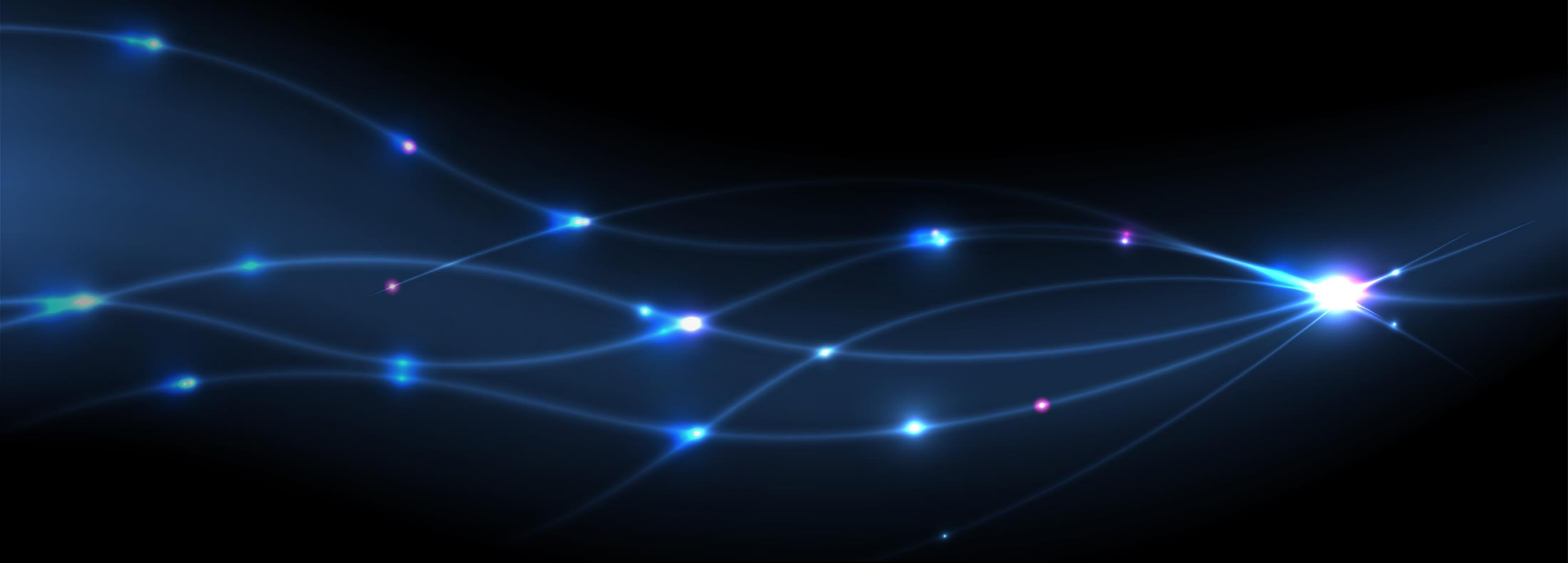


Severity and Unpredictability of NMOSD

Contents & learning objectives

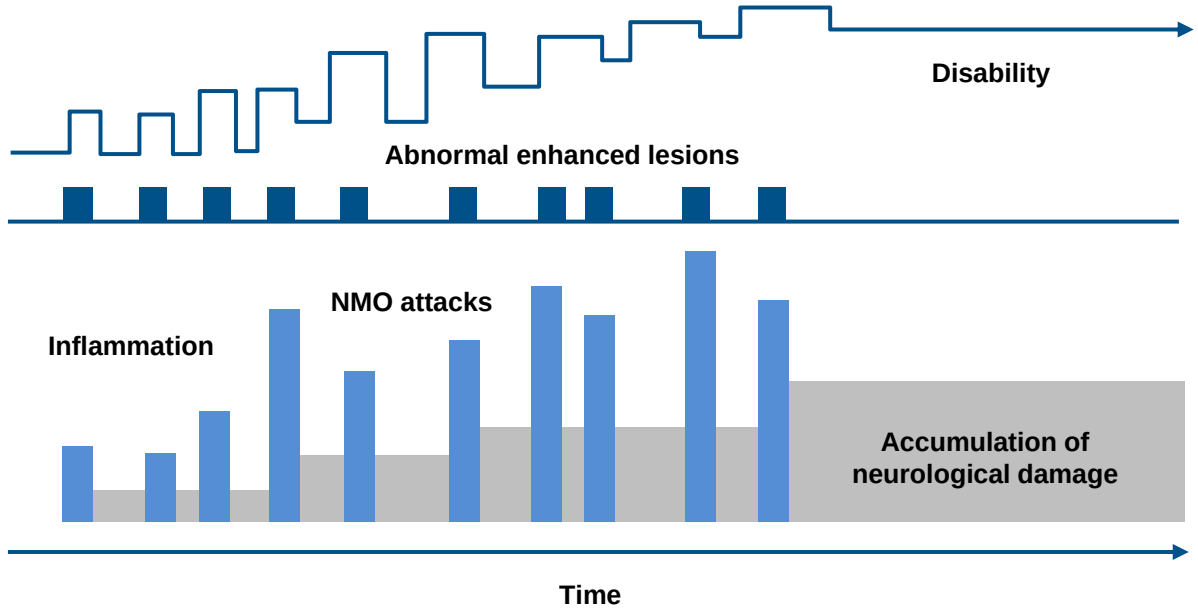
Learning objective	Content	Slide number
1. Refresh your memory on the difference in typical disease course between NMOSD and MS	MS and NMOSD disease course	3
2. Understand that NMOSD attacks vary in frequency and severity, and how that affects disability accrual	Introduction to the EDSS	4
	Relapses and their symptoms	5
3. Learn that relapses are unpredictable, and tend to occur in clusters of several attacks of a similar phenotype	Unpredictability of relapses	7
4. Evaluate some of the prognostic factors that help predict NMOSD relapse risk, and understand why early diagnosis and treatment is vital	Risk factors for relapses	12
Summary		14

Patients with NMOSD frequently experience a relapsing disease course, with repeated attacks leading to accumulating neurological disability[1,2]

The disease course differs between NMOSD and MS

- Unlike in MS, it is rare for patients with NMOSD to experience a progressive, subtle accumulation of disability[3]
  - Instead, inflammation and the accumulation of neurological damage in NMOSD are tied to relapse events[3]
- Residual disability, or incomplete recovery, is common with relapses in NMOSD[1]

NMOSD disease course[3]



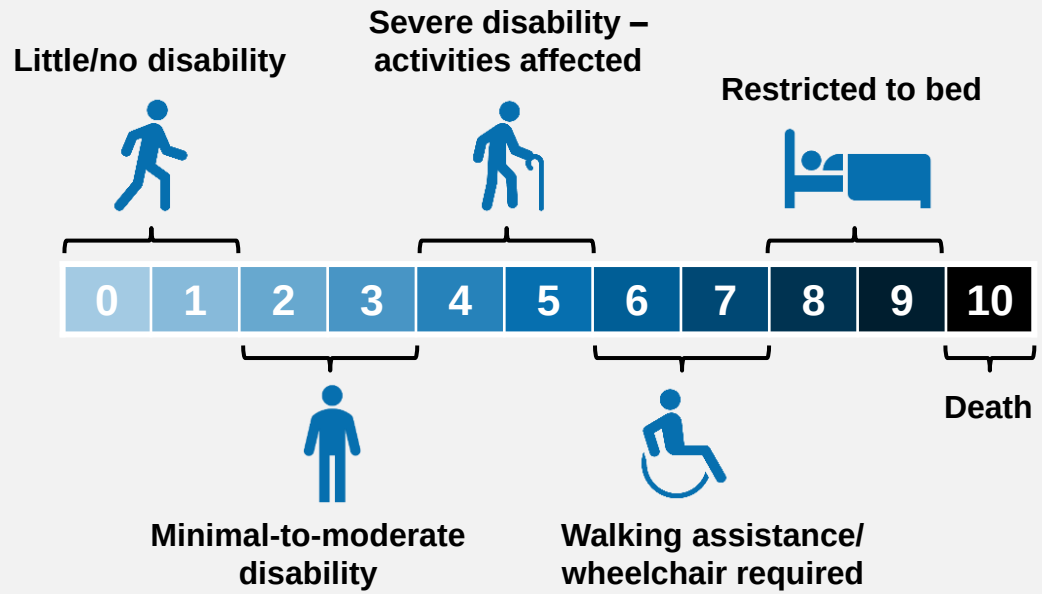
MS, multiple sclerosis; NMOSD; neuromyelitis optica spectrum disorder.

1. Oh J Levy M. *Neurol Res Int* 2012;2012:460825; 2. Kessler RA et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e269; 3. Kawachi I et al. *J Neurol Neurosurg Psychiatry* 2017;88:137–145.

Disability in MS and NMOSD can be measured using the Expanded Disability Status Scale

- The **EDSS**, originally developed for MS, is an instrument that enables neurologists to **score patients' disability out of ten**
  - Higher scores indicate greater disability
- A patient's EDSS score is based on measures of impairment across **eight functional systems**:
  - Visual
  - Cerebellar
  - Brainstem
  - Sensory
  - Bowel and bladder
  - Cerebral or mental
  - Pyramidal motor function
  - Other
- To view a copy of the full EDSS assessment criteria, please click here[2]

The EDSS[1]



EDSS, expanded disability status scale; MS, multiple sclerosis; NMOSD; neuromyelitis optica spectrum disorder.

1. Kurtze JF. *Neurology* 1983;33:1444–1452; 2. Kurtzke Expanded Disability Status Scale (EDSS). National MS Society. http://www.nationalmssociety.org/nationalmssociety/media/msnationalfiles/brochures/10-2-3-29-edss_form.pdf. Accessed October 2020.

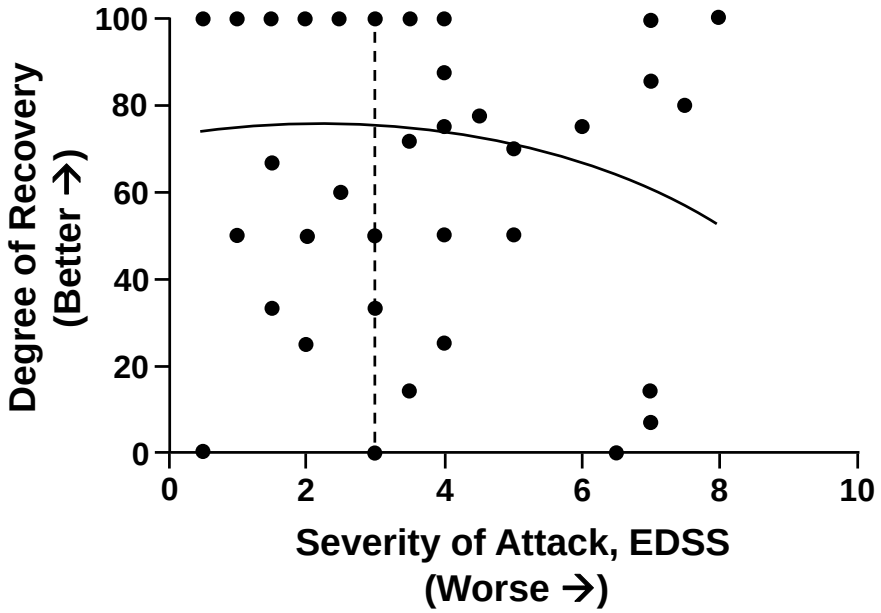
A single NMOSD attack can cause permanent disability and/or bilateral vision loss[1,2]

One in four patients with NMOSD experience **significant, long-term disability** (EDSS score ≥6) as a result of their **first attack**[1]

The first NMOSD attack may be so severe that **41%** and **21%** of patients develop **blindness in one or both eyes**, respectively[1]

Severe NMOSD attacks (i.e. those that cause an increase in EDSS score of ≥3 points) are **significantly more likely to cause permanent disability** than less severe attacks[2]

However, for most patients with NMOSD, **multiple relapses** are required in order to **accumulate significant disability**[1,3]



Reproduced from Banerjee A et al. 2019.[2]

EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder.

1. Palace J et al. *Brain* 2019:142;1310–1323; 2. Banerjee A et al. *Mult Scler Relat Disord* 2019;28:60–63; 3. Sellner J et al. *Eur J Neurol* 2010;17:1019–1032.

In general, the symptoms associated with NMOSD relapses are more severe than with MS relapses

- Acute NMOSD attacks of **optic neuritis** and/or **transverse myelitis** can be **severe** or **fatal**[1–3]
- The symptoms of NMOSD attacks are often more disabling than in MS, with poorer recovery if untreated[1,3]
- In contrast with MS, progression independent of relapse activity (PIRA) is not thought to be a driver of disease worsening in NMOSD[4]

Optic neuritis

Optic neuritis in NMOSD is usually more severe and more extensive than in MS

- Attacks are more likely to be bilateral and recurrent,[2,5] and result in more severe residual vision loss[6,7]

Longitudinally extensive transverse myelitis (LETM)

Transverse myelitis in NMOSD is frequently severe, leading to motor, sensory, and/or bowel and bladder dysfunction[8]

- In contrast to MS, myelitis in NMOSD tends to span ≥3 vertebral segments (LETM), and often affects the motor, sensory, and autonomic neurological pathways simultaneously[9]

Area postrema syndrome

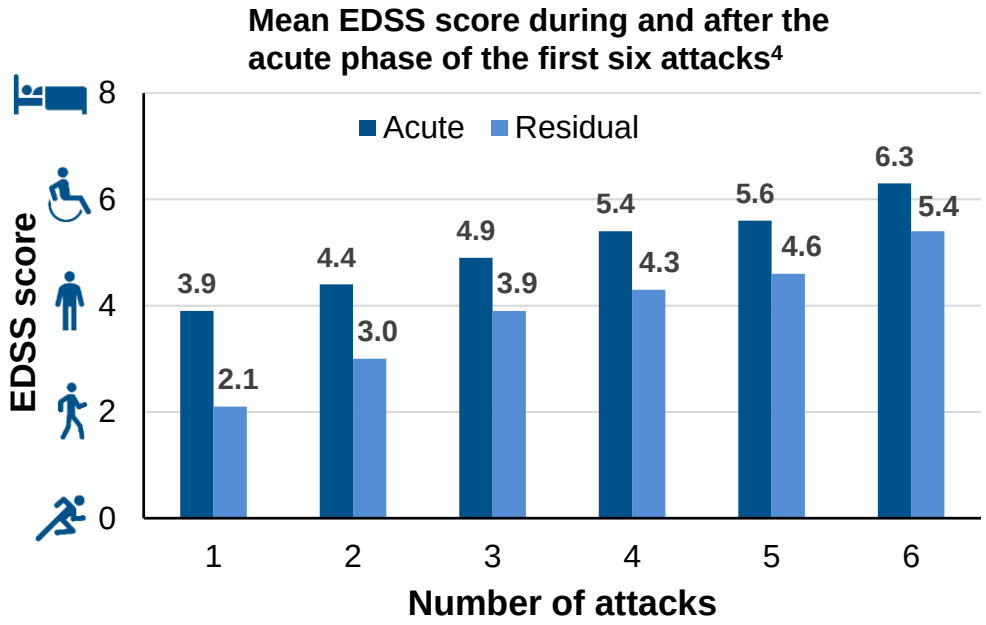
Area postrema syndrome is also relatively common in NMOSD but rare in MS, with patients developing intractable hiccups and/or nausea/vomiting[5]

EDSS, expanded disability status scale; LETM, longitudinally extensive transverse myelitis; MS, multiple sclerosis; NMOSD; neuromyelitis optica spectrum disorder.

1. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 2. Kawachi I, Lassmann H. *J Neurol Neurosurg Psychiatry* 2017;88:137–145; 3. Jarius S et al. *Clinical and Experimental Immunology* 2014;176:149–164; 4. Akaishi T et al. *Scientific Reports* 2020;10:13890; 5. Wingerchuk DM et al. *Neurology* 2015;85:177–189; 6. Finke C et al. *JAMA Neurol* 2018;75:296–303; 7. Levin MH et al. *Prog Retin Eye Res* 2013;36:159–171; 8. Kim S-M, et al. *Ther Adv Neruol Disord* 2017;10:265–89; 9. Romeo AR et al. *Curr Opin Rheumatol* 2019;31:250–255.

NMOSD relapses can occur frequently and without warning, leading to the rapid accumulation of disability

- Occurrence of relapses can be random,[1] with the time between attacks lasting anywhere from weeks to years[2]
- Up to 90% of patients with NMOSD show a recurrent episodic attack disease course[2]
  - Of these patients, up to 60% relapse within 1 year and 90% relapse within 3 years[2,3]
- Several cohort studies identified a mean annualized relapse rate of 0.8–1.3, with an average time to first relapse of 10–17 months[3–5]
- Because patients with NMOSD can experience relapses at a relatively high frequency, they can accrue disability more quickly than in MS[6]



Reproduced from Ghezzi A et al. 2004.[4]

EDSS, expanded disability status scale; NMOSD; neuromyelitis optica spectrum disorder.

1. Akaishi T et al. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e640; 2. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 3. Kitley J et al. *Brain* 2012;135:1834–1849; 4. Ghezzi A et al. *J Neurol* 2004;251:47–52; 5. Seok JM et al. *J Neurol Sci* 2016;368:209–213; 6. Jarius S et al. *Clinical and Experimental Immunology* 2014;176:149–164.

While NMOSD relapses remain clinically unpredictable, some attacks have been shown to cluster in timing and anatomical region

NMOSD relapses are highly unpredictable[1–3]

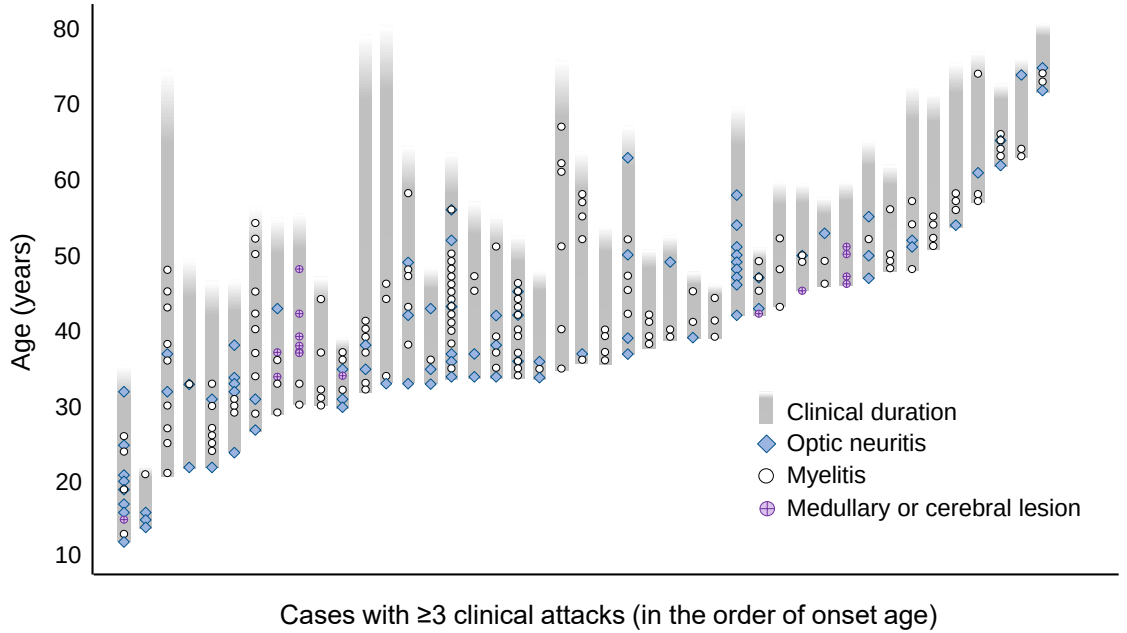
- It is not possible to accurately predict the timing or CNS location of future NMOSD relapses[1,2]
- However, some patients with NMOSD show unpredictable periods of frequent ‘clustered’ relapses, separated by ‘non-clustered’ intermittent periods with sparse relapses[1–3]

Clustered relapse periods

- Clustered relapses often occur within 6–12 months of the previous attack[2]
- Clinical attacks may manifest in the same anatomic region and display the same attack phenotype, for example, in the optic nerve (optic neuritis) or spinal cord (myelitis)[2]

Non-clustered periods

- Relapses are entirely unpredictable in nature, with limited or no relation to previous NMOSD attacks in CNS location[2]



Cases with ≥3 clinical attacks (in the order of onset age)

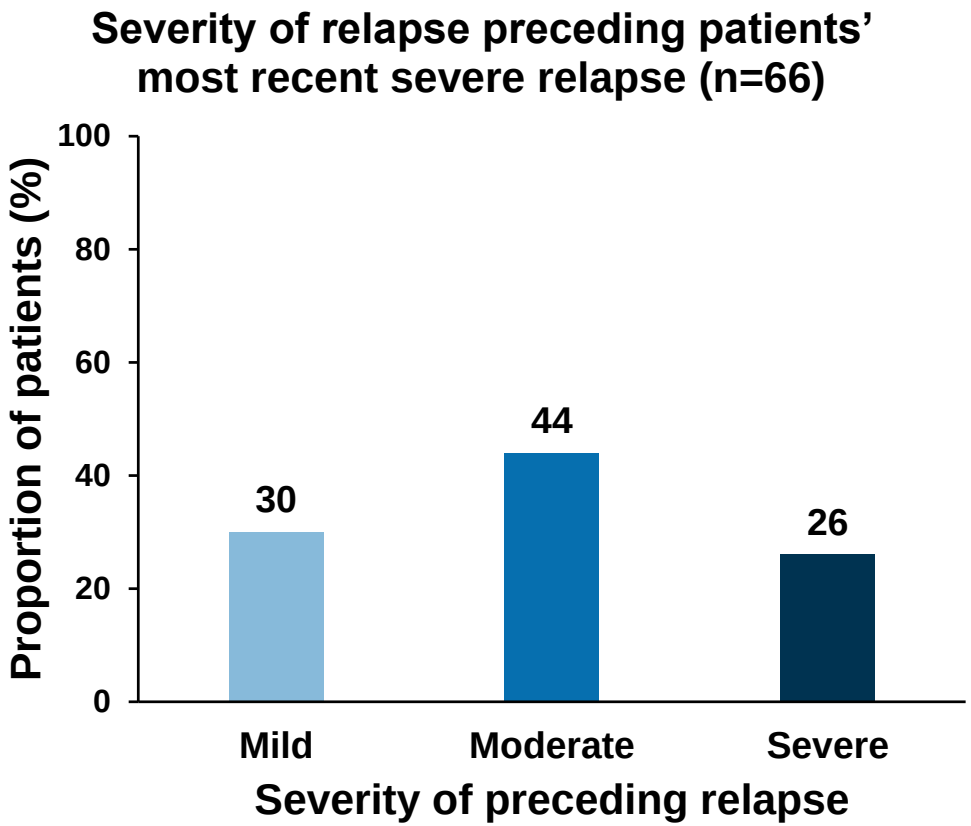
Reproduced from Akaishi T, et al. 2020.[2]

AQP4-IgG, aquaporin-4 immunoglobulin G; CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorder.

1. Wingerchuk DM et al. *Neurology* 1999;53:1107–1114; 2. Akaishi T et al. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e640; 3. Sellner J et al. *Eur J Neurol* 2010;17:1019–1032.

No correlation has been observed between the occurrence of a severe relapse and the severity of the preceding relapse

- Around three-quarters of patients (74%) will have had a **mild** or **moderately severe** relapse prior to their most recent severe relapse
  - **Two-thirds** (66%) experience a severe relapse **within 12 months** of their previous relapse
- The severity of the most recent relapse **cannot predict** the severity of the subsequent relapse



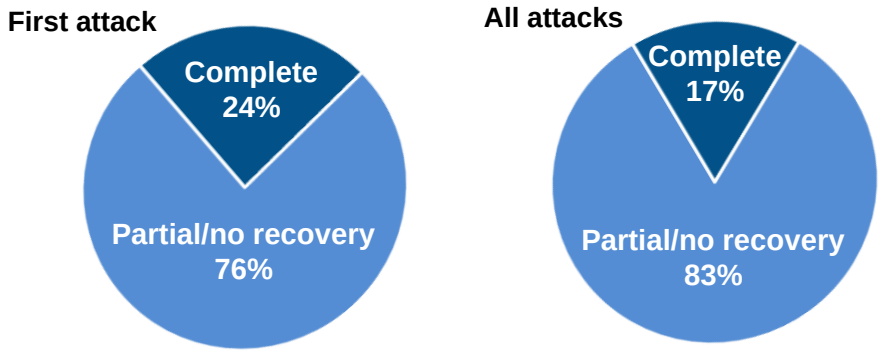
Unpublished data – not for distribution

Capobianco M et al. Data awaiting publication.

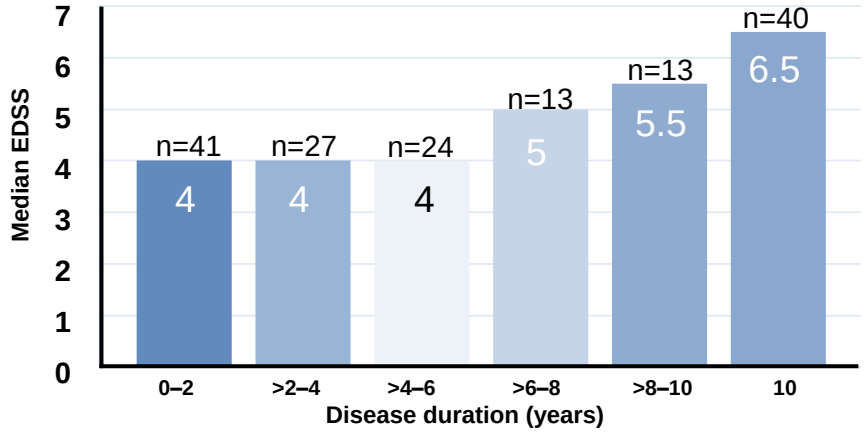
Increasing disability and disease burden in NMOSD are driven by multiple severe relapses and incomplete recovery

- Most relapses develop quickly, worsen over the course of a few days, and then plateau, before slowly improving in the following weeks–months[1–3]
- For **myelitis**, the rate of no or incomplete recovery after the first event is high (76%), and worsens with the number of subsequent relapses[4]
- In line with the increasingly low rate of recovery from myelitis, a **median EDSS of 4*** is notable even early in the disease course[4]

Recovery from myelitis[4]



EDSS at last follow-up[4]



*Indicating a restricted walking range.
EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder.
1. Sellner J et al. *Eur J Neurol* 2010;17:1019–1032; 2. Wingerchuk DM et al. *Neurology* 1999;53:1107–1114; 3. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 4. Jarius S et al. *J Neuroinflammation* 2012;9:14.

AQP4-IgG seropositive patients with NMOSD may experience more severe relapses than patients who are AQP4-IgG seronegative

A number of clinical features that are reflective of **increased disease severity** occur more frequently in AQP4-IgG seropositive (AQP4-IgG+) NMOSD than in the seronegative disease[1], including:

- Severe reduction in vision during acute optic neuritis
- Motor symptoms (e.g. paraparesis)
- Significant muscle weakness
- Higher total spinal cord lesion load
- Larger lesions (≥6 vertebral segments), sometimes extending to entire spinal cord involvement

The AQP4-IgG seronegative population can be split into two categories, depending on the presence of antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG)

‘Double-seronegative’ (DSN) NMOSD

Most AQP4-IgG seronegative patients are **DSN** (negative for both AQP4-IgG and MOG-IgG)[2]

- These patients relapse at similar rates to AQP4-IgG+ patients, but are more likely to experience simultaneous optic neuritis and transverse myelitis (TM), compared with TM only in AQP4-IgG+ patients[3]

MOG-IgG seropositive (MOG-IgG+) NMOSD

Up to 42% of AQP4-IgG seronegative patients are **MOG-IgG seropositive**[2]; these patients have similar relapse rates to AQP4-IgG+ and DSN patients, but tend to show less disability[3]

- Compared with DSN NMOSD, MOG-IgG+ patients have different clinical phenotypes – they are more likely to have optic neuritis only, or TM plus brain involvement[3]
- MOG-IgG+ patients’ disease course appears to differ depending on the age of the patient[4]

AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, expanded disability status scale; NMOSD; neuromyelitis optica spectrum disorder.

1. Jarius S et al. *J Neuroinflammation* 2012;9:14. 2. Narayan R, et al. *Mult Scler Relat Disord* 2018;25:66–72. 3. Kim HW, et al. Presented at ECTRIMS 2019;278294:P10924. Cobo-Calvo A, et al. *Ann Neurol* 2020: doi: 10.1002/ana.25909.

The exact cause of relapse events in NMOSD is unknown, but a number of prognostic factors can be used to predict the risk of relapse

Suggested triggers for relapse events in NMOSD include **infections**, **vaccinations**, and **systemic autoimmune diseases**[1–3]

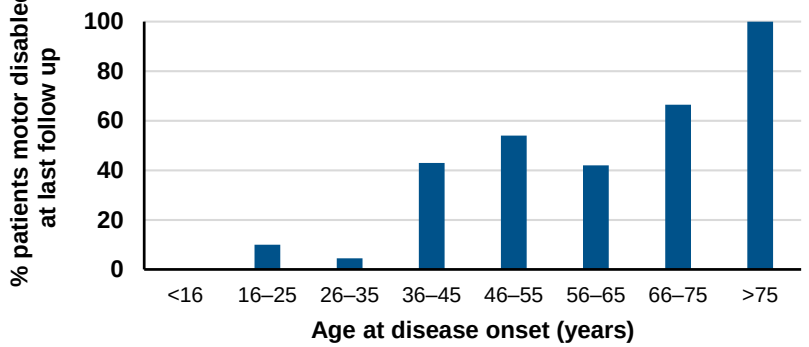
The presence of **AQP4-IgG** antibodies does not appear to affect relapse risk, but attack severity appears to be greater in AQP4-IgG seropositive vs seronegative patients[1]

The following factors have all been associated with i**ncreased risk of relapse**, **disability**, and **fatality** in NMOSD[4–9]

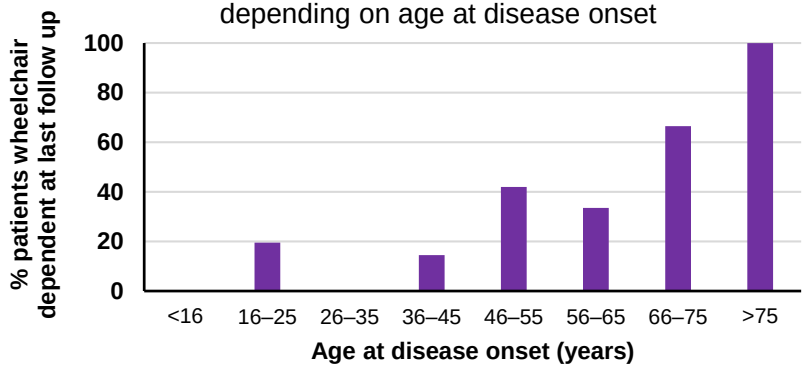
- A history of other autoimmune diseases
- Older age at onset
- Female gender
- Caucasian or African ethnicity
- Higher attack frequency during the first 2 years of disease
- Incomplete recovery from the index event

Recently developed prognostic models use combinations of these factors to predict the likelihood of developing attacks and disability in individual patients, according to their baseline features and disease history[8]

Probability of developing **permanent motor disability** depending on age at disease onset



Probability of developing **wheelchair dependence** depending on age at disease onset



Reproduced from Kitley J et al. 2012.[9]

AQP4-IgG, aquaporin-4 immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

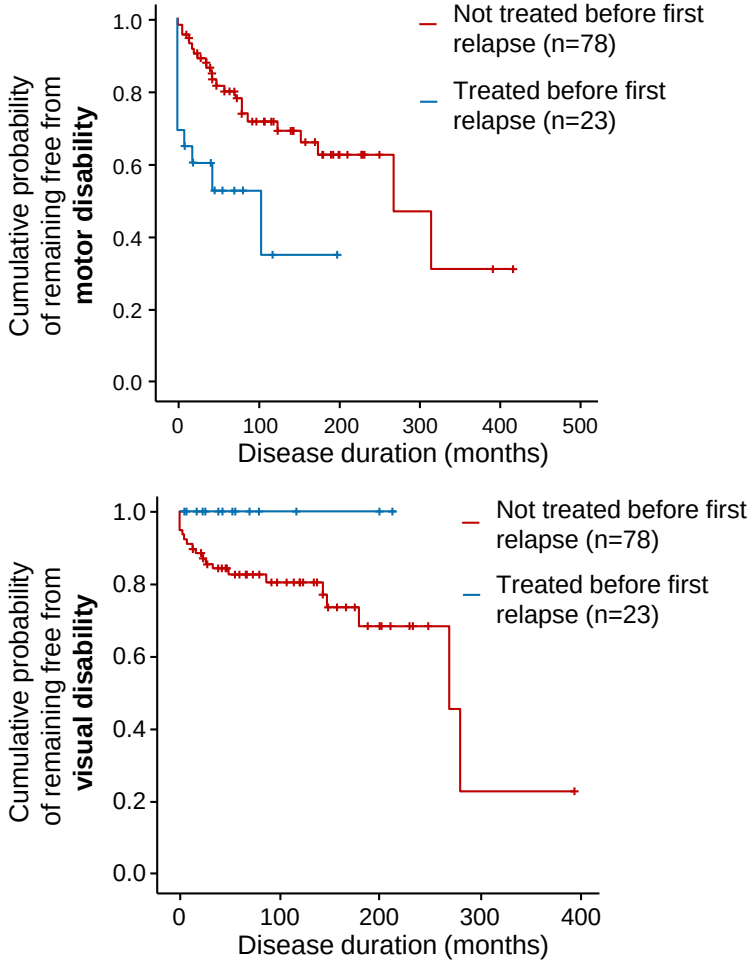
1. Jarius S et al. *J Neuroinflammation* 2012;9:14; 2. Wingerchuk DM et al. *Neurol* 1999;53:1107–1114; 3. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 4. Sellner J et al. *Eur J Neurol* 2010;17:1019–1032; 5. Wingerchuk DM, Weinshenker BG. *Neurol* 2003;60:848–853; 6. Bichuetti DB et al. *Mult Scler* 2009;15:613–619; 7. Cabre P et al. *J Neurol Neurosurg Psychiatry* 2009;80:1162–1164; 8. Palace J et al. *Brain* 2019:142;1310–1323; 9. Kitley J et al. *Brain* 2012;135:1834–1849.

Early diagnosis and initiation of maintenance treatment for NMOSD may reduce long-term disability

- Because a single relapse in NMOSD can have devastating consequences, the prevention of relapses is the primary goal of long-term NMOSD treatment[1]
  - Reducing the severity of relapses may also limit disability accrual

- Relapses can occur in quick succession, so it is important to provide patients with a rapid and accurate diagnosis after their onset attack, so that they can begin treatment as soon as possible[2]

- Most patients require multiple attacks to accumulate significant disability (EDSS score ≥6, or blindness in one/both eyes), so preventing future relapses can greatly affect patient outcomes[2]



Reproduced from Kitley J et al. 2012.[3]

EDSS, expanded disability status scale; NMOSD; neuromyelitis optica spectrum disorder.

1. Palace J et al. Presented at MSVirtual 2020. FC.01.03; 2. Palace J et al. *Brain* 2019:142;1310–1323; 3. Kitley J et al. *Brain* 2012;135:1834–1849.

Summary

- NMOSD attacks vary in their severity, with more severe attacks carrying a higher risk of causing permanent disability
- Relapses occur frequently, often in clusters of attacks, leading to the rapid accumulation of disability
- Early diagnosis and initiation of maintenance treatment for NMOSD may reduce long-term disability
- A number of characteristics, such as AQP4-IgG serostatus and disease history, may help to predict patients' risk of relapse

AQP4-IgG, aquaporin-4 immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.