Editorial

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COVID-19 post vaccination neuronal adverse events: probable mechanisms and treatment possibilities

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> "the incidence of neurological adverse effects (NAEs) and cardiovascular adverse effects with these vaccines are reported to be higher than has been previously observed with vaccines for other viral infection epidemics"

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Early in the COVID-19 pandemic, a few cases of affected individuals with SARS-CoV-2 infection and neurological deficits were observed, but it was not until late 2020/early 2021 that these cases were validated as NeuroCOVID and SARS-CoV-2 were implicated in neuroinflammation and possible direct damage observed during COVID-19 [1]. During this period, multiple vaccines against SARS-CoV-2 that prevented serious complications and reduced hospitalization were granted emergency use authorization and began to be rolled out worldwide. Problems have recently surfaced, however, as the incidence of neurological adverse effects (NAEs) and cardiovascular adverse effects with these vaccines are reported to be higher than has been previously observed with vaccines for other viral infection epidemics [2]. Incidences of Bell's palsy, Guillain–Barré syndrome, transverse myelitis, optic neuritis and diverse peripheral nerve lesions along with cerebrovascular (non-neural causes) lesions have been reported following variable periods of COVID-19 vaccines [2,3]. Small fiber neuropathies following COVID-19 vaccination have also been reported [4,5]. Ramsey Hunt Syndrome after COVID-19 vaccination has been reported to cause facial nerve palsy, vestibulocochlear neuropathy and glossopharyngeal nerve neuropathy, resulting in numbness of the face, tongue and hearing loss [5]. Acute disseminated encephalomyelitis has also been observed after the first and second doses of the vaccine [6]. The emergence of post-COVID-19 vaccine autoimmune diseases has been co-reported with cases of neurological diseases or new-onset systemic lupus erythematosus which can evoke diverse NAEs [7]. NAEs are particularly concerning as their incidence continues to be difficult to quantify, and their underlying cause remains uncertain. Of the 314,610 adverse events following COVID vaccination recorded in the Vaccine Adverse Event Reporting System (VAERS; representing 0.10% of all doses administered) 105,214, or 33% were neurological adverse events representing 0.03% of all vaccine doses administered [8].

With the use of a fixed dose of the COVID-19 vaccine in a defined age group of people within a particular region, the best explanation for NAEs or other organ damage may be the differential immune response that is mounted in response to antigen exposures, including the spike (S) protein. mRNA vaccines induce the synthesis of an S protein that differs from the viral S protein in two proline substitutions at the 986 and 987th amino acids, in some cases with additional substitutions at the furin cleavage site and with substitutions that prevent the S protein interaction with ACE2 and other receptors associated with SARS-CoV-2 entry into host cells. Normally, mRNA vaccines are expected to induce S protein synthesis for shorter periods, providing ample duration of exposure to the immunogenic regions of S protein and yet also sufficient time to mount an immune response. The complex ways

in which the viral S protein can evade antibodies and induce an autoimmune response as seen in long-COVID may also result in autoimmunity following vaccination with the mRNA vaccine. Immune profiling of patients for HLA-Class I and Class II antigens could therefore provide a clue regarding susceptibility and identify those who are at most risk of developing NAEs and adverse effects in general. Genetic heterogeneity could also be behind some cases of sustained production of the S protein after a fixed dose of the COVID-19 mRNA vaccine. It is also worth noting that mRNA vaccines also contain components like polyethylene glycol, which may cause an anaphylactic response.

Post vaccination, the overproduction of the S protein and its secretion into body fluids, escape of the vaccine solution into general circulation and lymphatic dissemination of the vaccine and, importantly, an aberrant immunological response are a few factors that should be considered when trying to explain NAEs. The effects of the S protein on neurons and glial cells are yet to be clarified, but one issue with this in the context of NAEs is that neither the S protein nor the antibodies mounted against it can normally cross the highly selective blood–brain barrier (BBB). Transport across the barrier is only possible if it has already been breached or injured by circulating S protein, which has been suggested by recent findings in an encephalitis patient that had received the AZD1222 (AstraZeneca) and mRNA-1273 (Moderna) COVID-19 vaccines [9]. Some *in vitro* studies have also shown similar effects of the S protein on the BBB. Diverse interactions of the S protein with receptors like neuropilin-1 (NRP-1), tyrosine-protein kinase receptor UFO (AXL) and CD147 could affect the cellular function or entry into cells by internalization, and studies have also shown that the cytokines derived from S1 protein-activated glial cells can induce neuronal cell death in mice [10]. After crossing the BBB, it has been suggested that circulating immune complexes of the S protein and IgG antibodies can bind Fc-receptors of cells in the peripheral and central nervous systems in some cases that have shown NAEs [2,9,10]. Abnormal S protein-IgG complexes are thought to cause a prothrombotic state, leading to ischemic damage to nerves. Demyelination and tissue damage can therefore manifest as optic neuritis, peripheral neuritis, Bell's palsy, transverse myelitis and Guillain–Barré syndrome. Leakiness of the BBB and damage caused by S protein-IgG deposition within the CNS may therefore explain the inflammatory injury reported in NAEs after vaccination.

As discussed above, it seems that the underlying mechanisms in NAEs involve a combination of inflammatory, vascular pathology and immune system mediated damage to neuronal tissue. Known anti-neuroinflammatory and neuroprotective drugs are important to prevent the progression of NAEs. Natural products and nutraceuticals could also be considered for the treatment of NAEs for their antioxidant and anti-neuroinflammatory effects. One advantage of natural products when used in combination is that they can reduce the intensity of NAEs more efficiently by drug synergism and, therefore, can be used in lower doses. This would both minimize their side effects and magnify their clinical efficacy in cases of NAEs. Examples of plant products with proven neuroprotective and anti-neuroinflammatory effects include baicalin, quercetin, Diosmin−Hesperidin, curcumin and Piperine [11] and could be investigated in clinical trials for their efficacy in treating NAEs post vaccination. Spike-protein-derived amyloid like fibrils is thought to be generated during infection [12] or as a response to vaccination and can benefit from the neuroprotective effects of formulations that contain agents like baicalin, quercetin, diosmin−hesperidin, curcumin and piperine, which also are capable of binding the receptor binding domain of the S protein that interacts with the ACE2 receptors expressed in selective neurons in the CNS [1]. Many of the above listed are anticoagulants as well, which could further minimize thrombosis-related NAEs such as strokes, transient ischemic attack and cerebral venous sinus thrombosis. Immunomodulatory amides could also be investigated based on the effects shown in traumatic brain injury, another condition dominated by inflammation and neuronal damage [13,14]. Recently, drugs like low dose naltrexone, lumbrokinase/Nattokinase, nicotinamide adenine dinucleotide, butyrate and food supplements to compensate for impaired delta-6 desaturase (D6D) metabolic pathways have been suggested to improved long-COVID and could therefore be investigated for NAEs. Other active molecules in brown algae, bromelain, fisetin and N-acetyl cysteine are currently being investigated for improving S protein-mediated neuronal damage in long-COVID and could prove to be effective in NAEs as well. The use of intravenous immunoglobulin (IVIG) to treat small fiber neuropathies could also be explored for uncommon NAEs [4,5]. With literature emerging on detection of circulating S protein in Post-COVID-19 mRNA vaccine causing myocarditis [15] and neurological injuries [15–18], it is important to design therapies that not only target the SARS-CoV-2 associated S protein but the virus-independent S protein that can produce deleterious effects on the body in general and nervous system in particular.

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