NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) AND THE CONSEQUENCES OF AN ATTACK

THE IMPORTANCE OF ANTI-AQUAPORIN-4 (AQP4) ANTIBODIES, RELAPSE, TERMINAL COMPLEMENT, AND THE BURDEN YOUR PATIENTS FACE

ALEXION®

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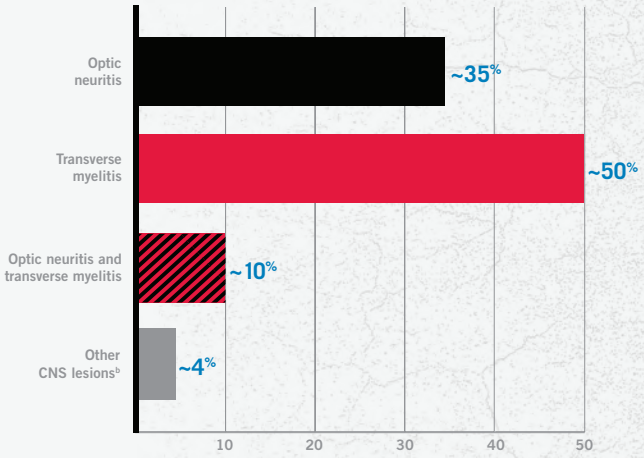
*The terms “attack” and “relapse” are used interchangeably.

NMOSD IS AN AUTOIMMUNE DISEASE OF THE CENTRAL NERVOUS SYSTEM[1]

THE OPTIC NERVES OR SPINAL CORD IS TYPICALLY ATTACKED FIRST[2,3]

INITIAL PRESENTATION[2,a]



[a]Based on a retrospective study of medical records from 187 patients with NMOSD over 5 years from 3 large US medical centers.[2]

[b]Other CNS lesions can be found in the area postrema, with symptoms of hiccups, nausea, and vomiting.[3,4]

Initial presentation varies depending on the type and location of neuronal damage.[2,3]

Patients most commonly present with optic neuritis and/or transverse myelitis.[2,3]

THE SITE OF INITIAL PRESENTATION CAN BE AN INDICATOR OF FUTURE DISABILITY[1]*

When the first attack was myelitis:

- Motor symptoms at first myelitis attack indicated more severe long-term motor disability (compared to sensory symptoms)[1,5]
- More than 1 myelitis attack in the first year predicted more severe long-term disability (compared to 1 myelitis attack)[5]

When the first attack was optic neuritis:

- Severity of first optic neuritis attack was a predictor of visual disability over time[1]*

*Based on a retrospective review of 106 patients with anti-AQP4 antibody-positive NMOSD from 3 tertiary centers in the United Kingdom and Japan. Median disease duration at last follow-up was 75 months.[1]

INITIAL PRESENTATION

RECOGNIZE THE INITIAL SIGNS OF NMOSD—THE FIRST ATTACK CAN BE AN INDICATOR OF FUTURE DISABILITY[1*]

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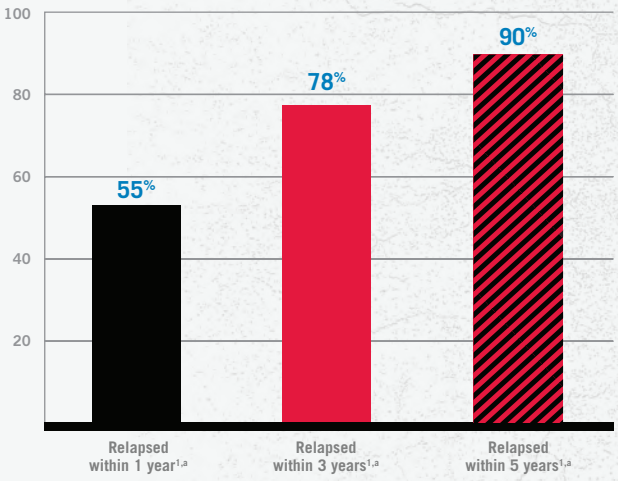
NMOSD ATTACKS ARE UNPREDICTABLE AND CAN HAVE POTENTIALLY DEVASTATING CONSEQUENCES[1-5]

UP TO 92.7%* OF NMOSD PATIENTS WHO ARE ANTI-AQP4 ANTIBODY POSITIVE HAVE RELAPSED, WITH RELAPSES OFTEN RESULTING IN PERMANENT DISABILITY[2-4]

Relapses can result in cumulative disability, potentially including:

- **Blindness[4]**
- **Paralysis[3,4]**
- **Pain[5]**
- **Anxiety[5]**
- **Depression[5]**
- **Mortality[3]**

PERCENT OF PATIENTS WHO RELAPSED WITHIN 1, 3, AND 5 YEARS OF THEIR INITIAL RELAPSE[1]



[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. Data based on time between first relapse (used to define a relapsing course) and final relapse.[1]

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ATTACKS

NMOSD ATTACKS CAN POTENTIALLY LEAD TO IRREVERSIBLE DAMAGE— DON'T IGNORE THE SIGNS

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References:

1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology*. 1999;53(5):1107-1114. **2.** Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain*. 2012;135(pt 6):1834-1849. **3.** Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation*. 2012;9:14. **4.** Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology*. 2013;81(14):1197-1204. **5.** Mealy MA, Boscoe A, Caro J, Levy M. Assessment of patients with neuromyelitis optica spectrum disorder using EQ-5D. *Int J MS Care*. 2018.

NMOSD RELAPSES CAN POTENTIALLY LEAD TO PERMANENT DISABILITY

RATES OF VISUAL DISABILITY ARE HIGH[1]

At 5 years after disease 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.**[1*]

PAIN AND PARALYSIS CAN PREVENT MOBILITY[1,2]

At 5 years after onset[1*]:

1 IN 5 More than 1 in 5 (22%) patients with anti-AQP4 antibody-positive NMOSD would **require a walker** (EDSS 6).[1]

1 IN 11 Nearly 1 in 11 (8%) patients with anti-AQP4 antibody-positive NMOSD would **require a wheelchair** (EDSS 8).[1]

76% of patients reported pain and discomfort.[2†]

*Based on Kaplan-Meier analyses from a retrospective study of 140 anti-AQP4 antibody-positive NMOSD patients identified from Mayo Clinic records from 2005 to 2011.[1]

†Based on a study of NMOSD patients (N=21, with an average disease duration of 8.2 years).[2]

IMPACT OF A RELAPSE

NMOSD CAN POTENTIALLY LEAD TO PERMANENT VISION LOSS AND IMMOBILITY[1]

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PATIENTS MAY BE MISDIAGNOSED WITH MS

In a retrospective study of patients with NMOSD, **42.5% (31/73) with available data were initially misdiagnosed with multiple sclerosis (MS).**[1]

- The wrong diagnosis of MS became less common after anti-AQP4 antibody testing became commercially available in 2005 (20% vs 54.2% before 2005; *P*<0.007)[1]*

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

LOOK BEYOND SHARED SYMPTOMATOLOGY TO DIFFERENTIATE NMOSD FROM MS

Pathophysiology is a key differentiator of these diseases.[2]

	NMOSD	MS
Anti-AQP4 antibodies	Yes (73% of patients[3])	No
Primary site of damage	Astrocytes	Oligodendrocytes and myelin
Complement mediated	Yes	No

Compared to MS, the long-term impact of relapses is greater in NMOSD.[4,5]

- Poorer relapse recovery (patients are less likely to return to baseline)
- Relapses that directly lead to cumulative disability

The demographics of patients and median age of onset also differ.[6]

NMOSD	MS
9:1 female	2:1 female
Median age of onset 39 years old	Median age of onset 29 years old

NMOSD vs MS

DON'T LET SIMILARITIES TO MS DELAY A CRITICAL NMOSD DIAGNOSIS

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1. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation*. 2012;9:14. **2.** Kawachi I, Lassmann H. Neurodegeneration in multiple sclerosis and neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. 2017;88(2):137-145. **3.** Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. 2017;264(10):2088-2094. **4.** Masuda H, Mori M, Uzawa A, et al. Recovery from optic neuritis attack in neuromyelitis optica spectrum disorder and multiple sclerosis. *J Neurol Sci*. 2016;367:375-379. **5.** Kim SM, Kim SJ, Lee HJ, Kuroda H, Palace J, Fujihara K. Differential diagnosis of neuromyelitis optica spectrum disorders. *Ther Adv Neurol Disord*. 2017;10(7):265-289. **6.** Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.

CELL-BASED ASSAY IS THE PREFERRED METHOD OF ANTI-AQP4 ANTIBODY TESTING[1]

The likelihood of false-negative results with ELISA methodology is between 1.5 and 15 times greater when compared to cell-based assay.[2]

FALSE NEGATIVES CAN HAPPEN FOR A VARIETY OF REASONS, INCLUDING[1,2]:

- Patient is recovering from a relapse
- Patient is currently taking immunosuppressive therapies
- Use of a less accurate testing method

IF CLINICAL SUSPICIONS OF NMOSD REMAIN, CONSIDER A RETEST IN 3 TO 6 MONTHS AFTER NEGATIVE RESULT[2]

73% Approximately 73% of patients with NMOSD **have pathogenic antibodies against AQP4**.[3]

92.7% In a clinical study, up to **92.7% of anti-AQP4 antibody-positive NMOSD patients relapsed**.[4-6*]

*From a 2009 to 2011 retrospective study of the German NEMOS database, which included 137 anti-AQP4 antibody-positive NMOSD patients with a median disease duration of 60 months.[5]

ANTI-AQP4 ANTIBODY TESTING

IF NMOSD IS SUSPECTED, TEST YOUR PATIENTS FOR ANTI-AQP4 ANTIBODIES[1,2]

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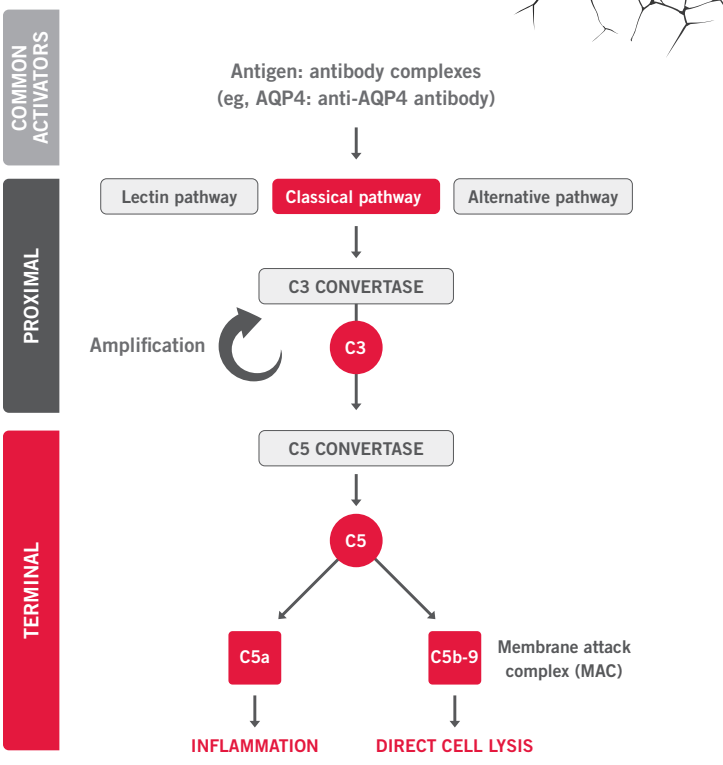
References:

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189. **2.** Waters PJ, Pittock SJ, Bennett JL, Jarius S, Weinshenker BG, Wingerchuk DM. Evaluation of aquaporin-4 antibody assays. *Clin Exp Neuroimmunol*. 2014;5(3):290-303. **3.** Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. 2017;264(10):2088-2094. **4.** Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology*. 2013;81(14):1197-1204. **5.** Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation*. 2012;9:14. **6.** Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain*. 2012;135(pt 6):1834-1849.

UNDER NORMAL CIRCUMSTANCES, THE COMPLEMENT SYSTEM AIDS IN IMMUNE RESPONSE[1-5]



- Binding of antigen to antibody activates the classical complement pathway[1,2]

- Proximal complement describes the 3 pathways upstream of the C5 complement protein that can initiate complement activation following different stimuli[4]

- Terminal complement includes C5 and its cleavage products C5a and C5b[1,2]
- C5a and C5b are proinflammatory molecules[1]
- C5b leads to formation of the MAC and cell lysis[1]

COMPLEMENT CASCADE

THE COMPLEMENT SYSTEM PLAYS A ROLE IN THE INNATE IMMUNE SYSTEM[6,7]

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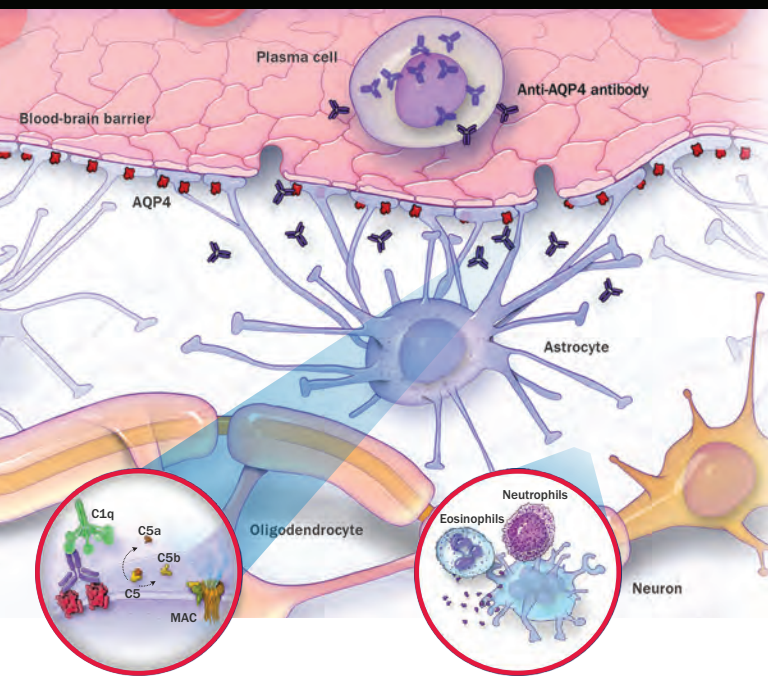
References:

1. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res.* 2010;20(1):34-50. **2.** Morgan BP. *Immunology.* 7th ed. Philadelphia, PA: Elsevier Ltd; 2006:87-104. **3.** Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood.* 2013;121(25):4985-4996. **4.** Emlen W, Li W, Kirschfink M. Therapeutic complement inhibition: new developments. *Semin Thromb Hemost.* 2010;36(6):660-668. **5.** Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol.* 2012;8(11):622-633. **6.** Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. Complement system part II: role in immunity. *Front Immunol.* 2015;6:257. **7.** Walport MJ. Complement: first of two parts. *N Engl J Med.* 2001;344(14):1058-1066.

WHAT IS COMPLEMENT?

The complement pathway is an innate immune component responsible for the formation of the MAC and bacterial lysis.[1,2]

- Complement cascade, or complement pathway, is a vital component of the body's immune system, most abundant in blood[1,2]
- Following injury or infection, the complement system acts quickly to detect, destroy, and eliminate microbes or cellular debris[3]
- The cascade is executed by a complex and tightly regulated group of more than 40 blood proteins known as complement proteins. The proteins include soluble and cell surface-bound components that work with receptors and regulators[1,3]
- Imbalances in the activation or regulation of the complement pathway are implicated in autoimmune diseases[4]



COMPLEMENT DAMAGE IN NMOSD

1 The complement cascade leads to MAC being deposited on the astrocyte membrane, where it recruits and activates neutrophils (via C5a as a chemoattractant)[2,5]

2 C5a preactivated neutrophils provide an inflammatory microenvironment[5,6]

- Neutrophils, eosinophils, monocytes, and macrophages

NMOSD AND COMPLEMENT

COMPLEMENT ACTIVATION IS ONE OF THE UNDERLYING CAUSES OF DAMAGE IN NMOSD[5-8]

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References:

1. Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. Complement system part II: role in immunity. *Front Immunol*. 2015;6:257. **2.** Walport MJ. Complement. First of two parts. *N Engl J Med*. 2001;344(14):1058-1066. **3.** Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res*. 2010;20(1):34-50. **4.** Ricklin D, Mastellos DC, Reis ES, Lambris JD. The renaissance of complement therapeutics. *Nat Rev Nephrol*. 2018;14(1):26-47. **5.** Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. *Nat Rev Neurosci*. 2013;14(4):265-277. **6.** Piatek P, Domowicz M, Lewkowicz N, et al. C5a-preactivated neutrophils are critical for autoimmune-induced astrocyte dysregulation in neuromyelitis optica spectrum disorder. *Front Immunol*. 2018;9:1694. **7.** Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. *Mayo Clin Proc.* 2017;92(4):663-679. **8.** Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805-815.

COMPLEMENT ACTIVATION IS ONE OF THE UNDERLYING CAUSES OF DAMAGE IN NMOSD[1-4]

1. INFILTRATION OF THE BLOOD-BRAIN BARRIER

Made by plasmablasts, anti-AQP4 antibodies cross the blood-brain barrier into the CNS.[5]

2. ANTI-AQP4 ANTIBODY BINDING

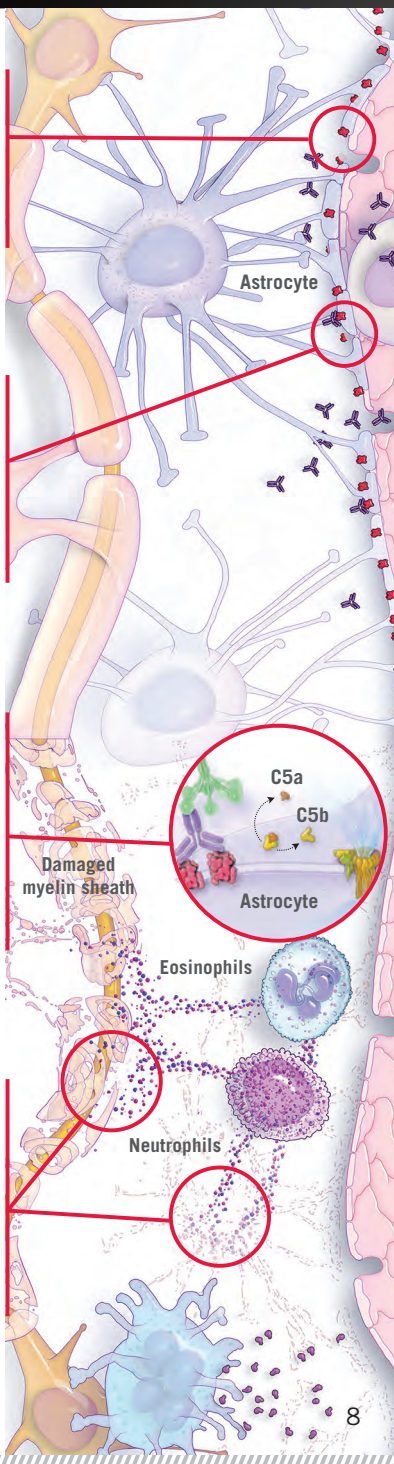
When anti-AQP4 antibodies bind to AQP4 on the foot processes of astrocytes, the complement cascade is activated.[2]

3. COMPLEMENT SYSTEM ACTIVATION

Within the cascade, cleavage of complement protein C5 into C5a and C5b causes downstream inflammation, MAC formation, and astrocyte injury.[2]

4. COMPLEMENT-MEDIATED DESTRUCTION

Continuous complement activation and ongoing inflammation lead to astrocyte necrosis, demyelination, and neuronal death.[2,6]



PATHOPHYSIOLOGY

COMPLEMENT ACTIVATION RESULTS IN DEMYELINATION AND NEURONAL DEATH[2,6]

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A HIGH BURDEN OF DISEASE IS EXPERIENCED BY NMOSD PATIENTS

WITHIN 1 YEAR OF A PATIENT'S INDEX DATE[1]*

35% TO 60%

of patients **required an ER visit,** many of whom had multiple visits.

2.8 TO 5.2 AVERAGE

number of ER visits per patient in a 12-month period.

22% TO 54%

of patients **required inpatient admission.**

7.8 TO 9.6 AVERAGE

number of days spent in the hospital per admission.

NMOSD PATIENTS ALSO REPORTED A SIGNIFICANT EMOTIONAL IMPACT[2]

71%

of patients reported having **anxiety and/or depression** (EQ-5D-5L).[2†]

*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).[1]

†Based on a prospective study of NMOSD patients (N=21, with an average disease duration of 8.2 years).[2]

DISEASE BURDEN

PATIENTS WITH NMOSD EXPERIENCED INCREASED ER VISITS AND HOSPITALIZATIONS COMPARED TO INDIVIDUALS WITHOUT NMOSD[1*]

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References:

1. Ajmera MR, Boscoe A, Mauskopf J, Candrilli SD, Levy M. Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica. *J Neurol Sci.* 2018;384:96-103. **2.** Mealy MA, Boscoe A, Caro J, Levy M. Assessment of patients with neuromyelitis optica spectrum disorder using EQ-5D. *Int J MS Care.* 2018.

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DISEASE FACT SHEETS

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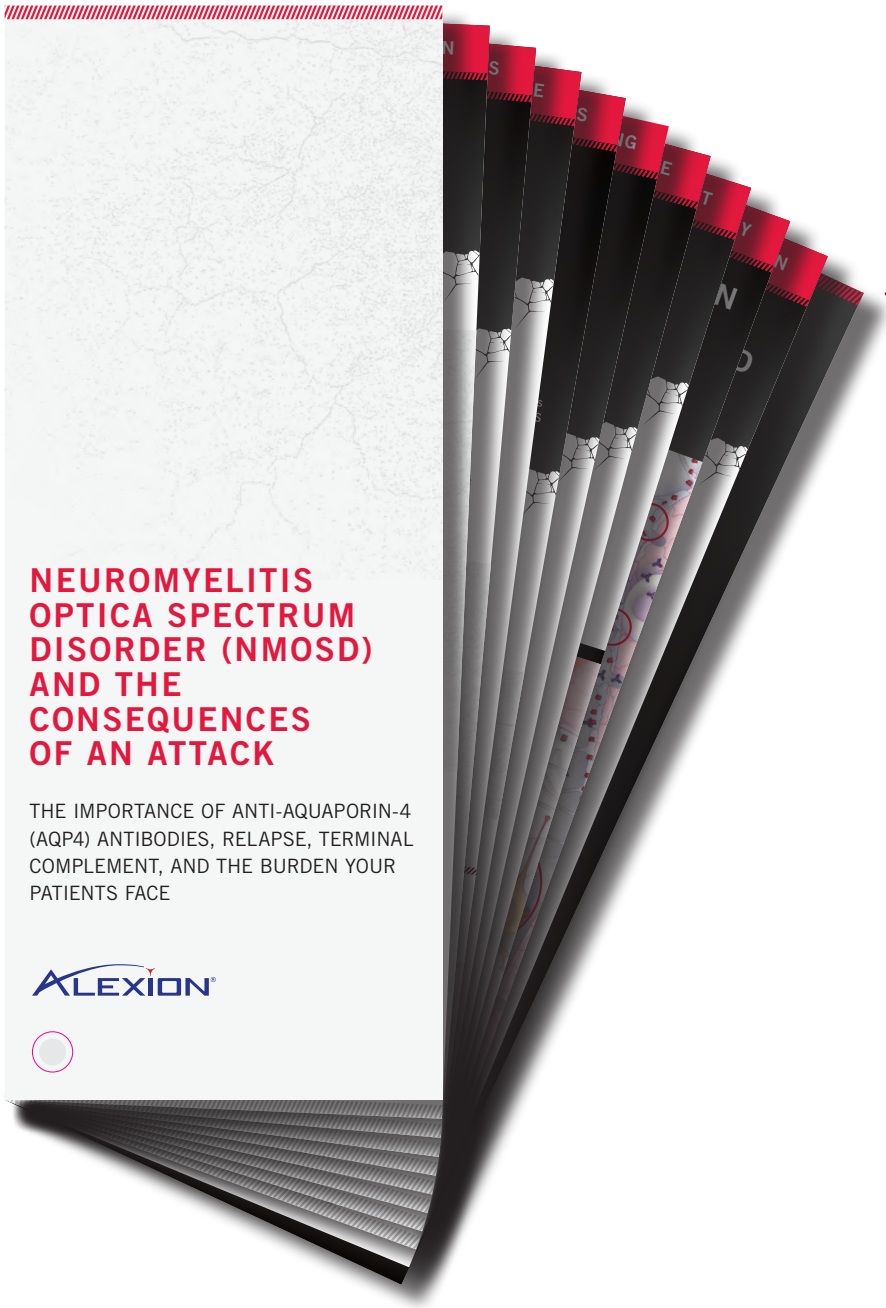

BACK

DISEASE FACT SHEETS - COVER

FRONT COVER

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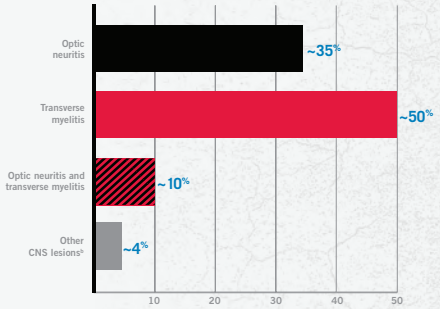

[a]Based on a retrospective study of medical records from 187 patients with NMOSD over 5 years from 3 large US medical centers.[2]

[b]Other CNS lesions can be found in the area postrema, with symptoms of hiccups, nausea, and vomiting.[3,4]

Initial presentation varies depending on the type and location of neuronal damage.[2,3]

Patients most commonly present with optic neuritis and/or transverse myelitis.[2,3]

THE SITE OF INITIAL PRESENTATION CAN BE AN INDICATOR OF FUTURE DISABILITY[1]*

When the first attack was myelitis:

- Motor symptoms at first myelitis attack indicated more severe long-term motor disability (compared to sensory symptoms)[1,5]
- More than 1 myelitis attack in the first year predicted more severe long-term disability (compared to 1 myelitis attack)[5]

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DISEASE FACT SHEETS - ATTACKS

FRONT

ATTACKS

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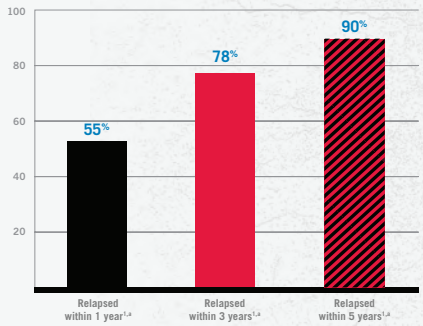
- **Paralysis[3,4]**
- **Pain[5]**
- **Anxiety[5]**
- **Depression[5]**
- **Mortality[3]**

PERCENT OF PATIENTS WHO RELAPSED WITHIN 1, 3, AND 5 YEARS OF THEIR INITIAL RELAPSE[1]



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BACK

ATTACKS

NMOSD ATTACKS CAN POTENTIALLY LEAD TO IRREVERSIBLE DAMAGE— DON'T IGNORE THE SIGNS

FIND OUT MORE AT

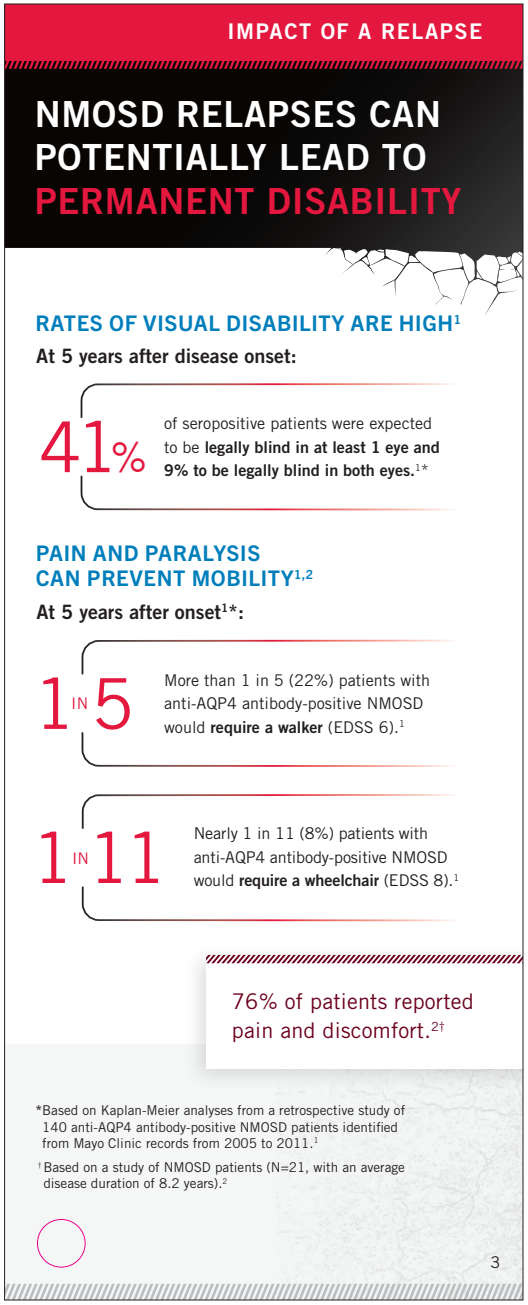
EveryAttackMatters.com

References:

1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology.* 1999;53(5):1107-1114. **2.** Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain.* 2012;135(pt 6):1834-1849. **3.** Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation.* 2012;9:14. **4.** Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology.* 2013;81(14):1197-1204. **5.** Mealy MA, Boscoe A, Caro J, Levy M. Assessment of patients with neuromyelitis optica spectrum disorder using EQ-5D. *Int J MS Care.* 2018.

DISEASE FACT SHEETS - IMPACT OF A RELAPSE

FRONT



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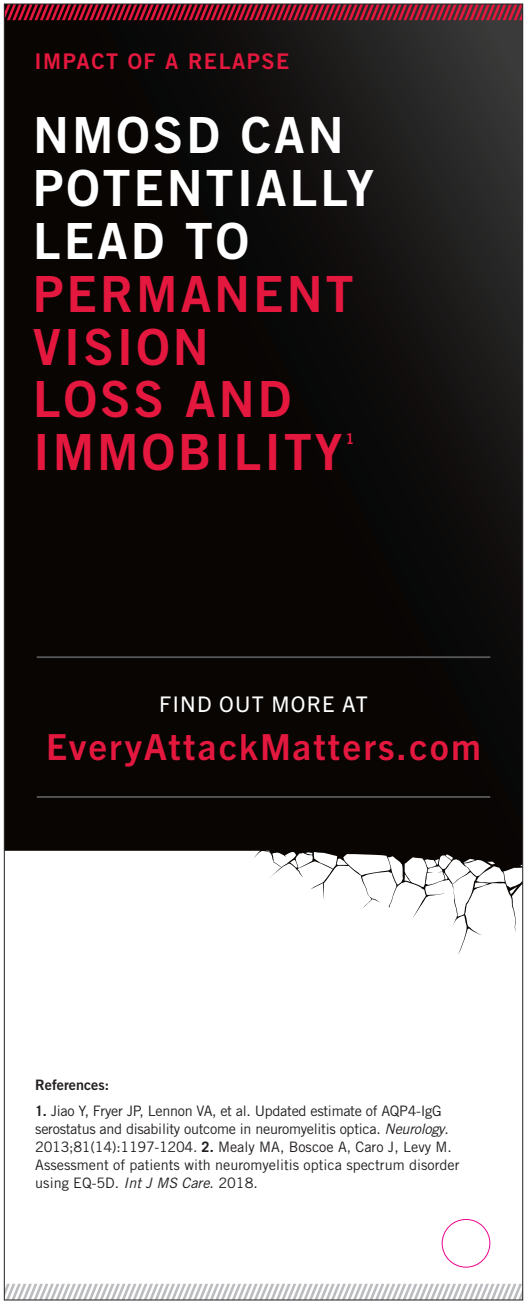

DISEASE FACT SHEETS - NMOSD VS MS

FRONT

PATIENTS MAY BE MISDIAGNOSED WITH MS

In a retrospective study of patients with NMOSD, **42.5% (31/73) with available data were initially misdiagnosed with multiple sclerosis (MS).**[1]

- The wrong diagnosis of MS became less common after anti-AQP4 antibody testing became commercially available in 2005 (20% vs 54.2% before 2005; *P*<0.007)[1]*

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

LOOK BEYOND SHARED SYMPTOMATOLOGY TO DIFFERENTIATE NMOSD FROM MS

Pathophysiology is a key differentiator of these diseases.[2]

	NMOSD	MS
Anti-AQP4 antibodies	Yes (73% of patients[3])	No
Primary site of damage	Astrocytes	Oligodendrocytes and myelin
Complement mediated	Yes	No

Compared to MS, the long-term impact of relapses is greater in NMOSD.[4,5]

- Poorer relapse recovery (patients are less likely to return to baseline)
- Relapses that directly lead to cumulative disability

The demographics of patients and median age of onset also differ.[6]

NMOSD	MS
9:1 female	2:1 female
Median age of onset 39 years old	Median age of onset 29 years old

BACK

DON'T LET SIMILARITIES TO MS DELAY A CRITICAL NMOSD DIAGNOSIS

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References:

1. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation*. 2012;9:14. **2.** Kawachi I, Lassmann H. Neurodegeneration in multiple sclerosis and neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. 2017;88(2):137-145. **3.** Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. 2017;264(10):2088-2094. **4.** Masuda H, Mori M, Uzawa A, et al. Recovery from optic neuritis attack in neuromyelitis optica spectrum disorder and multiple sclerosis. *J Neurol Sci*. 2016;367:375-379. **5.** Kim SM, Kim SJ, Lee HJ, Kuroda H, Palace J, Fujihara K. Differential diagnosis of neuromyelitis optica spectrum disorders. *Ther Adv Neurol Disord*. 2017;10(7):265-289. **6.** Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.

DISEASE FACT SHEETS - ANTI-AQP4 ANTIBODY TESTING

FRONT

ANTI-AQP4 ANTIBODY TESTING

CELL-BASED ASSAY IS THE PREFERRED METHOD OF ANTI-AQP4 ANTIBODY TESTING[1]

The likelihood of false-negative results with ELISA methodology is between 1.5 and 15 times greater when compared to cell-based assay.[2]

FALSE NEGATIVES CAN HAPPEN FOR A VARIETY OF REASONS, INCLUDING[1,2]:

- Patient is recovering from a relapse
- Patient is currently taking immunosuppressive therapies
- Use of a less accurate testing method

IF CLINICAL SUSPICIONS OF NMOSD REMAIN, CONSIDER A RETEST IN 3 TO 6 MONTHS AFTER NEGATIVE RESULT[2]

73% Approximately 73% of patients with NMOSD **have pathogenic antibodies against AQP4**.[3]

92.7% In a clinical study, up to **92.7% of anti-AQP4 antibody-positive NMOSD patients relapsed**.[4-6*]

*From a 2009 to 2011 retrospective study of the German NEMOS database, which included 137 anti-AQP4 antibody-positive NMOSD patients with a median disease duration of 60 months.[5]

BACK

ANTI-AQP4 ANTIBODY TESTING

IF NMOSD IS SUSPECTED, TEST YOUR PATIENTS FOR ANTI-AQP4 ANTIBODIES[1,2]

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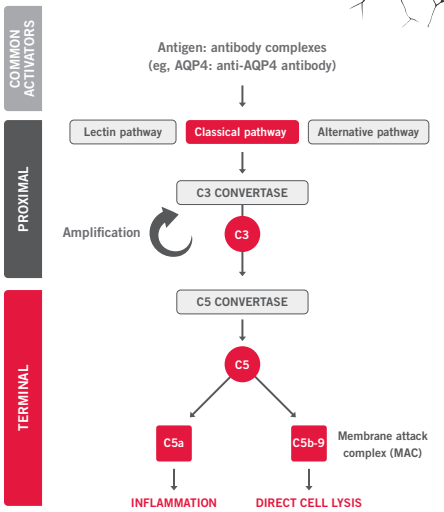
1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2):177-189. **2.** Waters PJ, Pittock SJ, Bennett JL, Jarius S, Weinshenker BG, Wingerchuk DM. Evaluation of aquaporin-4 antibody assays. *Clin Exp Neuroimmunol.* 2014;5(3):290-303. **3.** Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol.* 2017;264(10):2088-2094. **4.** Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology.* 2013;81(14):1197-1204. **5.** Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation.* 2012;9:14. **6.** Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain.* 2012;135(pt 6):1834-1849.

DISEASE FACT SHEETS - COMPLEMENT CASCADE

FRONT

COMPLEMENT CASCADE

UNDER NORMAL CIRCUMSTANCES, THE COMPLEMENT SYSTEM AIDS IN IMMUNE RESPONSE[1-5]



- Binding of antigen to antibody activates the classical complement pathway[1,2]

- Proximal complement describes the 3 pathways upstream of the C5 complement protein that can initiate complement activation following different stimuli[4]

- Terminal complement includes C5 and its cleavage products C5a and C5b[1,2]
- C5a and C5b are proinflammatory molecules[1]
- C5b leads to formation of the MAC and cell lysis[1]

6

BACK

COMPLEMENT CASCADE

THE COMPLEMENT SYSTEM PLAYS A ROLE IN THE INNATE IMMUNE SYSTEM[6,7]

FIND OUT MORE AT

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1. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res.* 2010;20(1):34-50. **2.** Morgan BP. *Immunology.* 7th ed. Philadelphia, PA: Elsevier Ltd; 2006:87-104. **3.** Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood.* 2013;121(25):4985-4996. **4.** Emlen W, Li W, Kirschfink M. Therapeutic complement inhibition: new developments. *Semin Thromb Hemost.* 2010;36(6):660-668. **5.** Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol.* 2012;8(11):622-633. **6.** Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. Complement system part II: role in immunity. *Front Immunol.* 2015;6:257. **7.** Walport MJ. Complement: first of two parts. *N Engl J Med.* 2001;344(14):1058-1066.

DISEASE FACT SHEETS - NMOSD AND COMPLEMENT

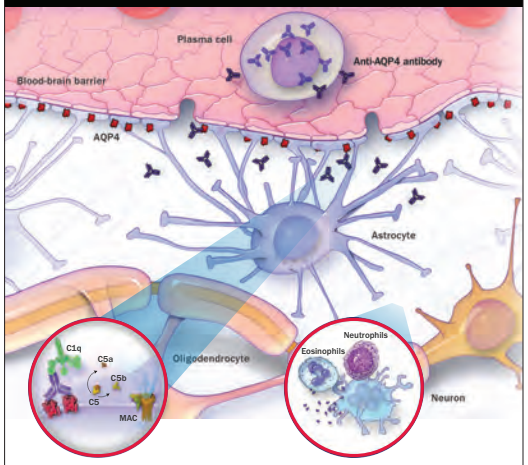
FRONT

NMOSD AND COMPLEMENT

WHAT IS COMPLEMENT?

The complement pathway is an innate immune component responsible for the formation of the MAC and bacterial lysis.[1,2]

- Complement cascade, or complement pathway, is a vital component of the body's immune system, most abundant in blood[1,2]
- Following injury or infection, the complement system acts quickly to detect, destroy, and eliminate microbes or cellular debris[3]
- The cascade is executed by a complex and tightly regulated group of more than 40 blood proteins known as complement proteins. The proteins include soluble and cell surface-bound components that work with receptors and regulators[1,3]
- Imbalances in the activation or regulation of the complement pathway are implicated in autoimmune diseases[4]



COMPLEMENT DAMAGE IN NMOSD

1 The complement cascade leads to MAC being deposited on the astrocyte membrane, where it recruits and activates neutrophils (via C5a as a chemoattractant)[2,5]

2 C5a preactivated neutrophils provide an inflammatory microenvironment[5,6]

- Neutrophils, eosinophils, monocytes, and macrophages

BACK

NMOSD AND COMPLEMENT

COMPLEMENT ACTIVATION IS ONE OF THE UNDERLYING CAUSES OF DAMAGE IN NMOSD[5-8]

FIND OUT MORE AT

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1. Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. Complement system part II: role in immunity. *Front Immunol.* 2015;6:257. **2.** Walport MJ. Complement. First of two parts. *N Engl J Med.* 2001;344(14):1058-1066. **3.** Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res.* 2010;20(1):34-50. **4.** Ricklin D, Mastellos DC, Reis ES, Lambris JD. The renaissance of complement therapeutics. *Nat Rev Nephrol.* 2018;14(1):26-47. **5.** Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. *Nat Rev Neurosci.* 2013;14(4):265-277. **6.** Piatek P, Domowicz M, Lewkowicz N, et al. C5a-preactivated neutrophils are critical for autoimmune-induced astrocyte dysregulation in neuromyelitis optica spectrum disorder. *Front Immunol.* 2018;9:1694. **7.** Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. *Mayo Clin Proc.* 2017;92(4):663-679. **8.** Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805-815.

DISEASE FACT SHEETS - PATHOPHYSIOLOGY

FRONT

PATHOPHYSIOLOGY

COMPLEMENT ACTIVATION IS ONE OF THE UNDERLYING CAUSES OF DAMAGE IN NMOSD[1-4]

1. INFILTRATION OF THE BLOOD-BRAIN BARRIER

Made by plasmablasts, anti-AQP4 antibodies cross the blood-brain barrier into the CNS.[5]

2. ANTI-AQP4 ANTIBODY BINDING

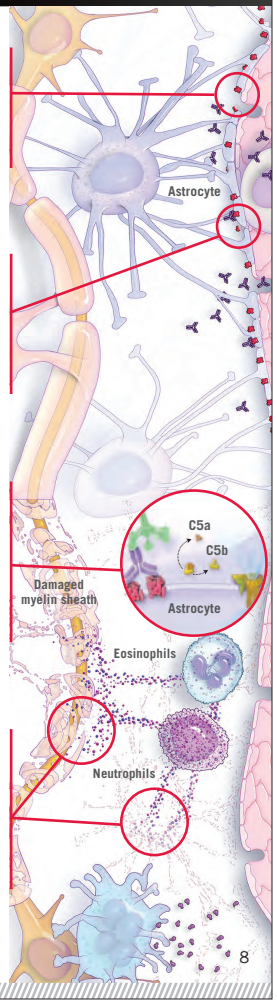
When anti-AQP4 antibodies bind to AQP4 on the foot processes of astrocytes, the complement cascade is activated.[2]

3. COMPLEMENT SYSTEM ACTIVATION

Within the cascade, cleavage of complement protein C5 into C5a and C5b causes downstream inflammation, MAC formation, and astrocyte injury.[2]

4. COMPLEMENT-MEDIATED DESTRUCTION

Continuous complement activation and ongoing inflammation lead to astrocyte necrosis, demyelination, and neuronal death.[2,6]



BACK

PATHOPHYSIOLOGY

COMPLEMENT ACTIVATION RESULTS IN DEMYELINATION AND NEURONAL DEATH[2,6]

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DISEASE FACT SHEETS - DISEASE BURDEN

FRONT

DISEASE BURDEN

A HIGH BURDEN OF DISEASE IS EXPERIENCED BY NMOSD PATIENTS

WITHIN 1 YEAR OF A PATIENT'S INDEX DATE[1]*

35% TO 60%

of patients **required an ER visit,** many of whom had multiple visits.

2.8 TO 5.2 AVERAGE

number of ER visits per patient in a 12-month period.

22% TO 54%

of patients **required inpatient admission.**

7.8 TO 9.6 AVERAGE

number of days spent in the hospital per admission.

NMOSD PATIENTS ALSO REPORTED A SIGNIFICANT EMOTIONAL IMPACT[2]

71% of patients reported having **anxiety and/or depression** (EQ-5D-5L).[2†]

*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).[1]

†Based on a prospective study of NMOSD patients (N=21, with an average disease duration of 8.2 years).[2]

BACK

DISEASE BURDEN

PATIENTS WITH NMOSD EXPERIENCED INCREASED ER VISITS AND HOSPITALIZATIONS COMPARED TO INDIVIDUALS WITHOUT NMOSD[1*]

*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).[1]

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1. Ajmera MR, Boscoe A, Mauskopf J, Candrilli SD, Levy M. Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica. *J Neurol Sci.* 2018;384:96-103. **2.** Mealy MA, Boscoe A, Caro J, Levy M. Assessment of patients with neuromyelitis optica spectrum disorder using EQ-5D. *Int J MS Care.* 2018.

DISEASE FACT SHEETS - BACK COVER

BACK COVER