Neuromyelitis Optica

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KEYWORDS

• Neuromyelitis optica • Longitudinally extensive transverse myelitis • Optic neuritis • Area postrema syndrome • Aquaporin-4

KEY POINTS

- Neuromyelitis optica spectrum disorders (NMOSD) are rare inflammatory diseases of the central nervous system caused by astrocyte injury and secondary demyelination.
- It manifests clinically as acute, recurrent attacks of optic neuritis complicated by vision loss, longitudinally extensive transverse myelitis, and/or area postrema syndrome (intractable hiccups or nausea/vomiting).
- Aquaporin-4 autoantibodies (AQP4-IgG) are pathogenic, and detection in the serum confers moderate sensitivity and high specificity for the disease.
- Current treatment involves aggressive immunosuppression with pulse-dose steroids during acute attacks and long-term immunosuppression for attack prevention.

INTRODUCTION

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSDs) are rare antibody-mediated disorders of the central nervous system (CNS) with a predilection for the spinal cord and optic nerves.[1] The hallmark manifestations are recurrent longitudinally extensive transverse myelitis and optic neuritis (ON). NMOSD was previously thought to be a variant of multiple sclerosis (MS), but the identification of aquaporin 4–immunoglobulin G (AQP4-IgG; also known as NMO-IgG), a serologic antibody against AQP4, has led to an appreciation of these diseases as distinct entities. Whereas older diagnostic criteria defined NMO and NMOSD separately based on clinical criteria, the newest diagnostic criteria define a single diagnosis under the term NMOSD.

EPIDEMIOLOGY

Cases of NMO have been reported across all major ethnic groups, with a reported prevalence that ranges broadly across studies between 0.5 and 10 per 100,000.[2–5]

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Similar to other autoimmune disorders, there is a strong female predilection. In the case of the more common recurrent form of the disease, which represents 80% to 90% of cases, women are overrepresented with a ratio of 5 to 10:1.[6] The median age of onset is 39,[7] which differs from most patients with MS for whom the first manifestation is younger, typically between ages 20 and 40 years.[5,6,8]

The frequency of NMO/NMOSD is roughly the same worldwide, but cohort studies demonstrate a slightly higher proportion of AQP4-antibody–positive patients among Asian individuals with idiopathic demyelinating CNS diseases compared with whites.[1] Additionally, US cohort studies suggest higher prevalence among self-identified blacks.[4] This observation was supported by a population-based study that compared incidence and prevalence across 2 different counties. The prevalence in Olmsted County, Minnesota, a primarily Caucasian community, is 3.9 per 100,000 compared with 10 per 100,000 in Martinique, an island in the eastern Caribbean Sea where Afro-Caribbean ethnicity predominates.[5] The ethnicity-specific prevalence in these 2 counties was similar and 2.4 times higher among blacks relative to whites.

PATHOPHYSIOLOGY

In contrast to MS, NMO is more accurately considered an astrocytopathy as opposed to a primary demyelinating disease. Studies in animals and humans suggest a pathophysiologic model in which AQP4-IgG autoantibodies produced in the periphery enter the CNS where they bind astrocyte foot processes, inducing complement-mediated cell damage, granulocyte infiltration, and astrocyte death.[9–13] Astrocyte death results in secondary oligodendrocyte death, demyelination, and ultimately neuronal cell death. Mature NMO lesions demonstrate pan-necrosis with widespread infiltration of macrophages surrounded by AQP4-positive reactive astrocytes.[10]

Several studies in vitro and in vivo have demonstrated the importance of AQP4-IgG (also known as NMO-IgG) in the etiopathogenesis of NMO.[9–14] Aquaporin 4 is a water-selective channel that is predominately expressed in the CNS where it functions by facilitating bidirectional water flow across cell membranes in response to osmotic gradients.[10] Investigators have reproduced NMO lesions by injecting immunoglobulin from patients seropositive for NMO along with human complement into mice brains.[12] Seven days after injection, the animal brains develop key histologic features of NMO, including extensive inflammatory cell infiltrate, perivascular deposition of activated complement, loss of aquaporin-4 expression, demyelination, and neuronal cell death.

The pathogenicity and clinical relevance of AQP4-IgG has been confirmed in human studies. Patients with high serum antibody titers demonstrate higher disease activity and longer spinal cord damage on MRI during exacerbations.[13,14] Patients with high titers are also at increased risk for complete blindness and large cerebral lesions on MRI.[13] In a longitudinal study of 8 seropositive patients, serum antibody levels declined significantly after treatment with immunosuppressive agents, such as rituximab, azathioprine, or cyclophosphamide.[14]

The absence of autoantibody generation intrathecally in patients with NMO suggests that AQP4-IgG is produced in the periphery and enters the CNS secondarily.[15,16] Researchers have identified a subpopulation of interleukin (IL)-6–dependent B cells (CD27+ CD38+ CD180−) that are increased in the peripheral blood of patients with NMO and produce most of AQP4-IgG.[17] These B cells are morphologically and phenotypically identical to plasmablasts, expand during NMO relapse, and increase AQP4-IgG production in response to IL-6 signaling. Furthermore, blockade of IL-6 by anti-IL-6 receptor antibody reduces plasmablast survival in vitro, therefore raising interest in IL-6 inhibition as a therapy for this disease.[17]