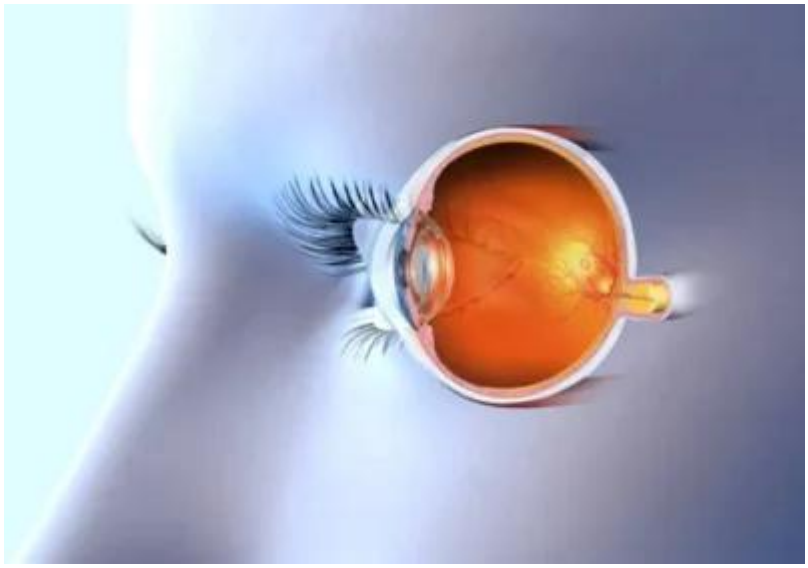
Neuromyelitis optica spectrum disorder (NMOSD) is a rare, chronic, relapsing, demyelinating, autoantibody-mediated disease of the central nervous system (CNS). The classical presentation of this disease involves transverse myelitis, optic neuritis, area postrema syndrome (bouts of intractable vomiting and hiccoughs), and acute brainstem syndrome. Approximately 75% of patients with NMOSD have antibodies against aquaporin-4 (AQP4), a water channel expressed on astrocytes. In this article, the authors from the United States conducted a systematic review of the published literature to investigate *de novo* onset or relapse of NMOSD after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 vaccination.

Many previous case reports have linked the SARS-CoV-2 infection with CNS diseases such as transverse myelitis, acute demyelinating encephalomyelitis, multiple sclerosis, and NMSOD.
https://discovermednews.com/acute-demyelinating-disease-of-the-cns-acute-disseminated-encephalomyelitis-associated-with-sars-cov-2-infection-or-anti-sars-cov-2-vaccination/

https://discovermednews.com/sars-cov-2-infection-is-associated-with-optic-neuritis/

Also, previous studies have reported the occurrence of new-onset autoimmune phenomena following COVID-19 vaccination, including immune thrombocytopenia, autoimmune liver diseases, rheumatoid arthritis, systemic lupus erythematosus, immunoglobulin A nephropathy (IgAN), and others.
https://discovermednews.com/glomerular-disease-after-covid-19-mrna-vaccination/ BNT162b2 (Pfizer- BioNTech) and mRNA 1273 (Moderna) vaccines were the first messenger RNA (mRNA)-based vaccines ever approved. In both vaccines, an mRNA sequence determines the structure and assembly of the immunogen, the SARS-CoV-2 spike (S) glycoprotein.



About the Study and *Results*

In this review article, the authors conducted a Boolean search of the medical literature using Medline, Cochrane Library, Embase, Trip Database, Clinicaltrials.gov, Scopus, and Web of Science databases. All case reports and case series that met the study criteria and reported NMOSD that developed after acute SARS-CoV-2 infection or COVID-19 vaccination were included. The review comprises articles indexed in the peer-reviewed literature, whereas poster and symposium abstracts, non-peer-reviewed publications, and clinical trials were excluded. Articles reporting other demyelinating disorders were also excluded. After removing articles based on exclusion criteria, 34 articles were analyzed.

The review included 41 patients diagnosed with NMSOD associated with SARS-CoV-2 infection or COVID-19 vaccination. 15 patients developed *de novo* NMOSD onset after SARS-CoV-2 infection, 21 developed *de novo* NMOSD onset after COVID-19 vaccination, three patients with a previous diagnosis of NMOSD experienced a relapse following COVID-19 vaccination, and two patients had a presumed diagnosis of multiple sclerosis that was manifested as NMOSD after COVID-19 vaccination. 76% of all included patients were women.

Cases who developed NMOSD after acute SARS-CoV-2 infection

This group included 15 patients, 73% were women, and the median age was 37.5 years (ranging from 7.5 to 71 years). The cases came from twelve countries. Two patients (13%) had a previous medical history of an immune-mediated disease, one had juvenile arthritis,

and one had an episode of suspected acute demyelinating encephalomyelitis.

The median time between the first symptoms of SARS-CoV-2 infection and the first symptoms of NMOSD was 14 days (ranging from 3 to 120 days).

Transverse myelitis was the most common neurological clinical presentation, diagnosed in 67% of patients (10 cases). Optic neuritis was diagnosed in 47% of patients (7 cases), and area postrema syndrome, manifested as intractable nausea, vomiting, or hiccoughs that persisted for at least 48 hours, was diagnosed in 13% of patients (2 cases). 33% of patients (5 cases) had brain stem involvement.

The examination of cerebrospinal fluid (CSF) showed a pleocytosis in 5 patients (33%), while two patients (13%) had a normal white blood cell count. Two patients (13%) had high CSF protein levels. Ten patients (67%) tested positive for AQP4 antibodies, while four (27%) were AQP4 antibody-negative.

Almost all patients (92%) were initially treated with intravenous methylprednisolone. In addition to methylprednisolone, patients were treated with plasmapheresis and intravenous immunoglobulins. 84% (11 of 13 patients) recovered fully or partially after the treatment, whereas 2 of 13 patients (15%) died. The first patient died from multiorgan failure and sepsis secondary to the SARS-CoV-2 infection, and the second patient died from respiratory insufficiency and lymphopenia after cyclophosphamide treatment.

Cases that developed NMOSD following COVID-19 vaccination

This group included 26 patients. The median age was 50 years (ranging from 19 to 80 years). The cases came from 13 countries. Eight patients (31%) had a personal medical history of an immune-mediated condition, and four patients (15%) had a family medical history of an immune-mediated condition.

The median interval between COVID-19 vaccination and NMOSD first symptom onset was 10 days (ranging from one to 97 days). 54% (14/26) of cases received an mRNA vaccine, 31% (8/26) received a viral vector vaccine, and 15% (4/26) received an inactivated COVID-19 vaccine.

21 patients had *de novo* NMOSD onset, whereas three patients with previously diagnosed NMOSD experienced a relapse after the vaccination. One patient with a previous diagnosis of NMOSD was stable and relapse-free for eight years before he experienced a relapse triggered by vaccination. Two patients had a presumed multiple sclerosis that was

manifested as NMOSD after the vaccination.

Out of the 26 cases that developed NMOSD following COVID-19 vaccination, 58% (15 patients) developed their first neurological symptoms after the first dose of the vaccine, 23% (6 patients) after the second dose, and two patients (8%) after the third dose of the vaccine. One patient did not specify which dose induced neurological symptoms.

35% of cases (nine patients) were diagnosed with NMOSD after receiving the mRNA BNT162b2 (Pfizer-BioNTech) vaccine, 23% (six patients) after the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) viral vector vaccine, 19% (5 patients) after the mRNA-1273 vaccine (Moderna), 15% (four patients) after the Sinovac or Sinopharm inactivated COVID-19 vaccine and one case (4%) after receiving Sputnik V adenovirus viral vector vaccine.

The most common neurological clinical presentation was transverse myelitis, diagnosed in 65% (17 patients). Optic neuritis was diagnosed in 19% (five patients), area postrema syndrome in 12% (three patients), and brainstem syndrome in 12% (three patients).

The CSF examination demonstrated pleocytosis in 55% (11 of 20 patients) and elevated CSF protein levels in 45% (9 of 20 cases). 88% (22 patients) tested positive for AQP4 antibodies, while 12% (three patients) were AQP4 antibody-negative.

Almost all patients (96%) were initially treated with intravenous methylprednisolone. In addition to methylprednisolone, patients were treated with plasmapheresis and intravenous immunoglobulins. The maintenance immunotherapy included rituximab, azathioprine, cyclophosphamide, eculizumab, and mycophenolate mofetil. 88% (22 patients) recovered fully or partially after treatment, two patients (8%) did not have any improvement, and one patient (4%) died.

Conclusion

This review article has shown that SARS-CoV-2 infection and COVID-19 vaccination are associated with *de novo* onset or relapse of NMSOD. The authors discussed possible pathological mechanisms underlying NMOSD associated with COVID-19 or vaccination. As evidence suggests that SARS-CoV-2 may cross the blood-brain barrier, neuroinvasion by SARS-CoV-2 or its antigens may release CNS antigens such as AQP-4 into the systemic circulation, triggering the bystander immune cascade. Other mechanisms include the activation of toll-like receptors or the production of autoantibodies against myelin *via* molecular mimicry.

Although causation cannot be proven, cases with a short latency between the first symptoms of SARS-CoV-2 infection or COVID-19 vaccination and NMOSD manifestations (less than 28 days) are less likely to be coincidental. NMOSD manifestations may be coincidental in cases with longer latency, more than 28 days after the exposure. The authors concluded that the observed findings of NMOSD after acute SARS-CoV-2 infection or COVID-19 vaccination require further research in a larger population.

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Journal Reference

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