

Review Paper

Possible COVID-19 Vaccine-associated Diseases



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ABSTRACT

A safe and effective vaccine would be the best solution to eradicate the COVID-19 pandemic. Classic platforms are used to develop vaccines including live-attenuated vaccines, inactivated vaccines, protein subunit vaccines, and viral vectors. The high vaccine production rate has raised concerns about their safety, although vaccines are still the sole promising solution to vanish COVID-19. The reported severe adverse effects have raised fear about their complications. Previous studies have unveiled that some vaccines like measles, mumps, rubella, influenza, Hepatitis A, Hepatitis B, human papillomavirus, diphtheria, tetanus, and acellular pertussis induce some diseases. It becomes critical to know whether COVID-19 vaccines will cause neurologic disorders, ischaemic stroke, encephalomyelitis, acute transverse myelitis, myocarditis, kidney disease, myositis, and allergic reactions. We exemplify potential problems these vaccines could cause by looking at previous studies. By reviewing the reports of side effects of different COVID-19 vaccines, we have investigated some diseases that may be associated with vaccination; however, it should be noted that the observation of the long-time effect is still needed.

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1. Introduction

Millions of people have been killed around the world by the novel virus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Effective vaccines have been introduced to eradicate the pandemic and control virus outbreaks. With more knowledge of this virus, scientists used a broad range of technology platforms to produce efficient COVID-19 vaccines [1]. The first vaccine produced was the Pfizer-BioNTech vaccine. It used a platform that had not been used previously. The Pfizer BNT162b2 and Moderna mRNA-1273 formulas are based on a pioneering mechanism, a lipid nanoparticle nucleoside-modified mRNA encoding a SARS-CoV-2 spike protein containing medicate to prevent host attachment and viral entry. AstraZeneca's vaccine contains chimpanzee adenovirus vectors that are replication-deficient and embed the SARS-CoV-2 S protein.

A study involving vaccine recipients found that the subjects' T cells responded by expanding both CD8+ and CD4+ cells, generating an immune response biased towards Th1 with the production of interferon, tumor necrosis factor, interleukin-2, and antibodies (Abs) containing predominantly immunoglobulin G1 (IgG1) and IgG3 subclasses [2, 3].

In each type of platform, scientists must consider a lot of points to make vaccines with fewer side effects. For illustration, purification techniques and the nature of the adjuvants which are used in the inactivated vaccine are pretty important to reduce side effects [4]. There are a variety of adjuvants that affect the immune response, including infectious agents and chemicals such as silicone, alum, and pristane, which can cause autoimmunity on their own [5, 6]. Also, viral vector vaccines consist of a recombinant virus that has aroused concerns about inducing cancer [7]. Over the past decades, some studies have unveiled post-vaccination complications, especially more neurologic side effects were reported [8]. The most neurological trouble in previous vaccines against Hepatitis B, human papillomavirus, influenza, and rabies was demyelination disease [9-11].

Some studies also reported myocarditis following influenza and smallpox vaccination [12, 13]. Furthermore, getting e influenza vaccine can lead to acute kidney injury [14]. Other vaccines that are accused of causing kidney disorders are pneumococcal and Hepatitis B vaccines [15].

The high vaccine production rate has raised concerns about their safety, although vaccines are still the sole promising solution to eradicate COVID-19 infection. In various COVID-19 vaccines, it is important to know that these vaccines are safe enough. By reviewing the reports of side effects of different COVID-19 vaccines, we have investigated some diseases that may be associated with vaccination.

Neurological effects of the COVID-19 vaccines

COVID-19 vaccination generally results in mild, transient neurologic reactions like fever, chills, headache, fatigue, myalgia, arthralgia, swelling, redness, or pain at the injection site. These mild neurological symptoms are common following the administration of all kinds of COVID-19 vaccines [16, 17]. Many COVID-19 vaccine recipients report mild neurological complaints soon after receiving vaccines, including headaches [18, 19].

A serious adverse reaction is defined as one that requires hospitalization, causes life-threatening complications, or results in severe disabilities after vaccination. Some studies have manifested the neurologic side effects after immunization, mainly demyelinating diseases. In 2006, more than 175 million doses of quadrivalent human papillomavirus (qHPV) vaccines have been distributed worldwide [20]. In the medical literature, a growing number of case reports describing cases who developed multiple sclerosis and other demyelinating diseases have raised concerns about the safety of qHPV [21, 22]. However, according to Nikolai Madrid Scheller, multiple sclerosis and other demyelinating diseases are not associated with qHPV vaccines given to girls or women [10]. According to studies conducted to date, no adequate evidence has been found to indicate a causal link between measles, mumps, rubella, influenza, Hepatitis A, Hepatitis B, human papillomavirus (HPV), diphtheria, tetanus, acellular pertussis, or meningococcus [23-27].

The neurological complications caused by COVID-19 vaccination were divided into three groups by Adline L Goss and colleagues. According to the vaccine adverse event reporting system (VAERS), there have been 17 strokes, 32 cases of GBS, 190 cases of facial palsy, 9 cases of transverse myelitis, and 6 cases of acute disseminated encephalomyelitis [28].

COVID-19 vaccination and facial palsy

Bell's palsy (BP) is one of the most common mononeuropathies among women that present with weak facial muscles [29]. Reports from (VAERS) indicate that facial nerve palsy

following first and second doses of mRNA COVID-19 vaccines is highly reported [30-32]. In addition to Pfizer and Moderna vaccines, inactivated (CoronaVac) SARS-CoV-2 vaccines are also accused of triggering BP [32].

We should remind this tip that, no association was found between immunization and developing facial nerve palsy but we should follow people who have been vaccinated as well as prone to facial palsy due to their family history. Another occurrence that coincides with the onset of BP and should be considered in vulnerable people is rocketing immunoglobulin M and immunoglobulin G-specific antibodies after vaccination [34].

Guillain-barre syndrome (GBS) and COVID-19 vaccines

GBS is an acute polyradiculoneuropathy that starts with symptoms such as muscle weakness classified as an autoimmune disorder that can also lead to acute paralysis [35]. Previous studies have manifested that vaccines including Hepatitis B, Polio, Tetanus, Meningococcus, and Rabies are associated with the occurrence of GBS. However, it does not establish causation [36]. According to studies, a number of those who had received mRNA vaccine, DNA-based Johnson & Johnson vaccine, and ChAdOx1 nCov-19 vaccine have developed GBS shortly after vaccination, and GBS cases after ChAdOx1 nCov-19 vaccine were more than others [37, 38].

The pathophysiological mechanism for causing GBS following vaccination is still unclear. However, due to information about GBS following SARS COV-2, it can be justified as follows: Due to the molecular similarity between spike protein of SARS COV-2 and human neural cells, cross-reactive antibodies eventually lead to neuronal damage [39].

Although scientists have not been able to establish a cause-and-effect relationship between the vaccination against SARS-COV-2 and GBS, it should be noted that after mass vaccination, GBS should be monitored [40].

Ischaemic stroke and COVID-19 vaccines

An Ischaemic stroke happens when the brain's blood supply is cut off and a blockage occurs; respiratory infections may trigger an Ischaemic stroke [41]. One of the common respiratory viruses is influenza which caused the pandemic in 1918. For containing this infection, general vaccination was performed [42]. An interesting point about the influenza vaccine is that, in addition to decreasing influenza incidence, studies have shown that influenza vaccinations reduce the risk of stroke as well [43].

Some studies have shown that receiving the first dose of COVID-19 vaccines can trigger vaccine-induced immune thrombotic thrombocytopenia that ultimately leads to promoted clotting and Ischaemic stroke. Indeed, viral proteins and free DNA, which are components of the vaccine, bind to platelet factor 4 and result in producing neoantigens and eventually antibodies against platelets inducing platelet activation [44].

Researchers have observed that women who receive the first dose of the ChAdOx1 nCoV-19 vaccine experience severe thrombotic events two weeks after the vaccination. This occurrence has been observed especially in older women under 60 years of age [44]. Not only is the ChAdOx1 nCoV-19 vaccine associated with coagulopathy events, but (mRNA)-based vaccines produced by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) have also reported cases of immune thrombocytopenia [45, 46].

Encephalomyelitis and acute transverse myelitis following COVID-19 vaccines

These two neurological complications are among the rarest after receiving the COVID-19 vaccines [28].

Encephalomyelitis following COVID-19 vaccines

Some viruses induce immoderate inflammation. Encephalitis is considered an autoimmune disease that is caused by viral infection especially herpes simplex virus (HSV) type 1 [47]. The University of Bielefeld has reported a case series of post-vaccinal encephalitis in temporal correlation to vaccination with ChAdOx1 nCov-19 and their patients responded well to immunosuppressive therapy [48].

Indeed, the fact that administering Hepatitis A, B, poliovirus, diphtheria, tetanus, and COVID-19 vaccines give rise to T-cell responses and proinflammatory cytokines are strongly expressed. Therefore, hyperactivation of the immune system leads to proinflammatory cytokines reaching the brain and microglia activation; ultimately, the brain develops autoimmune encephalitis [48].

Acute transverse myelitis following COVID-19 vaccines

Acute transverse myelitis (ATM) involves acute inflammation of gray and white matter in one or more adjacent spinal cord segments, usually thoracic. Multiple sclerosis, neuromyelitis optica, infections, autoimmune or postinfectious inflammation, vasculitis, and certain

Table 1. Case reports of atm following COVID-19 vaccines

COVID-19 Vaccines	Cases	References
ChAdOx1 nCoV-19	72-year-old male	[49]
	A 58-year-old male	[50]
	A 45-year-old male	[51]
CoronaVAC vaccine	A 78-year-old female	[52]
Moderna	A 76-year-old female	[53]

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drugs can cause it. As a result of ATM, one experiences weakness, sensory disturbances, and bladder and bowel problems [49].

Different COVID-19 vaccines can cause ATM. In [Table 1](#), a variety of COVID-19 vaccines which can induce ATM have been listed.

Myocarditis and COVID-19 vaccines

Myocarditis is a self-limiting inflammation of the heart muscle that can lead to rapid or abnormal heart rhythms (arrhythmias). Myocarditis can result from infection with a virus. If this disorder becomes severe, it can affect your heart output. Forming clots and persistent inflammation can cause stroke eventually ([Table 1](#)) [54].

The inactivated influenza vaccination can cause inflammation in the myocardium. The relationship between influenza vaccination and the development of myocarditis is still a controversial issue [55]. Some people who have underlying diseases like diabetes or hypertension have increased the risk of developing myocarditis following the influenza vaccine. Indeed, this vaccine may induce an increase in platelet activity as well as inflammatory cytokines and monocyte activation. Also, there are recognized notable correlations between the changes in inflammatory factors and cardiac autonomic responses to vaccination. The influenza vaccine can induce abnormalities in the heart, such as the activation of platelets and the imbalance of cardiac sympathovagal activity, when given to high-risk patients [56].

According to the studies, some patients have developed myocarditis after BCG vaccination [57]. Also, cases of myositis have been described in adults after Hepatitis B vaccination [58].

It is one of the rare side effects of a COVID-19 vaccination. The most reported myocarditis following COVID-19 vaccines is mRNA vaccines. It has been

reported that in many cases, patients with myocarditis presented with chest pain 2 to 3 days after receiving a second dose of the mRNA vaccination, along with elevated cardiac troponin levels. Although, some cases have faced an increased level of autoantibody against certain self-antigens. However the causes of myocarditis are not clear, they are likely to include molecular mimicry between the spike protein of the SARS Coronavirus-2 (SARS-CoV-2) and self-antigens, triggering pre-existing dysregulated immune pathways during infection in high-risked individuals [59, 60]. However, the cause of male predominance in myocarditis cases is a secret, there may be a relationship between sex hormones and immune response [61]. In addition to mRNA vaccines, adenovirus vector-related vaccines can be related to developed myocarditis.

COVID-19 vaccine-related adverse events can be minimized through early diagnosis and appropriate treatment based on clinical presentation, laboratory findings, and radiologic findings [62].

Kidney disease follow vaccines

In addition to affecting the body’s ability to clean blood, kidney disease can affect how much water is filtered from the blood and how much blood pressure is controlled. As well as affecting the production of red blood cells, it can also affect the metabolism of vitamin D, which is essential for bone growth. Acute kidney injuries refer to a decline in kidney function over a period of 1 week or less, while chronic kidney disease is defined as a decline in kidney function over a period of more than 3 months [63].

Nephrotic syndrome and vaccination

A major reason for nephrotic syndrome in both children and younger adults is minimal change nephrotic syndrome (MCNS). Although the exact cause of MCNS is not clarified, the improper function of T cells results in

the production of a glomerular permeability factor. Disturbing glomerular function leads to marked proteinuria ultimately [64]. Some studies have reported MCNS cases after immunization with tetanus-diphtheria-poliomyelitis, pneumococcus, influenza, measles, and Hepatitis B vaccines. This issue has justified that, the activation of the immune system after vaccination influences the cytoskeleton of podocytes. Hence, their integrity could, under certain preconditions, be altered and lead to proteinuria [65, 66].

Nephrotic syndrome and COVID-19 vaccines

Several reports have been published concerning the development of nephrotic syndrome following the administration of Pfizer-BioNTech's Coronavirus disease 2019 vaccine and the ChAdOx1 nCoV-19 vaccine. However, the number of nephrotic syndrome cases following the AstraZeneca vaccine are fewer than other vaccines. In addition, Aydın MF et al. have reported a case of nephrotic syndrome after the first dose of Sinovac's COVID-19 vaccine [67]. In addition, Jeong-Hoon Lim et al. reported the case of a healthy person with minimal change of disease after receiving Ad26.COV2.S, who developed nephrotic syndrome with severe proteinuria and acute kidney injury [68]. Most of the patients had no history of nephrotic syndrome and had developed this disorder within some days after vaccination. Also, following the first SARS-CoV-2 vaccination, some patients developed the nephrotic syndrome, while others developed it after the seco vaccination [69-71]. Inflammatory cytokines and poly-specific antibodies can be induced by mRNA vaccines in response to SARS-CoV-2 S-specific neutralizing antibodies. As mentioned, these immune responses may induce nephrotic syndrome because it is not a cause-and-effect relationship [72].

Minimal change diseases (MCD) and vaccines

In MCD, there is damage to the glomeruli. In the nephron, tiny blood vessels filter blood and remove waste to make urine. The exact cause has not yet been discovered, but some causes include using NSAIDs, tumors, vaccinations, and viral infections that may be related to allergic reactions [73]. MCD following vaccination was reported in some vaccines such as influenza, Hepatitis B, pneumococcus, and measles [68-74].

Minimal change diseases and COVID-19 vaccines

Some studies have reported MCD following Oxford-AstraZeneca and Pfizer-BioNTech vaccines [69, 17, 75, 76]. In addition, Ahmet Burak Dirim reported one

case who developed MCD a week after the CoronaVac administration. Also, the Moderna mRNA-1273 SARS-CoV-2 vaccine caused MCD in one person after receiving the first (and only) dose, according to Amy Holzworth [77, 78]. In recent studies, it has been established that vaccination timing is related to MCD development [75]. Within two weeks of vaccination, the majority of MCD cases occurred after vaccination, and most of the patients were treated with high-dose steroids [68].

It is demanding to demonstrate that vaccines can trigger MCD. Although, several hypotheses can discuss how a vaccine could trigger MCD. Adenovirus vector-based vaccines (Oxford-AstraZeneca) and messenger RNA-based vaccines (Pfizer-BioNTech) may have a mechanism not directly related to the vaccine. T-cells response following vaccine administration can damage podocytes which are specialized epithelial cells that cover the outer surfaces of glomerular capillaries [79, 80]. Homology between the SARS-CoV-2 genome and podocyte, which is known as molecular mimicry, can produce antibodies against self-antigens. Therefore, these autoantibodies may bind to podocytes and injure them [79, 81].

Myositis and rhabdomyolysis following COVID-19 vaccines

Adverse reactions to vaccination injection sites are common and often characterized by transient pain, edema, and redness. COVID-19 vaccines such as AstraZeneca, Moderna, and modified mRNA have been reported to cause myositis and rhabdomyolysis in recent studies. Myositis is characterized by inflammation of the muscles which causes damage to the skeletal muscles. It can be caused by injury, infection, or autoimmune disease. Also, muscle pain or weakness are symptoms shared by all types of myositis [82]. Another muscle complication that can be triggered by vaccine administration is rhabdomyolysis. There are many causes of this life-threatening condition including overexertion, trauma, toxic substances, and diseases [83].

There is a possibility that the immune response elicited by the intramuscular injection of antigen is also related to the patient's immune response to the vaccine components. Myositis and rhabdomyolysis are taken into account among rare complications of COVID-19 vaccines [82-86].

SARS-CoV-2 vaccine allergic reaction risk

In recent decades, the prevalence of allergic disorders has increased alarmingly in the industrialized world.

During the same period, mass vaccination has increased, resulting in the hypothesis that there is a risk of allergic diseases associated with some vaccines and often attributed to various vaccine components [87]. Immunization may trigger allergic reactions through two mechanisms. First, treatment with a vaccine could directly affect the immune system. It has been proven that the Pertussis vaccine increases an individual's response to histamine 2, as well as their levels of immunoglobulin E [88]. The second possible mechanism is that vaccination lessens the burden of childhood diseases [89].

In the United States, 11.1% of doses of the Pfizer-BioNTech COVID-19 mRNA vaccine caused anaphylactic reactions. Moderna mRNA COVID-19 vaccine has also been associated with anaphylaxis. Although, according to CDC reports, other vaccines may cause a less frequent anaphylactic reaction than Pfizer-BioNTech's mRNA vaccine. It is not clear at this point what causes reactions to Pfizer-BioNTech and Moderna mRNA vaccines [87].

There is evidence that certain vaccine components may cause allergic reactions. In individuals with a history of anaphylaxis to polyethylene glycol (PEG), PEG derivatives, or polysorbate, the CDC recommends avoiding both mRNA COVID-19 vaccines [1].

2. Conclusion

Indeed, as a result of the COVID-19 pandemic and its effects on human life and increasing concerns about decreasing the observance of health recommendations by the people, over the past 2 years, several companies have been accelerating their vaccine production programs. The high rate of vaccine production has raised concerns about their safety. However, as a result of the COVID-19 vaccine, a wide range of serious complications have been reported including neurological complications, myocarditis, myositis, and kidney disorders. The causal association between these adverse events is controversial; large collaborative prospective studies are needed to prove it. Hindsight vaccines are still the only promising solution to eradicate COVID-19.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

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