Neuromyelitis Optica Spectrum Disorders (NMOSD)

About NMOSD

Neuromyelitis optica spectrum disorders (NMOSD) are rare and severe autoimmune diseases of the central nervous system (CNS). They are characterised by severe, recurrent attacks and can cause blindness, paralysis or even death.[1] NMOSD often has similar symptoms to multiple sclerosis (MS), but can be differentiated by the presence of antibodies against the water channel protein aquaporin-4 (AQP4-IgG).[2] These autoantibodies are produced by a subpopulation of B cells, more precisely plasmablasts and some plasma cells, and attack astrocytes in the CNS.[3]

In Europe, approximately **10,000** people are living with NMOSD[4]

- Affected people suffer from various symptoms[5]
- NMOSD is often misdiagnosed as MS[6]
- AQP4-IgG antibodies are an important indicator for a correct diagnosis[5,7]
- B cells play a central role in the pathogenesis[3,8,9]

People living with NMOSD suffer from various symptoms

A large proportion of those affected present with symptoms including numbness or tingling sensations, difficulty walking, or varying degrees of visual impairment.[10] Symptoms can worsen suddenly, or new ones can appear quickly as attacks tend to occur in clusters.[1,11] The disease has a relapsing course, with 90% of all patients experiencing further attacks within five years of the first attack.[12] Women are nine times more likely to be impacted by AQP4-IgG seropositive (AQP4-IgG+) NMOSD.[13]

THE SIX CORE CLINICAL SYMPTOMS OF NMOSD ARE:[5]

- Inflammation of the optic nerve (optic neuritis)
- Longitudinal extensive inflammation of the spinal cord (myelitis)
- Area-postrema-syndrome with intractable hiccups, vomiting and nausea
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD typical lesion
- Symptomatic cerebral syndrome with NMOSD typical lesion

NMOSD has both a physical and psychological impact on those living with it. In addition to financial burdens resulting from high treatment costs and a reduced ability to work, bladder and bowel problems and sexual dysfunction are also possible, occurrences that significantly impair people's quality of life.[10,14]

41% of all AQP4-IgG+ patients can experience blindness in at least one eye 5 years after disease onset[15]

75% of all AQP4-IgG+ patients experience some degree of pain and 40% suffer from depression, associated with the severity of their pain[16]

8% of all AQP4-IgG+ patients may be confined to a wheelchair five years after disease onset[15]

NMOSD is often misdiagnosed as MS

For a long time, NMOSD was considered a variant of MS. It was not until 2004 that the discovery of AQP4-IgG autoantibodies helped to establish NMOSD as a disease in its own right, separate to MS.[2] At the beginning of the disease course, NMOSD symptoms may be mild, making differential diagnosis sometimes challenging.[17] Due to the involvement of the CNS and the relapsing nature of the disease, 41% of NMOSD patients are estimated to be misdiagnosed with multiple sclerosis (MS).[10,a] Lack of treatment or administration of the wrong type of treatment can have adverse effects on people living with NMOSD.[18] Therefore, it is critical to accurately differentiate NMOSD from MS and to increase the chance of establishing the correct diagnosis.

a Based on a study cohort (n=193)[10]

Main differences between NMOSD and MS

Characteristic	NMOSD	MS
Median age at disease onset[13,17]	40 years	29 years
Affected cells/structures in the CNS[19]	Astrocytes	Oligodendrocytes and myelin
Inflammation of the optic nerve (optic neuritis)[17]	Relatively common (up to 25%)	Uncommon
Longitudinal extensive inflammation of the spinal cord (myelitis)[17]	Very common (30–70% at first attack)	Rare
Area-postrema-syndrome[17]	Relatively common (12–17%)	Rare
Secondary, progressive course[20]	Uncommon (2%)	Frequent
Recovery from attacks[6]	Rare (17–33%)	Frequent
Autoantibodies against AQP4 in serum[6,15,21]	Very common (>73%)	Not present

AQP4-IgG is an important indicator for a correct diagnosis

How is NMOSD diagnosed?

Since 2015, the international diagnostic criteria for NMOSD include:[5]

1. At least one of the six core symptoms
2. AQP4-IgG in the serum
3. Exclusion of differential diagnoses

To verify these criteria, in addition to a medical history and physical examination, the following diagnostic tools are recommended:[2,5]

MRI scan

MRI can be used to help identify NMOSD characteristics in the brain, optic nerves and spinal cord.[5]

Lumbar puncture

During a lumbar puncture, cells in the nerve fluid are examined. Increased cell counts are often detectable during NMOSD attacks.[7]

Blood tests

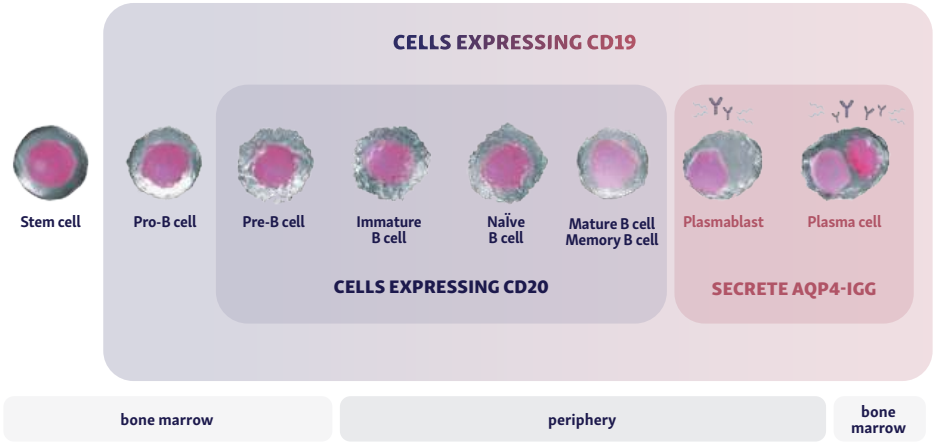
Among other inflammatory values, AQP4-IgG can be detected in the blood. It is recommended to use cell-based assays.[5]

While more than 73% of NMOSD patients have AQP4-IgGb, these are not detectable in MS.[6,7,15,21] Thus, the presence of AQP4-IgG in serum is a key feature for the differential diagnosis of NMOSD.[7] Since the AQP4 serostatus and antibody levels can change during the course of the disease, patients with suspected NMOSD should be retested if no autoantibodies have been initially detected.[7]

b Based on two study cohorts and the 2015 NMOSD criteria.5, 6, 7, 15, 21

B cells play a central role in NMOSD

B cells play a complex and fundamental role in the pathogenesis of NMOSD, with several mechanisms involved.[3] One of these is the production of the harmful AQP4-IgG. Their main sources are specific subpopulations of B cells.[9] These subpopulations, more specifically plasmablasts and some plasma cells, express the marker CD19 on their surface.[22]



Adapted from Siebert N et al. 2021.

The autoantibodies produced by CD19-positive (CD19+) plasmablasts and plasma cells are directed against the water channel protein AQP4 in the CNS, which is found on the surface of astrocytes.[7] This damages these cells and triggers a cascade, causing a complex autoimmune response.[3]

Therefore, because B cells play a central role in the pathogenesis of NMOSD, they represent an important therapeutic target for the treatment of NMOSD.[3] The targeted and effective depletion of B cells is particularly important in long-term therapy to prevent severe attacks.[5,18]

List of abbreviations

AQP4: Aquaporin-4

AQP4-IgG: Aquaporin-4-Immunglobulin G

AQP4-IgG+: Aquaporin-4-Immunglobulin G-seropositive

CD19: Cluster of Differentiation 19

CD19+: Cluster of Differentiation 19 positive

CD20: Cluster of Differentiation 20

CNS: Central nervous system

MS: Multiple Sclerosis

NMOSD: Neuromyelitis optica spectrum disorders

Glossary

Aquaporin-4: Water channel protein that is increased on the cell surface of astrocytes and is involved in the regulation of fluid and electrolyte balance in these cells

AQP4-IgG: Autoantibodies against aquaporin-4, which falsely signal the immune system to destroy the body's own structures

Area-postrema-syndrome: Caused by inflammatory lesions in the dorsal medulla and is characterised by persistent hiccups, nausea, and vomiting

Astrocytes: Cells in the CNS that perform important functions, including nourishment of nerve cells

B cells: Cells of the adaptive immune system that are responsible, among other things, for humoral defence by means of the production of antibodies

CD19: Surface protein characteristic of a broad spectrum of B cells

Lesion: Injury or disruption of function

MS: Chronic inflammatory disease of the CNS whose symptoms occur by demyelination

Myelin: Fatty substance used to insulate nerve cells, produced by oligodendrocytes and others

Myelitis: Inflammation of the spinal cord

Narcolepsy: Colloquially also called „sleeping sickness"; affected people tend to fall asleep suddenly

Optic neuritis: Inflammation of the optic nerves

Oligodendrocytes: Cells in the CNS that produce myelin

Plasmablasts: Maturation stage of B cells that already shows some characteristics of a plasma cell

Plasma cells: Differentiated B cells whose function is the formation and release of antibodies

Serology: Scientific study or diagnostic examination of blood serum

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