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Commentary: The spectrum of neurological manifestations related to COVID-19 and vaccinations

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It is just over eighteen months since the recognition of the novel coronavirus 2019 (COVID-19); as many areas of the world begin to take steps towards safely returning to normal, increasingly detailed understanding of viral mechanisms are being pursued. There was a pressing need in the beginning to understand the systemic manifestations but along the way it became clear that SARS-CoV-2 was also a neurovirulent virus. This has been evident through the several publications of para- and post- infectious neurological sequelae (Jeanneret et al., 2021; Moreno-Escobar et al., 2021; Papri et al., 2021; Sheikh et al., 2021). SARS-CoV-2 affects both the central and peripheral nervous system with the latter being more likely affected during acute viral illness (Sheikh et al., 2021).

Sheikh et. Al's systemic review of 64 articles related to Guillain-Barre Syndrome (GBS) during an active COVID-19 infection, confirmed through positive polymerase chain reaction (PCR) after nasal swab, describe a range of clinical findings. In contrast, post-infectious GBS was reported by Papri et. Al using the Brighton criteria in the setting of negative PCR and positive IgG antibodies (Papri et al., 2021). Para- and post-infectious clinical manifestations have ranged from sensorimotor forms, with lower extremity weakness being more common, to Miller Fisher Syndrome (MFS) and multiple cranial nerve involvement. Sheikh et. Al describes electrophysiological findings in three main GBS subtypes, acute idiopathic demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN). Symptom onset ranged from 0 to 10 days from systemic symptoms. The mean age was 56 ± 16 years, 65% were males, and paresthesias were the most common symptom present in 49%. Criticism from Finsterer et. Al highlights the need for cerebrospinal fluid (CSF) that can potentially demonstrate multiple inflammatory markers in COVID-19 associated GBS. However, timing and clinical utility of CSF or serum markers in this setting remains unclear (Finsterer et al., 2021). It does appear that SARS-CoV-2 detection in CSF via PCR or evaluation for intrathecal antibody synthesis may be rare (Lewis et al., 2021), and likely due to blood contamination. 78% of those with GBS were treated with intravenous immunoglobulins (IVIG) or with combinations of IVIG, steroids, and/or plasmapheresis. Less than a third recovered sensorimotor function while 7.5% did not improve. The current literature states approximately 20% of patients with GBS (unrelated to COVID-19) are unable to walk unaided at 6 months. Use of standard disability scales and follow up were not discussed in Sheikh et. Al review, but may be useful for long-term prognosis related to COVID-19 and provide a better understanding of post-hospitalization functional status (van den Berg et al., 2014). Finsterer and Ghosh's letter to the editor challenges the etiology of respiratory symptoms in the Sheikh et Al. review, as it remains unclear clinically whether respiratory deterioration is due to cardio-pulmonary involvement versus neurological sequela (Finsterer and Ghosh, 2021). If pulmonary imaging does not support the extent of vital capacity deterioration, neurological causes are likely the culprit. Further studies focusing on etiology of respiratory symptoms may shed more light on how the virus is involved.

Several mechanisms for viral involvement have been proposed, including development of a cytokine storm leading to fever, production of antibodies targeting myelin, fibrinogen, transthyretin, or albumin resulting in extensive damage. Interestingly, the ganglioside antibodies associated in AIDP were not significantly identified (Papri et al., 2021; Sheikh et al., 2021).

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Entry and activation in central nervous system (CNS) post-infectious presentations related to COVID-19 are currently under investigation. Multiplexed spatial analysis of the adaptive and innate immune system in brain sections from COVID-19 patients compared to controls have shown activation of endogenous disease-linked clusters of CD4 and CD8 T cells, significant immune infiltration, increased axonal damage, and their compartmentalization in distinct anatomical regions of the brain stem, olfactory bulb, and perivascular areas. The profound immune response may allude to the reason for several neurological pathologies related to SARS-CoV-2 (Schwabenland et al., 2021).

Moreno-Escobar et. Al describe secondary demyelination resulting in transverse myelitis approximately 2 weeks from acute infection. Clinical presentation included right sided weakness, T6 sensory level, hyperreflexia, and bowel/bladder incontinence. Like the PNS post-infectious cases, SARS-CoV-2 IgG was positive in the setting of negative PCR. Defining MRI features include longitudinal non-enhancing cervical and thoracic hyperintensities. Aside from a lymphocytic predominance, CSF was without significant results. Improvement was seen with intravenous steroids followed by an oral steroid taper. A unique aspect of this case was the presence of dysautonomia. A potential cause may be the inflammatory involvement of the cervical region. In a similar timeframe of 2 weeks, a case of rhombencephalitis was reported by Jeanneret et. Al presenting with dysarthria and gait instability and eventually becoming bedridden. Imaging showed extensive cerebellar and brainstem hyperintensity with diffusion restriction similar to other reports of post-infectious rhombencephalitis. Contrasting Moreno-Escobar et. Al, CSF was remarkable for elevated protein, however no pleocytosis. Given the extent of deficits, treatment beyond steroids was initiated and included PLEX and IVIG with some improvement.

With the distribution of vaccinations against COVID-19, incidence and hospitalizations have dropped significantly throughout the United States. However there has been concern for neurological complications, albeit rare. Similar to post-infectious manifestations in COVID-19, transverse myelitis was reported by Pagenkopf et. Al after administration of the AZD1222 AstraZeneca vaccine after rigorous work-up ruling out other inflammatory, infectious, and post-infectious SARS-CoV-2 syndromes. Antibodies were present in serum despite negative tests for active infection. Presence of low-level IgG-response to spike protein antigen alone and negative results for nucleocapsid-directed antibodies suggest a response to the vaccination based on its mechanism of action (Pagenkopf and Südmeyer, 2021). Clinical and MRI findings were similar with a longitudinal non-enhancing lesion. As the authors mention, myelitis associated with other vaccinations have been described through history, but the risk of neurological and systemic consequences far outweighs the risk of post-vaccination syndromes. Aladdin and Shirah describe another CNS related case with the ChAdOx1 Vaccine, a viral vector vaccine that uses the modified chimpanzee adenovirus. A woman of South African descent developed refractory seizures after this vaccination that only resolved with pulse steroids and plasmapheresis (Aladdin and Shirah, 2021). Although seizures have been reported with the SARS-CoV-2, this was secondary to other complications such as ischemia or increased oxidative stress. Pathophysiology here may be unique as the bilateral hippocampal involvement seen in this patient, is notable in autoimmune encephalitis. The authors propose that this specific mechanism of the vaccine may access the cerebral neuronal pathways and initiate an inflammatory cascade resulting in hyperexcitation. Both cases suggest potential for immune mediated inflammation post-vaccination, independent on effects from para- or post- infectious etiology. Although such cases have been reported since the pre-approval stages, incidence has been rare and the ongoing, larger benefit of vaccinations unequivocally support continued use and distribution.

As cases of neurological involvement become more clearly defined, clinical definitions for para-infectious versus post-infectious versus post-vaccination presentations are necessary to better confirm etiology of disease. Additionally, a focus on understanding mechanisms of involved inflammatory cascades and/or antibodies can help suggest appropriate and effective treatment. These reports and series are important contributions to our initial understanding of a virus that caused a global pandemic. Although many manifestations are similar to known viruses prior to 2019, it is important to delineate the specific characteristics and long-term implications that it seems SARS-CoV-2 possesses.

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