AFTER NMOSD ATTACKS, SHE MAY NEVER BE THE SAME[1]

COMPLEMENT IS A PRINCIPAL CAUSE OF THIS DEVASTATION

Aquaporin-4 immunoglobulin G positive (AQP4-IgG+) Neuromyelitis Optica Spectrum Disorder (NMOSD) is a relapsing autoimmune disease that primarily affects the optic nerve and spinal cord.[2,3]

ALEXION®

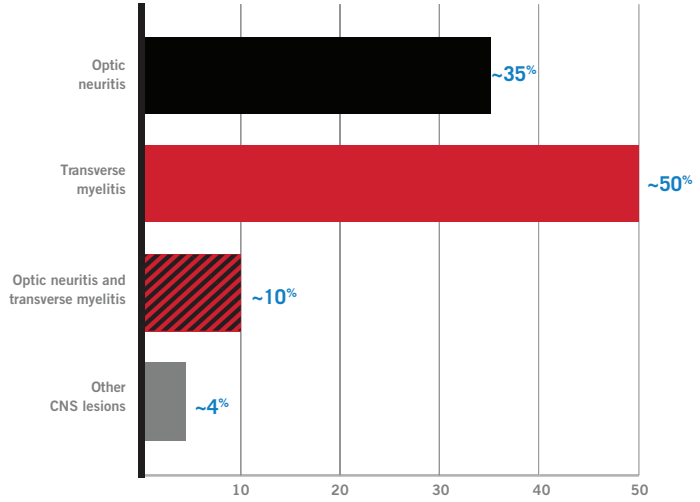
EVERY NMOSD ATTACK* MATTERS

ATTACKS CAN BE UNPREDICTABLE, SEVERE, AND RECURRENT[1,4,5]

- Relapses can cause permanent, cumulative disability, including blindness and paralysis, and some relapses can even lead to premature death[1,4,5]
- Initial presentation of NMOSD varies depending on the location of neural damage; however, an attack on the optic nerves or spinal cord typically occurs first[6]

76% of patients **did not fully recover** from the first myelitis or optic neuritis attack.[1†]

INITIAL PRESENTATION[6,a]



Other CNS lesions can be found in the area postrema, with symptoms of hiccups, nausea, and vomiting.[2,7]

[a]Based on a 5-year study of medical records from 187 patients with NMOSD from 3 large US medical centers.[6]

*In describing NMOSD, the words "attack" and "relapse" have been used interchangeably throughout this piece.

†Retrospective study based on the German Neuromyelitis Optica Study Group (NEMOS) registry that evaluated 175 Caucasian patients with NMOSD (defined by Wingerchuk et al 2006) and known AQP4-IgG antibody status.[1]

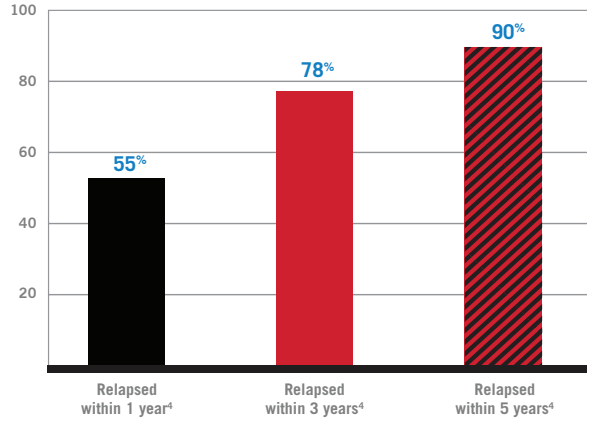
FOR THE MAJORITY OF PATIENTS WITH NMOSD, RELAPSE IS INEVITABLE[1,4]

NMOSD RELAPSES ARE UNPREDICTABLE AND OFTEN RECURRENT[1,5,8]

- Relapses often result in permanent disability

Up to **92.7%** of patients with AQP4-IgG+ NMOSD have relapsed.[1,5,8‡]

RATE OF RELAPSE OVER TIME IN PATIENTS WHO DEVELOP A RELAPSING COURSE (N=48)[4,a]



[a]Two-part study (retrospective from 1950 to 1993 and prospective from 1993 to 1997) based on a review of medical records from the Mayo Clinic that evaluated 48 patients with relapsing NMOSD; mean disease duration at last follow-up was 7.7 years.[4]

‡From a 2009 to 2011 retrospective study of the German NEMOS database, which included 137 AQP4-IgG+ NMOSD patients with a median disease duration of 60 months.[1]

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THE CRITICAL DIFFERENCES BETWEEN NMOSD AND MS

42.5% of patients with NMOSD were misdiagnosed with MS before AQP4-IgG testing.[1]*

- The wrong diagnosis of multiple sclerosis (MS) became less common after AQP4-IgG testing became commercially available in 2005 (20% vs 54.2% before 2005; $P<0.007$)[1]*
- Even after 2005, 1 in 5 patients continued to be misdiagnosed[1]*

KEY DIFFERENTIATORS OF NMOSD AND MS[2,9-18]

	NMOSD	MS
IMPACT		
Relapse-dependent disability	Relapses directly lead to cumulative disability	Largely independent of relapses
Median time to disability	12 years to EDSS 6	23.1 years to EDSS 6
DIAGNOSTIC CHARACTERISTICS		
ON	Common—severe	Common
TM	Common—characterized by longitudinal lesions[a]	Common
MRI	Longitudinally extensive lesions visible	No evidence of longitudinal lesions
CSF	Oligoclonal bands uncommon	Oligoclonal bands common
PATHOLOGY		
AQP4-IgG+	Yes (present in 73% of patients)	No (0% tested positive)
Complement mediated	Yes	No
Primary site of damage	Astrocytes	Oligodendrocytes and myelin sheath

Abbreviations: CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; ON, optic neuritis; TM, transverse myelitis.

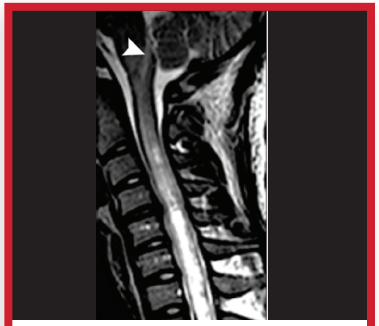
[a]Short lesions do not preclude a diagnosis of NMOSD.[19]

*Retrospective study based on the German NEMOS group registry of 175 patients with NMOSD and known AQP4-IgG antibody status; an expert panel of NEMOS members reviewed all cases from August 2009 to August 2011.[1]

THE MRI DIFFERENCES IN NMOSD AND MS

NEURAL DAMAGE IS VISIBLE ON MRIs[19]

NMOSD



Longitudinally extensive transverse myelitis, characteristic of NMOSD, extending into the area postrema

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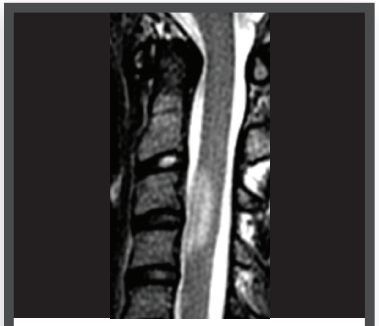
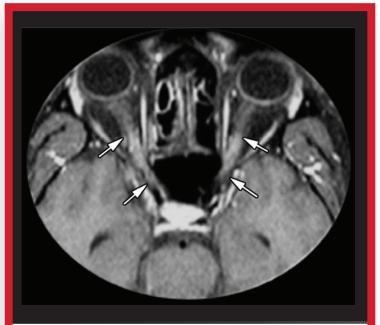
MS



Ovoid and longitudinally short lesions typical of MS myelitis

Reprinted with permission from *Radiographics*, 2018;38(1):169-193. ©RSNA.

NMOSD



Extensive bilateral gadolinium-enhancing lesions at the posterior portion of the optic nerves (arrows)

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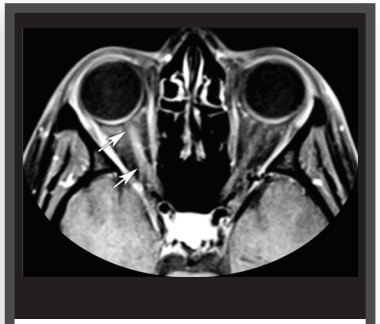
MS



Unilateral and short-length involvement of the right intraorbital optic nerve (arrows), showing the typical pattern of MS

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CONFIRM NMOSD BEFORE THE NEXT RELAPSE

2015 IPND DIAGNOSTIC CRITERIA FOR PATIENTS WITH AQP4-IgG+ NMOSD[20]

AT LEAST 1 CORE CLINICAL CHARACTERISTIC

- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Acute brain stem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

POSITIVE TEST FOR AQP4-IgG

EXCLUSION OF ALTERNATIVE DIAGNOSES, SUCH AS MS, SARCOIDOSIS, OR NEOPLASM

73% of NMOSD cases have AQP4-IgG antibodies present.[16]

AQP4-IgG antibodies are not present in MS cases.[10,17]

CELL-BASED ASSAY IS THE PREFERRED METHOD OF TESTING[20,21]

- ELISA testing could miss some of your most severe patients
- The likelihood of having a false-negative result with ELISA is between **1.5 AND 15 TIMES GREATER** when compared to the Mayo Clinic cell-binding assay

FALSE NEGATIVES CAN HAPPEN; IF SIGNS POINT TO NMOSD, A RETEST IS RECOMMENDED[20,21]

Common reasons include:

- Patient recovering from relapse
- Patient on immunosuppressant therapies
- Less accurate testing method was used

Abbreviation: IPND, International Panel for Neuromyelitis Optica Diagnosis.

DIAGNOSING NMOSD INVOLVES MULTIPLE ASPECTS

MEDICAL HISTORY AND PHYSICAL EXAM[22]

> **Perform detailed medical history, paying special attention to:**
  - Brain stem symptoms
  - Neuropathic pain
  - Painful tonic spasms

LABORATORY TESTS[20,22]

> **Blood work**

> **CSF diagnostics**

> **Test for serum AQP4-IgG antibodies**
  - Essential and most important test in the diagnosis of NMOSD
  - Rules out other infections/diseases

ELECTROPHYSIOLOGY ANALYSIS[22]

> **Visual evoked potentials**

> **Median and tibial somatosensory evoked potentials**

> **Motor evoked potentials**

IMAGING STUDIES[22]

> **MRI**
  - Image entire CNS
  - Central longitudinal spinal cord lesions are typical of NMOSD

> **Optical coherence tomography**

A positive test for AQP4-IgG antibodies is the most important component of the NMOSD diagnostic workup.[22]

ALEXION®

THE COMPLEMENT CASCADE IS A KEY CAUSE OF AQP4-IgG+ NMOSD

THE COMPLEMENT CASCADE, OR COMPLEMENT PATHWAY, IS A VITAL COMPONENT OF THE BODY'S IMMUNE SYSTEM[23,24]

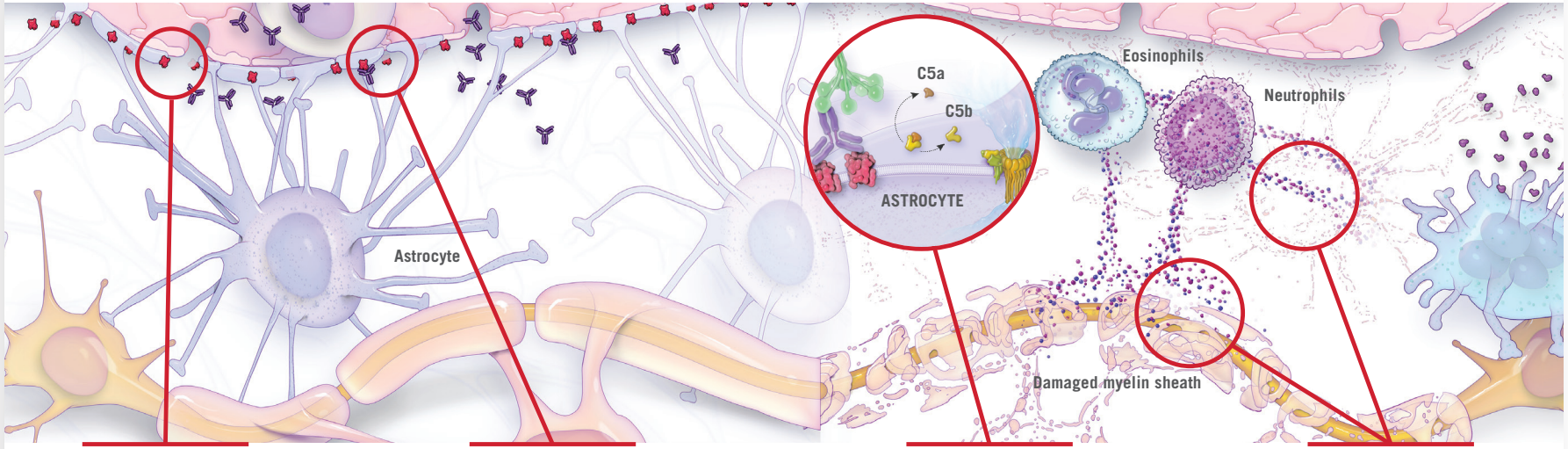
- Following injury or infection, complement acts quickly to detect, destroy, and eliminate microbes or cellular debris[25]
- Imbalances in the activation or regulation of the complement pathway are implicated in autoimmune diseases[26]

THE DEVASTATING CONSEQUENCES OF THE COMPLEMENT CASCADE

COMPLEMENT ACTIVATION RESULTS IN ASTROCYTOPATHY, INFLAMMATION, AND SUBSEQUENT DEMYELINATION AND NEURONAL DEATH[2,27,28]

- The complement cascade is activated by AQP4-IgG binding. This leads to the cleavage of C5[27]
- C5b initiates membrane attack complex formation on the astrocyte membrane and recruits and activates neutrophils[27]
- C5a preactivated neutrophils provide an inflammatory microenvironment[27]

PROGRESSION OF AQP4-IgG-MEDIATED COMPLEMENT ACTIVATION AND ASTROCYTOPATHY



1. INFILTRATION OF THE BLOOD-BRAIN BARRIER

Made by plasmablasts, AQP4-IgG crosses the blood-brain barrier into the CNS.[9]

2. AQP4-IgG BINDING

When AQP4-IgG binds to AQP4 on the foot processes of astrocytes, the complement cascade is activated.[27]

3. COMPLEMENT SYSTEM ACTIVATION

Within the cascade, cleavage of complement protein C5 into C5a and C5b causes downstream inflammation, membrane attack complex formation, and astrocyte injury.[27]

4. COMPLEMENT-MEDIATED DESTRUCTION

Continuous complement activation and ongoing inflammation lead to astrocyte necrosis, demyelination, and neuronal death.[27,28]

AN NMOSD ATTACK CAN LEAD TO IRREVERSIBLE DISABILITY

RATES OF VISUAL DISABILITY ARE HIGH[8]

At 5 years after onset:

41% of seropositive patients were expected to be **legally blind in at least 1 eye and 9% to be legally blind in both eyes.**[8*]

PAIN AND PARALYSIS CAN PREVENT MOBILITY[8]

At 5 years after onset*:

1 in 5 More than 1 in 5 (22%) patients with AQP4-IgG+ NMOSD would **require a walker** (EDSS 6).

1 in 11 Nearly 1 in 11 (8%) patients with AQP4-IgG+ NMOSD would **require a wheelchair** (EDSS 8).

76% of patients reported pain and discomfort, which can prevent mobility.[29†]

*Based on Kaplan-Meier analyses from a retrospective study of 140 patients with AQP4-IgG+ NMOSD identified from Mayo Clinic records from 2005 to 2011.[8]

†Based on a study of patients with NMOSD (N=21, with an average disease duration of 8.2 years).[29]

AN NMOSD ATTACK CORRELATES WITH A HIGH DEGREE OF BURDEN

EMERGENCY ROOM (ER) VISITS AND INPATIENT HOSPITAL CARE ARE COMMON[30]

35% to 60%

of patients **required an ER visit,** and many had multiple visits.[‡]

2.8 TO 5.2 AVERAGE
number of ER visits per patient.

22% to 54%

of patients **required inpatient admission.**[‡]

7.8 TO 9.6 AVERAGE
number of days spent in the hospital per admission.

FEAR OF A FUTURE ATTACK CAN TAKE A HEAVY EMOTIONAL TOLL[29]

The majority of patients with NMOSD experienced psychological consequences.

71% of patients reported having **anxiety and/or depression** (EQ-5D).[§]

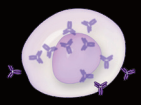
‡Based on a retrospective study of NMO patients (N=1349, of whom 134 had highly active NMO with ≥2 relapses in 12 months) that evaluated healthcare use within 12 months of a patient's first NMO encounter (index date) in a US administrative claims database. Respective numbers in the non-NMO control group (N=670) were 9.70% (of patients with ER visits), 0.49 (mean number of ER visits), 4.0% (of patients with inpatient admission), and 4.49 (average number of days/admission).[30]

§Based on a study of NMOSD patients (N=21, with an average disease duration of 8.2 years).[29]

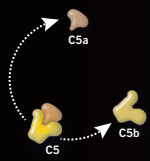
ALEXION®

EVERY RELAPSE MATTERS

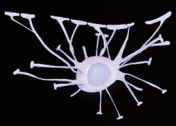
IN AQP4-IgG+ NMOSD, COMPLEMENT ACTIVATION IS A FUNDAMENTAL CAUSE OF RELAPSE[27]



AQP4-IgG BINDING ON ASTROCYTES ACTIVATES THE COMPLEMENT SYSTEM[10]



COMPLEMENT ACTIVATION RESULTS IN C5 CLEAVAGE, INFLAMMATION, FORMATION OF THE MEMBRANE ATTACK COMPLEX, AND INJURY TO ASTROCYTES[27]



ASTROCYTE INJURY AND LOSS LEADS TO NEURONAL DESTRUCTION[31]

LEARN ABOUT THE DESTRUCTION COMPLEMENT CAN CAUSE AT EveryAttackMatters.com

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