Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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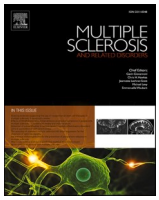

Commentary

Fatal neuromyelitis optica after COVID-19 vaccination

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Dear Editor,

We read with interest the report by Motahharynia and coworkers (Motahharynia et al., 2022) that showed a new-onset Neuromyelitis Optica diagnosis with a fatal outcome after COVID-19 vaccination. The authors report a 70-year-old woman who exhibited neurological symptoms (numbness and weakness in her left limbs) seven days after receiving the third dose of a SARS-CoV-2 inactivated vaccine (Sinovac: CoronaVac). She rapidly progressed to paraplegia, while spinal cord magnetic resonance imaging showed an extensive hemorrhagic lesion in the cervical cord (C1-C7). Cerebrospinal fluid analysis was unremarkable (including the absence of oligoclonal bands), but the patient tested positive for anti-Aquaporin-4. Unfortunately, the patient was refractory to all therapeutic interventions (methylprednisolone pulse therapy, plasma exchange and cyclophosphamide) and died two months after hospitalization (Motahharynia et al., 2022).

Neuromyelitis Optica Spectrum Disorder (NMOSD) is rare autoimmune neuro-inflammatory disease that affects the central nervous system (CNS) with predilection for causing lesions in the optic nerves/spinal cord. Usually, the median age for onset is 40-years, although the disease can occur at any age as proposed in this report. CNS-damage during NMOSD is mainly attributed to the presence of autoantibodies such as specific NMO-IgG against astrocyte-end-feet Aquaporin-4 (anti-AQP4) in association with complement system, innate cells (e.g., eosinophils/neutrophils) and pro-inflammatory cytokines (Jarius et al., 2020).

Considering the accumulated reports during the pandemic, we speculate that antiviral immune responses against SARS-CoV-2 natural infection/immunization may trigger CNS-damage in some individuals. Here, we hypothesize that repetition of vaccination with the same vaccine type (inactivated SARS-CoV-2) evoked a robust antiviral immune response including, among others: (I) effector or even senescent/exhausted $CD8^+$ T lymphocytes with massive cytotoxic capacity (e.g., granzymes); (II) pro-inflammatory cytokines derived from $CD4^+$ Th1 (IFN-γ, TNF-α) and Th17 (IL-17, IL-22); (III) neutrophil extracellular traps (NETs) and pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) derived from innate immune cells. All of these components are known to promote blood-brain barrier disruption. In parallel to neutralizing antibodies against SARS-CoV-2, autoreactive clones of B cells may differentiate in plasma cells and release anti-AQP4 due to loss of peripheral autotolerance. Furthermore, it is not possible so far to exclude that neutralizing antibodies against SARS-CoV-2 may also exhibit cross-reactivity with self-antigens in the CNS. More broadly, post-COVID syndrome as well as manifestations after COVID-19 vaccination may share common immunological features (summarized in Fig. 1).

The increasing number of reports suggest the occurrence of new-onset/exacerbating NMOSD and related disorders, such as Multiple Sclerosis, in the context of SARS-CoV-2 natural infection/immunization (Finsterer, 2022; Fragoso et al., 2022; Khayat-Khoei et al., 2022). Despite the need for continuous massive vaccination against SARS-CoV-2, which proved to be effective and safe, we should be aware of rare, aggressive and even fatal CNS-manifestations such as NMOSD in a small proportion of individuals.

Author's Contributions

V.O.B. and C.L.Y. wrote the manuscript.

Ethics approval

Was in accordance with ethical guidelines.

Consent to participate

Not applicable.

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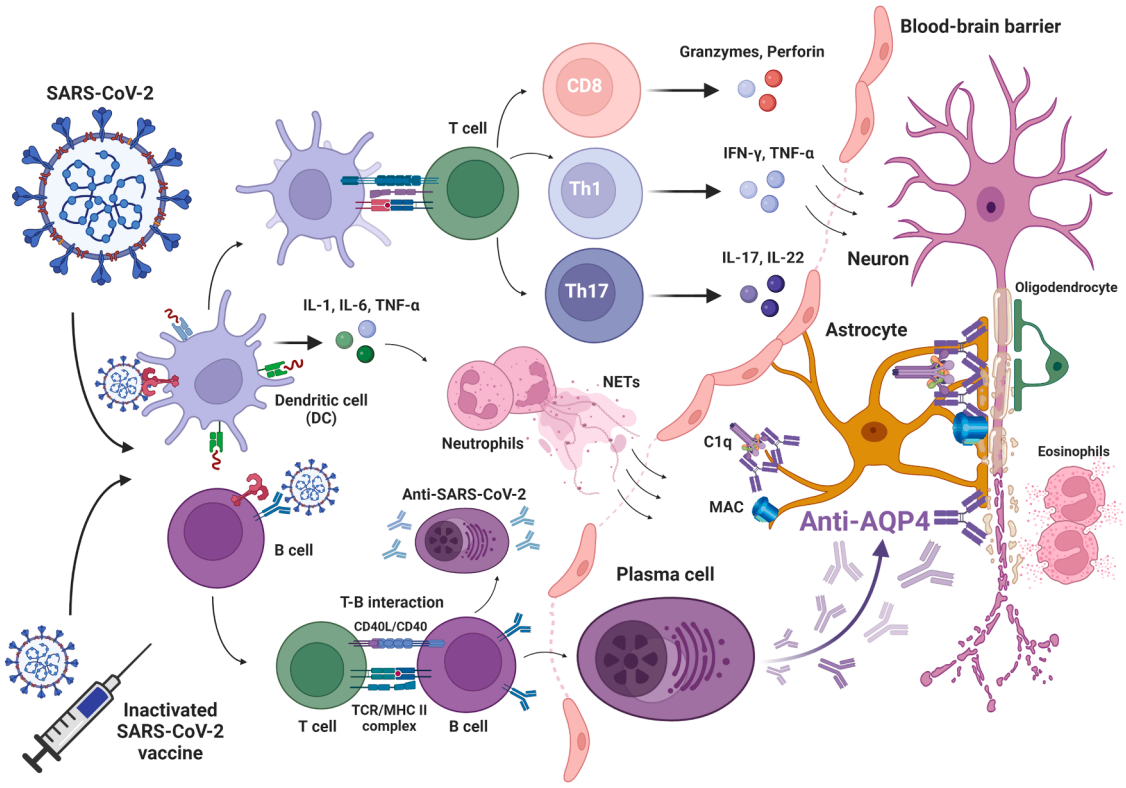

Fig. 1. Shared antiviral immune responses between natural SARS-CoV-2 infection/vaccination possibly implicated in NMO pathogenesis.
SARS-CoV-2 viral particles are sensed by pattern recognition receptors (e.g., Toll-like receptors - TLRs) present in innate (such as dendritic cells - DCs) and adaptive subsets (such as B cells). B cells can also sense SARS-CoV-2 through the specific B cell receptor (BCR). Both DCs and B cells are professional antigen presenting cells (APCs). During antiviral immune responses against SARS-CoV-2, DCs can interact with *naive* T lymphocytes generating effector $CD8^+$ T cells, as well as subsets $CD4^+$ Th1 and Th17. In the secondary lymphoid organs, cross-talk between T and B cells may induce the generation of memory B cells and release of neutralizing antibodies against SARS-CoV-2 (anti-SARS-CoV-2) by antibody-secretory cells (plasma cells). In parallel, pro-inflammatory milieu derived from innate cells (IL-1, IL-6, TNF-α), $CD4^+$ Th1 (TNF-α, IFN-γ) and Th17 (IL-17, IL-22) may promote loss of peripheral autotolerance in B cells. Autoreactive B cells may differentiate in plasma cells with the ability to release antibodies targeting Aquaporin-4 (anti-AQP4). Moreover, besides inflammatory cytokines, $CD8^+$ T lymphocytes with cytotoxic capacity (e.g., granzymes) and neutrophil extracellular traps (NETs) are also implicated in blood-brain barrier disruption.
Neuromyelitis optica spectrum disorder (NMOSD) lesions are mainly attributed to the entrance of anti-AQP4 in the central nervous system and binding with astrocyte end-feet, characterizing a primarily astrocytopathy. Deposition of complement system is also observed (C1q among other factors) and terminally leads to the formation of Membrane Attack Complex (MAC). Eosinophils and other innate cells (mainly neutrophils and macrophages/microglia, not shown) are also implicated in the oligodendrocyte and neuronal loss secondarily to the astrocytopathy during NMOSD. Created with BioRender.com.

Consent for publication

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Availability of data

Not applicable.

Declaration of Competing Interest

The author declares no conflicts of interest.

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