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# NEUROLOGICAL ASSOCIATIONS OF COVID-19 VACCINES

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## INTRODUCTION

It does not come as a surprise that the introduction of an unprecedented treatment for a recently notorious disease will cause concerns and raise some questions. As a race we have become cautious over the centuries about what treatment modalities we accept and reject. With the advent of social media and endless sources of information we find ourselves standing at an intersection of many pathways, thinking meticulously where to go from there? At one point the widely available stats and the complex way in which these vaccines work do not really interest the general population as much as how they actually affect the human body; things we can actually see, feel and experience.

By the end of August 2021, more than 5.02 billion doses globally <sup>(1)</sup>, above 47 million in Pakistan <sup>(2)</sup> and around 364 million in the United States <sup>(1)</sup> have been administered of the COVID-19 vaccines. As of now there are fifteen WHO authorized and approved COVID-19 vaccines, example of some of them are the Pfizer-BioNTech, Moderna, Johnson and Johnson, AstraZeneca, Sinopharm, Cansino, Sinovac and Sputnik and COVID-19 vaccines. Pakistan as an independent nation has so far approved the later five. In this article we will discuss some facts and ambiguity regarding the supposed neurological side effects of some of the aforementioned vaccines.

## MECHANISM OF ACTION OF COVID-19 VACCINES

In order to give a quick overview of the intrinsic functioning of these new COVID-19 vaccines; there are mainly four mechanisms that have been explored: DNA-based vaccines, mRNA-based vaccines, protein-based vaccines and inactivated virus. Example of DNA-based vaccines, AstraZeneca and Johnson and Johnson, introduce DNA that codes for the severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2) spike protein into cells using viral vectors based on human adenovirus, inducing cells to produce spike proteins. mRNA vaccines, for example Moderna and Pfizer vaccines, use a lipid nanoparticle to introduce messenger RNA into cells. Protein vaccines on the other hand use spike proteins themselves or its fragments. Lastly, many vaccines like the Sinopharm and Sinovac are made using the inactivated SARS-CoV-2 virus. Introducing these foreign particles into the human body stimulates the immune system to produce protective antibodies against the notorious COVID-19 virus that surrounds us.

However, it is possible that sometimes the vaccine constituents may have molecular makeup that is somewhat identical to certain tissues in our body. For instance, they may be similar in structure to tissues in the nervous system or blood vessels throughout the body via a mechanism known as 'molecular mimicry.' Our immune system then mounts an attack against the foreign particles while damaging the body's own tissues in the meantime. This is known as immune injury a mechanism that is linked to nervous system damage by certain viral infections as well <sup>(3)</sup> Certain theories also state that components of vaccines can make neoantigens by interacting with proteins like platelet factor 4 (PF4) <sup>(4)</sup>. The activation of platelets can lead to the formation of blood clots in various parts of the body.

## IMMUNE-MEDIATED NEUROLOGICAL DISORDERS: ANY ASSOCIATION WITH THE COVID-19 VACCINES?

It has since long been established that vaccines do not come without causing some minor and rare major side effects. The question is weighing these against the long-term immunity against preventable diseases that the population aspires to achieve. With respect to the novel COVID-19 vaccines, there is still ongoing post-marketing surveillance which suggests that as of now they are safe and highly efficacious however we do see a wide array of established general side effects like transient symptoms such as fever/chills, headache, fatigue, myalgia/arthralgia, lymphadenopathy, nausea, or local effects of swelling, erythema, or pain. <sup>(5)</sup>

In order to adjust our magnification aspects to focus on the neurological side effects of these vaccines, particularly the peripheral nervous system, we can look to where it all started. It could be possible to attribute it the fall of 2020 when two patients after receiving the Oxford/AstraZeneca vaccine developed transverse myelitis <sup>(6)</sup>. However out of the two, only one was determined to be related to the vaccine while the other was found to have a prior history of multiple sclerosis <sup>(7)</sup> Data from clinical trials of the mRNA vaccine showed that 7 out of 37,000 vaccinated cases developed Bell's palsy and none developed Guillain-Barré syndrome (GBS). The United States Food and Drug Administration (FDA) therefore reached a conclusion that the rate of Bell's palsy could not be assumed to be higher than that expected in the general population <sup>(8)</sup> Turning to the vaccine trial held by Johnson & Johnson group, one patient in each, the vaccinated and the placebo group developed Guillain barre syndrome. Likewise, no direct or causative link between COVID-19 infection and GBS has been found <sup>(9)</sup>

When it comes to the central nervous system There were also rising concerns about vaccinations against COVID-19 in people with a history of epilepsy. Can the vaccines trigger seizures? Up till now, due to limited data, there is no definitive evidence to confirm that statement although it is well known that one of the common side effects of vaccination is fever which in general is known to lower the seizure threshold. The International League Against Epilepsy issued a statement suggesting that there is currently no evidence that COVID-19 vaccines pose a higher risk to patients with epilepsy <sup>(10)</sup> therefore it is imperative to outweigh the risks of deferring vaccination.

To further explain and get a broader perspective on the connection between COVID vaccines and their effect on the neurosciences of the human body, we have at hand, one of the widely available databases of the centers for Disease Control (CDC). The Adverse Event Reporting System (VAERS); any associated symptomatology can be reported by patients, health-care providers, and even manufacturers to the FDA's Adverse Event Reporting System (FAERS) <sup>(10)</sup>. By early March 2021, 9,442 vaccine adverse reaction reports were submitted to VAERS. The most reported neurological symptoms included headache, pain, dizziness, muscle spasms, myalgias and paresthesia. The most reported neurological symptoms that occurred, both as an acute and transient effect of vaccination, included dizziness, headache, pain, muscle spasms, myalgia, and paresthesia There were a few cases of GBS, stroke, facial nerve palsy, transverse myelitis, and acute disseminated encephalomyelitis. Also, rare cases of tremors, diplopia, tinnitus, dysphonia, convulsions, and reactivation of shingles have been reported however they could not be evidently linked to the COVID-19 vaccines themselves. In the light of this the CDC, after a detailed review of the data base from first month of vaccination issued a publication that suggested no safety concerns <sup>(11)</sup>

We should however keep in mind the limitations there are to extensive databases like these since they are based on passive surveillance and prone to biases and errors. Additionally, due to the large number of patients vaccinated and the background rate of neurological conditions in a population, some cases of neurological conditions will occur within the post-vaccination window by chance, according to the study <sup>(12)</sup>

In Pakistan, one of the most widely used vaccines is from China named Sinopharm (BBIBP COVID-19 vaccine). WHO has identified two serious adverse events that may have been related to the vaccine: severe nausea and a rare neurological disorder known as acute disseminated encephalomyelitis. There has also been reported a case of a thrombus (blood clot) in the vaccinated group. However, the reviewers in their conclusion stated that even though there were eleven cases of facial nerve symptoms reported, they were most likely unrelated to the vaccine itself. Also, that there is a high level of confidence in the efficacy against PCR-confirmed COVID-19 cases(adults) and a moderate level of confidence that the risk of serious adverse events after one or two doses of BBIBP-CorV in adults (18-59 years) is low. <sup>(13)</sup>

### **COVID-19 VACCINES AND CLOTTING TENDENCIES?**

Let's continue our discussion by addressing some concerns about the neurological manifestation of certain hematological problems that COVID-19 vaccines are believed to cause. From April 13 to 23, the CDC and the FDA recommended a pause in the use of the Janssen vaccine after six cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia (platelet count <150,000 /  $\mu$ L blood) were reported in Janssen vaccine recipients <sup>(14)</sup>. On April 23, 2021, after a discussion of the benefits and risks of resuming immunization, the CDC's ACIP (The Advisory Committee on Immunization Practices) reaffirmed its interim recommendation for the use of the Janssen COVID-19 vaccine in all people  $\geq$ 18 years of age under the FDA's EUA, which now includes a warning that rare clotting events can occur after vaccination <sup>(15)</sup>, primarily in women aged 18 to 49.

Similarly, the use of AstraZeneca vaccine was suspended in Europe after similar thrombotic events occurred, mostly in females less than 60 years of age. More recently in May 2021 UK's MHRA (Medicines & Healthcare products Regulatory Agency) recommended offering an alternative to AstraZeneca vaccine to people under the age of 40. <sup>(16)</sup> Another study from the European Respiratory Journal noted cases of unexpected cerebral venous thrombosis (CVT) for the COVID-19 vaccines Moderna, Oxford-AstraZeneca and Comirnaty (Pfizer and BioNTech). The majority of cases were a particular form of CVT called CVST (Cerebral sinus vein thrombosis). Overall, the study's data generates a hypothesis that such thrombotic events could occur as an association with all three vaccines, but this can be challenged by further investigation, including extensive laboratory and clinical studies. <sup>(17)</sup>

There have been incidents of ischemic strokes after COVID-19 vaccinations. A study from the UK published in May 2021 reported three cases of ischemic stroke after receiving the Oxford-AstraZeneca vaccines <sup>(18)</sup> An important point to remember from all this is that these side effects are rare as compared to these thrombotic events occurring more commonly after COVID-19 vaccines itself <sup>(19)</sup>

### **COVID-19 VACCINES AND DISEASE MODIFYING THERAPY (DMT)**

The role of DMTs like anti-CD20, glatiramer and interferons in certain neurological illnesses e.g., multiple sclerosis is well-known and their importance clinically proven. With the advent of novel COVID vaccines questions arose regarding the proper vaccine recommendations that should be followed when it comes to patients already or about to commence this therapy. There is a chance that immunosuppression may render the vaccine somewhat ineffective therefore it is extremely important to administer vaccines in a timely fashion. For example, in patients already on ocrelizumab (anti-CD20 DMT) there should be a recommended gap of 3 weeks between first and second dose of vaccine while another wait of about 4-6 weeks before ocrelizumab re-administration <sup>(20)</sup>. However, one can broadly say that risking discontinuation or switching DMT for fear of affecting vaccine efficacy may prove to be harmful and result in disease flare-up and exacerbation. <sup>(21)</sup> Therefore, each case should be uniquely evaluated and the decision to vaccinate should be made considering the patient characteristics and disease activity.

### **FUNCTIONAL NEUROLOGICAL DISEASE OR SIDE EFFECTS OF VACCINES?**

On the other end of the spectrum, we see that there has been circulating on social media numerous videos of patients exhibiting neurological symptoms after administration of COVID-19 vaccines. The findings created alarm amongst the general public that is still at an edge with the proposed safety of these vaccines. Although it is not up to any particular entity to pass a final verdict on the truth behind such findings since the data at hand since the advent of these vaccines is still quite limited, however the Functional Neurological Disease society issued a statement in early 2021 saying "We have become aware of a very small number of high-profile social media videos suggesting major neurological complications following vaccination against COVID 19. Whilst we do not wish to comment specifically on any case, we would state, as general comment, that many of the clinical features reported and observed on video in some cases are those of functional neurological disorder (FND). FND can be diagnosed with good accuracy from videos on social media where they are often confused with other neurological condition" <sup>(22)</sup>

FND is an actual disorder that originates in the human brain and has connections with both neurology and psychiatry. In this patients develop a range of neurological symptoms precipitated and perpetuated by biological, psychological and / or environmental factors, reflecting the clinically formulated biopsychosocial model described by George Engel, MD <sup>(23)</sup>. It cannot be concluded that FND is directly triggered by the constituents of vaccines in that same way that some microorganisms cause a specific disease e.g., streptococcus pneumoniae is the cause of pulmonary infection <sup>(24)</sup>

The fact that vaccinations can cause a wide array of neurological complications is well known even though fortunately rare. Therefore, instead of directly jumping to conclusions and reporting adverse effects of vaccines to an already eager public, news organizations should consider neurological symptoms of FND as an explanation for what might be happening to certain individuals post vaccination.

### **CONCLUSION**

In general, it is imperative that we understand that the COVID-19 is an unpredictable and potentially lethal disease which requires a collective effort from all nations to curb its spread. Even though still limited but we do have promising evidence about the effectiveness of the COVID-19 vaccines. Minor side effects are always a part and parcel of mass

vaccination strategies, and neither is there any denying of possible major side effects be it neurological or affecting any system in the human body. The decision to vaccinate ourselves should be based on fair and evident presentation of any relevant data by the agencies and governments involved in the vaccination process as well as well us on understanding the responsibility we have as a unified world population to take steps to prevent this contagion from spreading.

The topic of this article is indeed an evolving landscape, therefore clinicians and neurologists should participate in efforts to collect ongoing data for evidence-based recommendations. The question of whether the vaccine can be a cause of onset of neurological disorders or lead to them accidentally, requires long-term monitoring - a cautiously optimistic approach to the safety of the vaccine in terms of neurological effect is appropriate.

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