NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) AND COMPLEMENT

Learn about anti-aquaporin-4 (AQP4) antibody positive NMOSD, the role of complement and the connection to life-altering attacks[1]

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NMOSD IS A RARE, AUTOIMMUNE DISEASE OF THE CENTRAL NERVOUS SYSTEM (CNS)[1]

Fast facts on NMOSD[1-4]

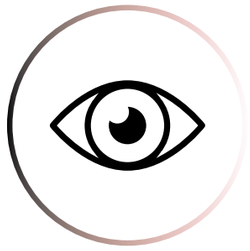
Gender bias	Average age at onset	Prevalence	Primary site of damage
9:1 females to males	39 years	0.5–4.4 per 100,000 people	Astrocytes

NMOSD is characterized by:[1,5]

Myelitis

- Longitudinal extensive transverse myelitis (LETM)
- Especially with paroxysmal tonic spasms

Bilateral optic neuritis



- Optic chiasm involvement
- Causes an altitudinal visual field defect OR
- Causes severe residual visual loss (acuity 20/200 or worse)

Area postrema syndrome

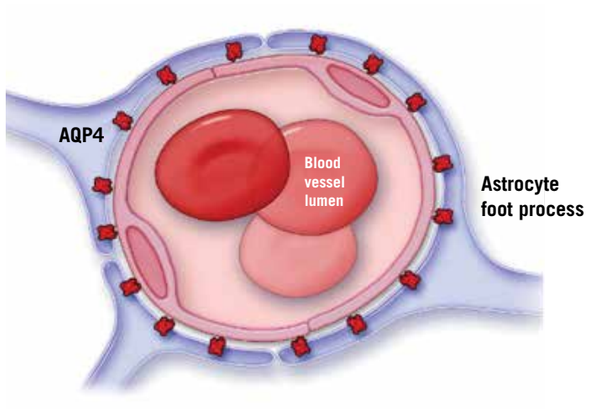
- Intractable hiccups
- Nausea and vomiting

NMOSD attacks are unpredictable and tend to be severe and recurrent.[4]

NMOSD attacks may result in cumulative disability with **devastating consequences**, including blindness, paralysis, and death.[1,4]

COMPLEMENT ACTIVATION, DUE TO AUTOANTIBODIES AGAINST AQUAPORIN-4 (ANTI-AQP4 Ab), IS ONE OF THE UNDERLYING CAUSES OF DAMAGE IN NMOSD[1]

What is aquaporin-4 (AQP4)?



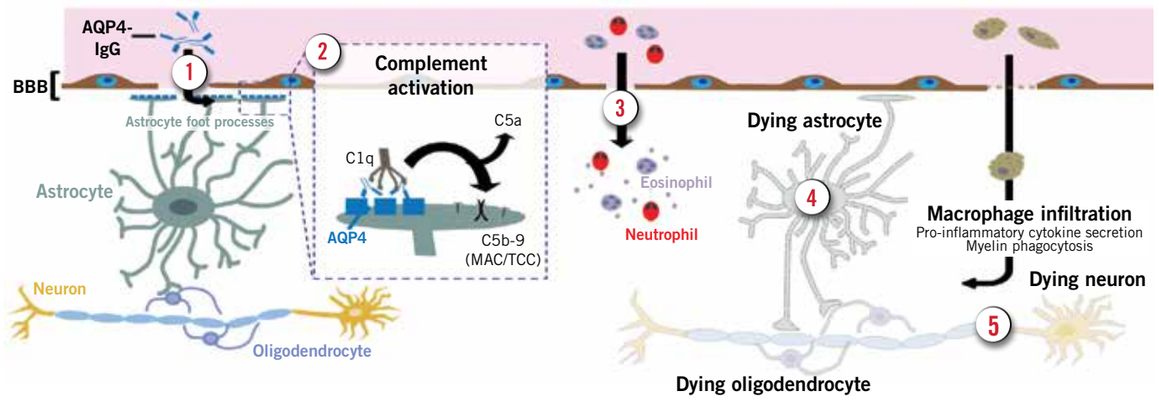
- A water channel protein most commonly found in the membranes of astrocytes[6]
- Facilitates water transport across the blood-brain barrier (BBB) and ependymal-cerebral spinal fluid (CSF) barriers[6]
- Highly expressed in:[7]
  1. The optic nerve, spinal cord, periventricular areas, hypothalamus, and subpial regions, as well as the brain stem and area postrema
  2. In Müller cells of the retina and in the retinal nerve fibre layer

What are anti-AQP4 antibodies?[8-12]

- Autoantibodies highly specific for NMOSD
- Extremely rare in healthy individuals
- Predominantly belong to the immunoglobulin G1 (IgG) subtype, the most potent immunoglobulin activator of the complement system
- Initiate formation of neuromyelitis optica lesions via complement activation after binding to AQP4
- Cell-based assay is the preferred method of serum testing for AQP4 autoantibodies

Approximately 75% of patients with NMOSD have antibodies against AQP4.[1]

THE ROLE OF THE COMPLEMENT SYSTEM IN ANTI-AQP4 ANTIBODY POSITIVE NMOSD[13,14]



BBB, blood-brain barrier; MAC, membrane attack complex; TCC, terminal complement complex.

1 AQP4-IgG accesses CNS through BBB[13]

AQP4-IgG accesses the CNS at areas of increased BBB permeability or injury or across endothelial cells by transcytosis. The antibody binds selectively to AQP4 antigen on astrocyte foot processes. The BBB is formed by various components, some of which are illustrated: endothelial cells and astrocyte foot processes.

2 Complement activation[14]

AQP4-IgG is predominantly of the IgG1 subclass, which strongly activates the complement system.

3 Leukocyte infiltration and degranulation[13]

The antigen-antibody binding leads to complement activation and downregulation of the AQP4 water channel. Activated complement increases blood-brain barrier permeability and leads to leukocyte infiltration, particularly neutrophils and eosinophils.

4 Loss of astrocytes[13]

Leukocyte degranulation results in astrocyte death.

5 Loss of other cells/demyelination[13]

Chemokines are released from leukocytes and dying astrocytes and attract macrophages. Macrophages produce pro-inflammatory substances that phagocytose the myelin, which is followed by oligodendrocyte and neuron death.

In NMOSD, complement activation can have destructive consequences.[1]

NOTES

EVERY ATTACK MATTERS

In NMOSD, complement activation can trigger attacks that may cause irreversible impairment, including blindness, paralysis, and death.[1]

References:
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