. HZ after vaccination has previously been well documented in immunocompetent and immunosuppressed individuals, but more frequently reported in the immunocompromised setting.

Pathophysiology

Overall, while these reactivation mechanisms of HZ following COVID-19 vaccination are happening, the pathophysiological mechanisms are still largely speculative. Proposed mechanisms include:

- **Immune Dysregulation:** COVID-19 vaccines induce strong immune responses including innate and adaptive immune responses. Such temporary immune activation may disturb the fragile equilibrium between VZV latency and immune surveillance, resulting in reactivation.[72]
- **Cytokine Release:** Release of pro-inflammatory cytokine levels (interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α]) following vaccination may induce reactivation of latent VZV.
- **Stress & Reactivation:** Physiological stress and/or stress post vaccination (fever and systemic inflammation) as well as prolonged bilateral arm movement in the elderly may be a trigger for reactivation of latent HZ (4–6) in susceptible populations.

Importantly, HZ reactivation has been described after other vaccines as well, particularly influenza and hepatitis B vaccines, alluding possibly to intersecting immunologic mechanisms.

Risk Factors

Risk factors for HZ reactivation after COVID-19 vaccination Several risk factors for HZ reactivation after COVID19 vaccination have been identified, including:

• Advanced age —High risk of severe disease are those older adults, because they are likely to have some compromise to cell-mediated immunity.
• Immunosuppression: Increased risk of HZ in patients with HIV, cancer, or undergoing immunosuppressive therapies.
• History of HZ: If a person has a past or previous history of HZ, this individual may be at elevated potential risk of repeat HZ following the vaccination.

Outcomes and Management

The outlook of HZ after COVID-19 vaccination is favorable, with most cases resolving with simple antiviral treatment, such as acyclovir, valacyclovir or famciclovir. Antiviral treatment should be started

as soon as possible to shorten the duration and severity of symptoms and to prevent complications like postherpetic neuralgia (PHN). Hospitalization and intravenous antiviral therapy may be necessary in immunocompromised patients or u patients with disseminated zoster.[73]

Although HZ is rarely reported after COVID-19 vaccination, it carries a potential risk for complications thereby requiring earlier recognition and treatment. This may also be a consideration in high-risk individuals prior to COVID-19 vaccination by previously providing vaccination against HZ (e.g., with the recombinant zoster vaccine) to decrease the likelihood of reactivation.

Comparative Risk: Vaccination vs. SARS-CoV-2 Infection

It is important to put the risk of HZ following COVID-19 vaccination in context of the risk of HZ following SARS-CoV-2 infection. Compared to vaccination, COVID-19 has been linked with a greater incidence of HZ reactivation, which could likely result from the significant immune dysregulation that the virus inflicts [74]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces lymphopenia, reduced T-cell activity, and increased cytokines, which could thereby facilitate VZV reactivation. In summary, the advantages of vaccination in preventing serious COVID-19 or complications thereof greatly exceed the risks of rare adverse events like that of HZ.

Conclusion

The literature from the vaccine studies states that side effects have been included within the mass vaccination strategy for years, but that the effect this mass ['vaccination'] would have is 'more significant' than the side effects. Generally, more adverse effects of COVID-19 vaccination have been observed in individuals with an immune disease history or whose age and physiological condition are more sensitive. Cerebral venous sinus thrombosis (more about AstraZeneca), transverse myelitis (more about Pfizer, Moderna, AstraZeneca, and Johnson & Johnson), Bell's palsy (more about Pfizer, Moderna, AstraZeneca), GBS (more about Pfizer, AstraZeneca, and Johnson & Johnson), and the first manifestation of MS (more about Pfizer); see fig-2. Lastly, whether these disorders are incidental or the vaccine is responsible for them is another question for future studies, continued documentation, and long-term follow-up.

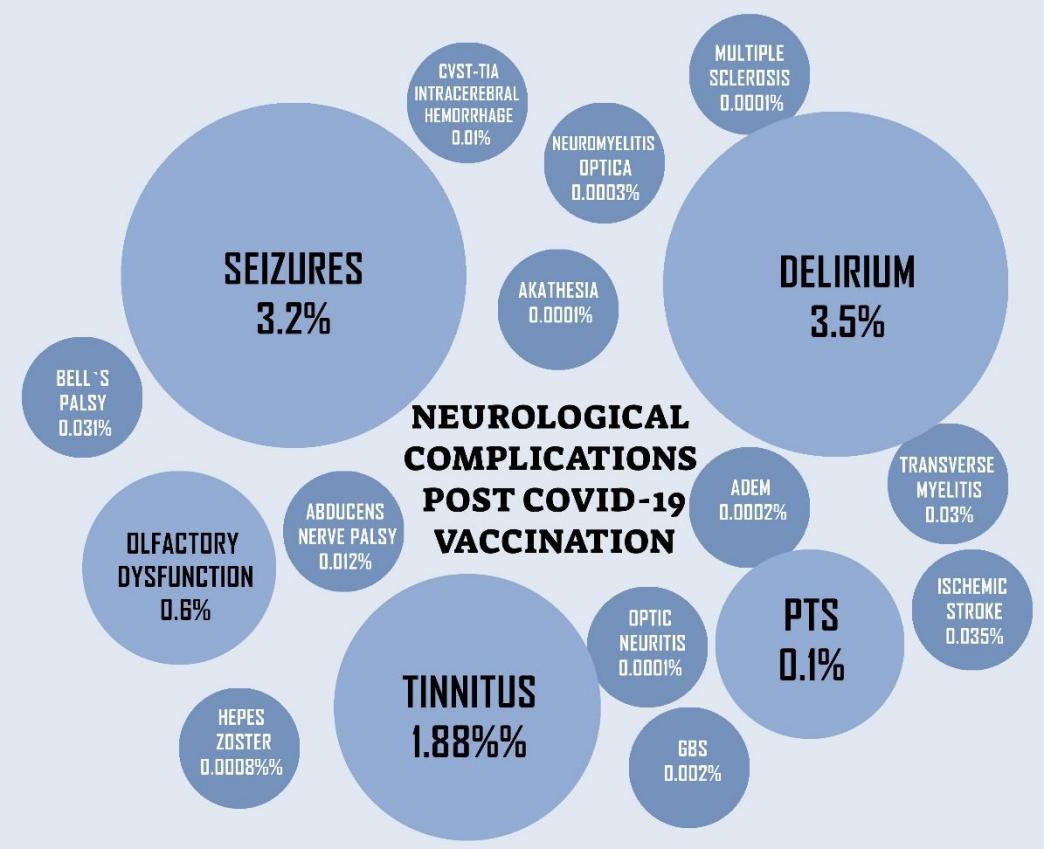

Figure 2: The most common and important complications of COVID-19 vaccinations.

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