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Neuromyelitis Optica Spectrum Disorder (NMOSD)

NMOSD attacks may be shattering to patients[1]

NMOSD is a disease of astrocyte destruction, characterized by recurrent unpredictable attacks that can result in cumulative disability, blindness, paralysis, or less commonly, premature death.[1-3]

- Rare diseases, like NMOSD, pose a unique challenge in the diagnosis of affected patients. The variable nature of clinical presentation of NMOSD combined with the rarity of the condition may lead to delay or miss in initial diagnoses.[4,5]
- Rapid identification of patients using cell-based assays to measure aquaporin-4 immunoglobulin G (AQP4-IgG) and MRI can help to ameliorate the long-term impacts of NMOSD.[1,3,6]

The deciphEHR™ program provides educational resources on disease characteristics and diagnostic best practices to help healthcare providers, health systems, hospitals, and specialty practices leverage their electronic health record (EHR) systems to triage suspect patients for further clinician evaluation leading to rapid, accurate diagnoses.

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Why is NMOSD patient recognition so important?

76% of NMOSD patients never fully recover from their first myelitis or optic neuritis attack, indicating NMOSD is a neurological emergency/crisis. By the time of diagnosis, some patients may have already experienced **multiple relapses*** and have **irreversible nervous system damage**.[†1]

At 5 years after disease onset,[‡] approximately **1 out of 5** patients with AQP4-IgG+ NMOSD would require a walker and **1 out of 11** patients will require a wheelchair.[3]

At 5 years after disease onset, **almost half (41%)** of seropositive patients are expected to be legally blind[§] in at least one eye and 9% to be legally blind[§] in both eyes.[3]

NMOSD has a higher prevalence and **disproportionately impacts patients of Asian and African descent** who may already have lack of access to the healthcare system.[7-10]

~43% of NMOSD patients were misdiagnosed/delayed in accurate diagnosis after initial consultation with a healthcare provider.[1] Misdiagnosis often favors more common diseases that share similar presentations, such as multiple sclerosis (MS).[‖11]

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Taking action is important: missed or delayed diagnoses may potentially increase mistreatment, mortality, and morbidity.[1] Consult the *NMOSD Program Implementation Guide* or visit deciphEHRrare.com to get started.

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

[†]Retrospective study based on the German NEMOS registry that evaluated 175 Caucasian patients with NMOSD (defined by Wingerchuk DM, et al. *Neurology*. 2006;66(10):1485-1489) and known AQP4 antibody status.

[‡]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 with some on therapy and some off therapy.

[§]Sustained visual acuity 20/200 or less for more than 6 months, with best possible correction.

[‖]The wrong diagnosis of MS became less common after aquaporin-4 immunoglobulin G (AQP4-IgG) testing became commercially available in 2005 (20% vs 54.2% before 2005; $P<0.007$).

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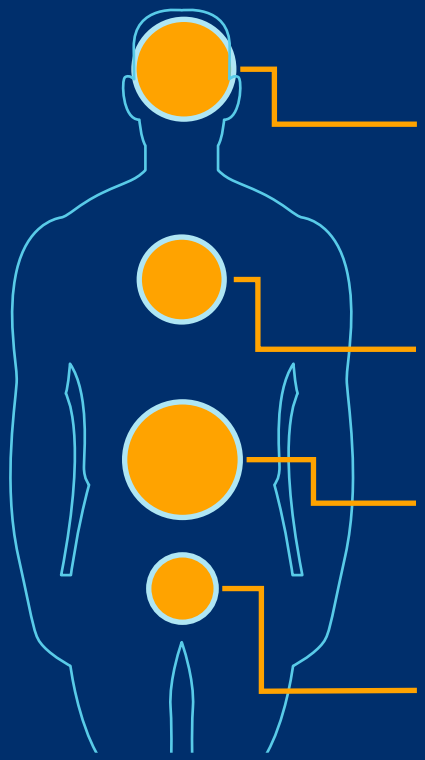
NMOSD is a serious and rare autoimmune disease of the central nervous system, frequently triggered by anti-aquaporin-4 (AQP4) antibody activation of the complement system. NMOSD can occur across the life span and across race and sex.

- **~1-10 per 100,000** is the estimated overall prevalence.[12]
- **80%** of the patients are females.[4]
- Patients of **African and Asian descent** have a **higher prevalence** of NMOSD and are **disproportionately impacted** by the disease (eg, more severe attacks at onset, a higher risk for developing blindness, higher mortality).[8-10,12]

NMOSD IS A HETEROGENEOUS DISEASE, COMPLICATING DIAGNOSIS. SIGNS AND SYMPTOMS CAN INCLUDE*[1,2,4,13,14]



- Vision impairments: eye pain, bilateral visual deficits, blindness
- Sensory disability
- Motor disability
- Excessive daytime sleepiness and fatigue
- Respiratory dysfunction/failure
- Intractable nausea and uncontrollable vomiting†
- Unexplained hiccups†
- Loss of bowel/bladder function
- Sexual dysfunction

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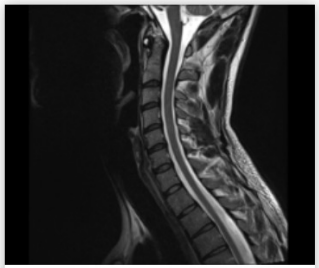
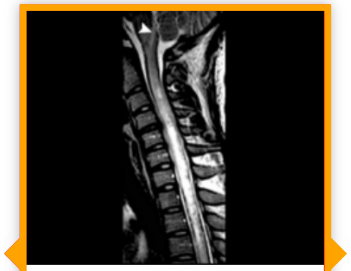
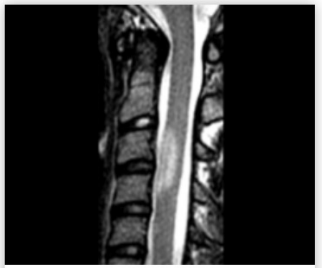
*List is not exhaustive. Less common symptoms may present (eg, delirium, seizures).
†Key differentiator for NMOSD.

~43% of NMOSD patients are misdiagnosed/delayed in diagnosis after first contact with a healthcare practitioner[1]

NMOSD is often underrecognized because the signs and symptoms overlap with other, very similar, neurological conditions, such as MS, myelin oligodendrocyte glycoprotein antibody disease (MOGAD), sarcoidosis, or neoplasm.[5,15] This has led to an average diagnostic delay of **~1-4 years.**[1]

MISDIAGNOSIS MAY BE AMELIORATED BY DIFFERENTIATION USING MRI TECHNOLOGY[6]

Most patients commonly present with optic neuritis (~35% of initial attacks), longitudinally extensive transverse myelitis (~50% of initial attacks), or both optic neuritis and transverse myelitis (~10% of initial attacks).*[16]

NORMAL[17]	NMOSD[18]	MS[18]
		
Sagittal T2-weighted image of normal cervical spine Courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 384181.	Longitudinally extensive transverse myelitis, characteristic of NMOSD, extending into the area postrema Reprinted with permission from *Radiographics*, 2018;38(1):169-193. ©RSNA.	Ovoid and longitudinally short lesions typical of MS myelitis Reprinted with permission from *Radiographics*, 2018;38(1):169-193. ©RSNA.

Misdiagnosis of MS can further exacerbate NMOSD as multiple currently prescribed medications for MS induce activation and accumulation of B cells in the peripheral blood, which can induce catastrophic disease activity of NMOSD.[9,11]

For more information on using MRI imaging as a differential diagnosis, consult the NMOSD Program Implementation Guide. In addition to MRI imaging, a positive serum antibody test is crucial for diagnosing AQP4 positive NMOSD.[6]

Other CNS lesions can be found in areas such as the area postrema, which can induce characteristic symptoms such as hiccups, intractable nausea, and vomiting.[14]

Images are illustrative and may not represent all NMOSD patients.

*Based on a retrospective review of medical records of 187 patients with NMOSD based on Wingerchuk DM, et al. *Neurology*. 2006;66(10):1485-1489 NMO Diagnostic Criteria.

Additional differential characteristics

Pathophysiology

Primary site of damage

NMOSD primarily targets astrocytes while MS primarily targets oligodendrocytes and myelin.[19]

The role of complement

Unlike MS, damage in NMOSD is complement mediated.[15,19]

Clinical characteristics for differentiation

Relapse-dependent disability

While in MS, disability is largely independent of relapses, in NMOSD, relapses may directly lead to cumulative disability.[15,20]

Median age of onset

In MS, the median age of onset is 29 years, whereas it's 39 years in NMOSD.[21]

Relapse recovery

Compared to MS, relapse recovery is poorer in NMOSD, with patients being less likely to return to baseline.[13]

Female to male ratio

The female to male ratio in MS is 2-4:1, but in NMOSD the ratio is 9:1.[10]

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Disease differentiation is important – EHR data may hold important information needed to triage patients.

Diagnostic criteria for patients with AQP4-IgG+* NMOSD[1]

At least 1 core clinical characteristic†:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome

Positive blood test for AQP4-IgG antibodies

False negatives are more likely to happen if:

1. A patient is recovering from relapse
2. A patient is currently on B cell or antibody-targeted therapies (plasma exchange, immunosuppressive drugs)
3. A less accurate method of testing was used – cell-based assays are the preferred method of testing relative to ELISA‡

If clinical suspicion remains, you may retest 3 to 6 months after a negative result.

Exclusion of alternative diagnosis such as MS, sarcoidosis, or neoplasm

*~ 1/4 of all NMOSD patients will be seronegative and can be diagnosed using more stringent diagnostic requirements.

For more information on diagnostic criteria, consult the NMOSD Program Implementation Guide.

†Additional, but more rare, core clinical characteristics include acute brain stem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions.[6]

‡The likelihood of false-negative results is 1.5-15 times greater with ELISA testing vs cell-based assay.[22]

Delays in diagnosis are possibly associated with more frequent attacks due to NMOSD[20]

NMOSD **attacks can be unpredictable, severe, and recurrent**.[23]
Every NMOSD attack may cause **potentially devastating and irreversible disability** such as vision loss, **pain, paralysis, and death in rare cases.**[1-3,23-25]

The severity of relapses/attacks often hospitalizes patients, requires them to make frequent visits to the doctors or pharmacy, or requires them to invest in ambulatory care.[26]

35%-60% of patients required an ER visit and many had multiple visits*[4]

Once patients are admitted to the hospital, they spend on average **~8-10 days** there[4]

22%-54% of patients require in-patient admission[4]

The average cost per relapse is estimated to be **~$11,883-$25,000** and patients experience on average **0.8-1.47 relapses a year**[26,27]

Patients with uncontrolled, relapsing NMOSD spend nearly **$70,000 more per year** than patients without relapses, with almost $25,000 coming from outpatient costs[27]

7x

The irreversible disability caused by NMOSD increases **average healthcare cost to the patient by almost 7x** compared to the average non-NMOSD, control patient[26]

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*Based on a retrospective study of patients with NMO (N=1349, of whom 134 had highly active NMO with ≥2 relapses in 12 months) that evaluated health care 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 9.7% (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).

Uncontrolled NMOSD can also have a negative impact on overall quality of life (QoL)

More than 70% of NMOSD patients surveyed reported that NMOSD negatively impacted their QoL. Factors most associated with decreased QoL included **pain, impact on career, and ability to work**.*[28]

~71% of NMOSD patients reported significant fatigue and poor sleep quality. This fatigue was found to be significantly correlated with negative QoL scores.†[29]

Lifetime depression and suicidality have been found to be significantly higher in NMOSD patients relative to patients with a similar neurological disorder (eg, MS).[30]

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*Based on a cross-sectional survey design to assess disease impact of 193 patients with NMOSD based on survey completion and results.

†Based on a retrospective study of 35 patients with NMOSD who were registered in the CNS Inflammatory Disease Registry at the Samsung Medical Center from June 2014 to May 2015 and completed the self-report questionnaires for the assessment of fatigue, sleep quality, depression, pain, and QoL.

Leveraging electronic health record (EHR) data may help healthcare organizations triage NMOSD patients for further clinical evaluation[31]

The problem

- NMOSD patients may face **delays in diagnosis**, which can result in **irreversible** attacks and **catastrophic** disease activity[1]
- Delays in diagnoses are driven in part due to **misdiagnoses** of similarly presenting conditions, such as MS[1,5]

deciphEHR™ may be able to help

- **Your EHR system can work for you to help triage suspect NMOSD patients** – Alexion provides resources for you to share with your EHR team
- deciphEHR™ program identifies **clinical features** that may be used to build **suspect patient lists** in your EHR to triage patients for further clinical evaluation
- **Best practice alerts** (BPAs) can be utilized in your EHR system to support healthcare providers as they navigate the NMOSD diagnostic process

The benefits

- EHR systems can help triage patients based on existing data, prioritize resources, and provide more **coordinated care to foster improved outcomes**[31]
- Automated **BPAs** and **order sets** assist providers in timely access to diagnostic best practices and **reduce inefficiency** by decreasing manual efforts[32-35]

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For more information on clinical features of NMOSD, suspect patient lists, and BPAs, consult the NMOSD Program Implementation Guide.

Alexion provides educational resources to help you leverage your EHR, which may decrease the diagnostic timeline for many NMOSD patients[33]

- A majority of NMOSD patients are facing large delays in diagnosis and misdiagnosis[1,5]
- Delays in diagnosis can result in repeated attacks that can induce irreversible nervous system damage[1]
- Misdiagnosis of MS can result in patients receiving B cell therapies that can induce catastrophic NMOSD disease activity due to accumulation of B cells in the peripheral blood[9,11]
- Delays in accurate diagnosis not only impact the patient but can increase burden on the healthcare system at large[4,26,27]
- The data needed to shorten diagnostic delays may exist in your EHR
- The deciphEHR™ program has suggested EHR codes that may be used to build patient lists to flag suspect NMOSD patients for further clinical evaluation

Visit deciphEHRrare.com or contact your Alexion representative to find out how utilizing your EHR system can help you triage patients who would benefit from further clinical evaluation for NMOSD.

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