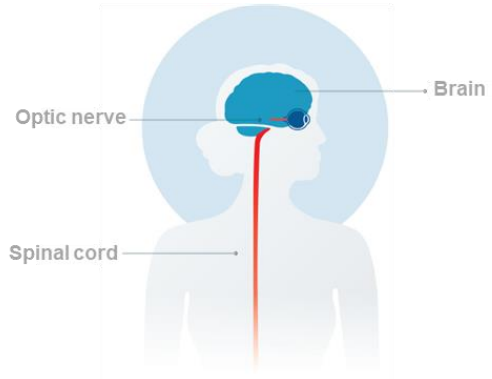
Introduction to Neuromyelitis Optica Spectrum Disorder (NMOSD)



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NMOSD is a rare, debilitating autoimmune disease of the CNS, characterized by lesions in the spinal cord, optic nerve, and brain stem

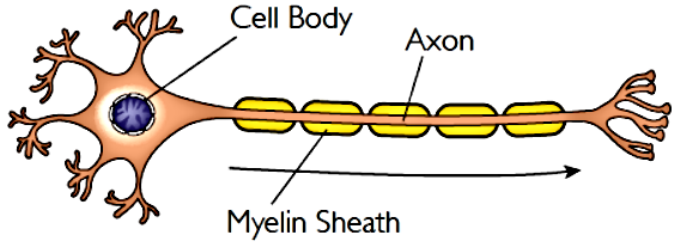
NMOSD is a heterogeneous disease, with a **complex and multifaceted pathophysiology**[1,2]

In NMOSD, symptoms are caused by **immune-mediated demyelination** and **damage to axons** in the spinal cord, optic nerve, and brain stem[3–6]

The exact mechanisms by which neurological injury occurs are not fully understood, but a number of inflammatory processes have been found to drive NMOSD disease activity[7,8]

Healthy neuron

Has normal axonal message conduction



Demyelinated neuron

Axonal message can be interrupted or not complete

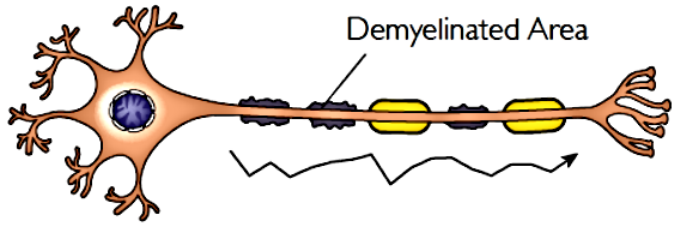


Figure adapted from NMO UK 2012[7]

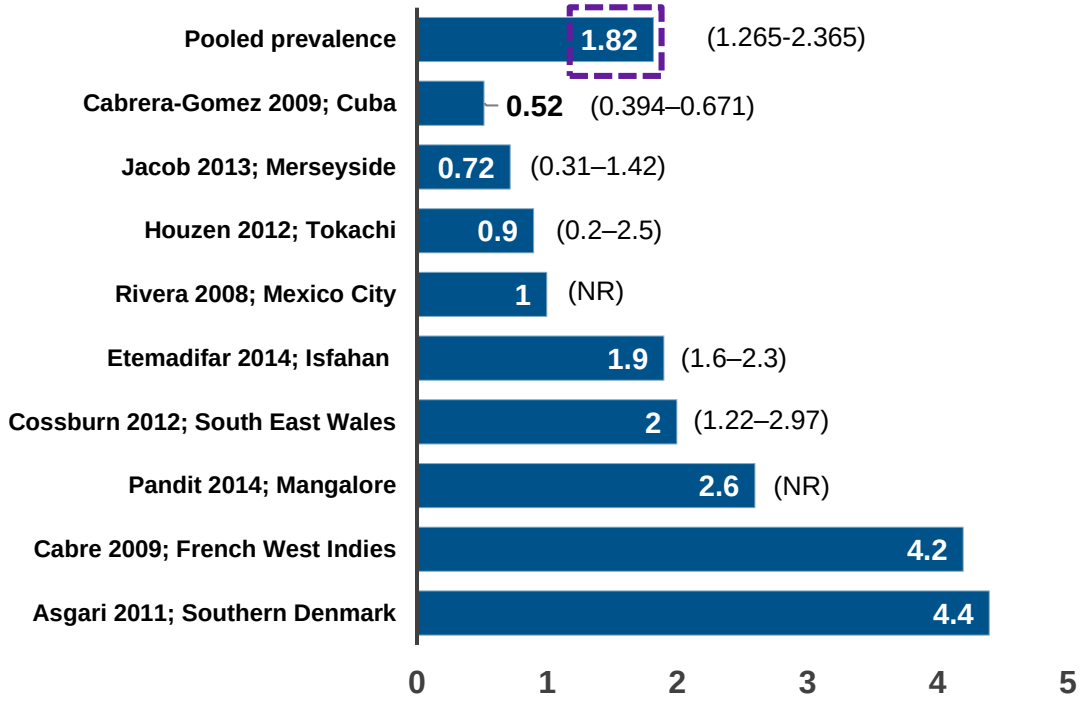
CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorder.

1. Guthy Jackson Foundation Patient Resource Guide (Third Edition). Available at: Link. Accessed September 2020; 2. Weinshenker BG, Wingerchuk DM. *Mayo Clin Proc* 2017;92:663–679; 3. Wingerchuk DM et al. *Neurology* 2015;85:177–189; 4. Papadopoulos MC et al. *Nat Rev Neurol* 2014;10:493–506; 5.Ghezzi A et al. *J Neurol* 2004;251:47–52; 6.Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 7. NMO UK. Neuromyelitis Optica. A guide to the condition. March 2012. Available at: Link. Accessed August 2020; 8. Glisson GC. UpToDate® Review on Neuromyelitis Optica Spectrum Disorders (August 2020). Available at: Link. Accessed September 2020.

NMOSD has an estimated global prevalence of 1.82 per 100,000

- NMOSD exists worldwide, but few studies have assessed the prevalence of NMOSD across different regions
- A systematic review and meta-analysis of nine studies (covering 1993–2013) reported a global prevalence of NMOSD of 1.82 per 100,000
- Prevalence of NMOSD is likely to be under-reported due to patients never receiving a diagnosis or being misdiagnosed with another auto-immune disorder

Prevalence of NMOSD per 100,000 (95% confidence interval)[1]

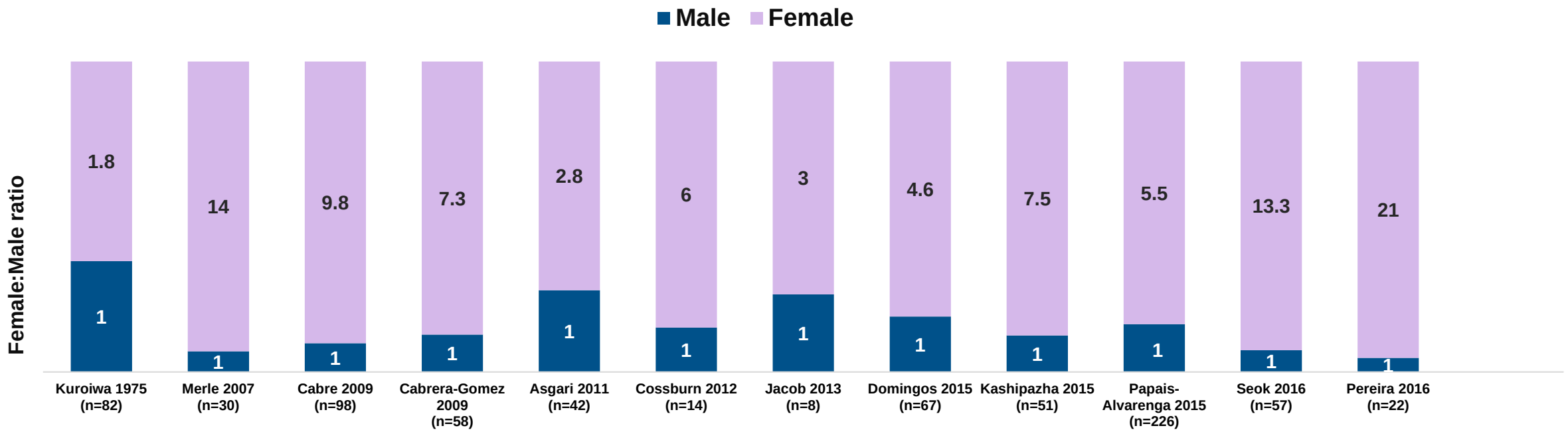


Study type: systematic review; **search period**: 1985 to 2015; **number of studies included**: 9.

NMOSD, neuromyelitis optica spectrum disorder; NR, not reported.

Etemadifar M et al. *Mult Scler Int* 2015;2015:174720.

NMOSD is more common among women than men, with female to male ratios ranging from approximately 1.8:1 to 21:1[1–12]



- It is worth noting that the female-to-male ratio in NMOSD is significantly affected by whether the patient has **autoantibodies against aquaporin-4 (AQP4-IgG)**, which are present in at least two-thirds of patients with NMOSD – *see module **Pathophysiology of NMOSD and the Role of IL-6** for further details on AQP4-IgG*
  - In AQP4-IgG-seropositive NMOSD, the female:male ratio is around 9:1, whereas in seronegative NMOSD, it is much lower – around 2:1[13]

NMOSD, neuromyelitis optica spectrum disorder.

1. Kuroiwa Y et al. *Neurology* 1975;25:845–851; 2. Merle H et al. *Opthalmology* 2007;114:810–815; 3.Cabre P et al. *Rev Neurol (Paris)* 2009;165:676–683; 4. Cabrera-Gomez JA et al. *J Neurol* 2009;256:35–44; 5. Asgari N et al. *Neurology* 2011;76:158901595; 6. Cossburn M et al. *Eur J Neurol* 2012;19:655–659; 7. Jacob A et al. *J Neurol* 2013;260:2134–2137; 8. Domingos J et al. *Clin Neurol Neurosurg* 2015;134:79–84; 9. Kashipazha D et al. *Iran J Neurol* 2015;14:204–210; 10. Papais-Alvarenga RM et al. *PLoS One* 2015;10:p.e0127757; 11. Seok JM et al. *J Neurol Sci* 2016;15:209–213; 12. Pereira WL et al. *Acta Neuropsychiatr* 2017;29:170–178; 13. Gold S et al. *Semin Immunopathol* 2019;41:177–188.

While anyone can be diagnosed with NMOSD, the disease appears to be more common among non-Caucasian individuals

- Recent studies suggest that, compared with Caucasian populations, **people of Asian or African ancestry have a higher tendency to develop NMOSD**[1,2]

Prevalence of NMOSD among Whites/Caucasians is around 1 in 100,000[1]

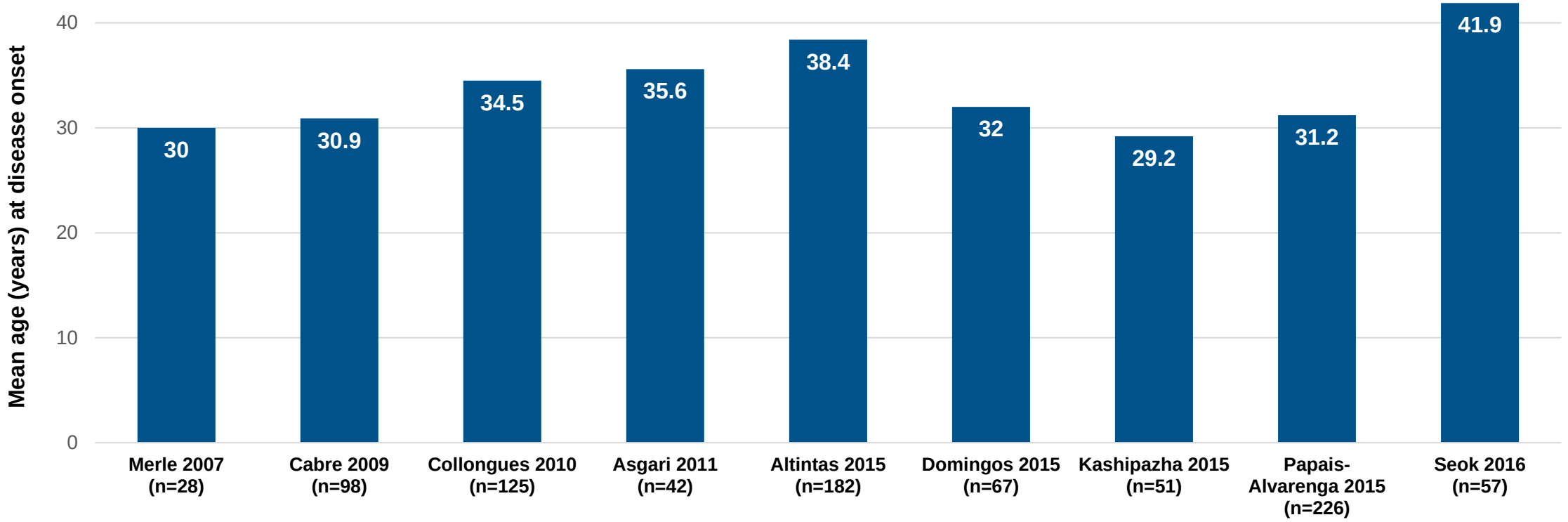
Among East Asians (Japanese, Chinese, Korean), the prevalence is around 3.5 in 100,000[1]

Prevalence of NMOSD in Black populations may be up to 10 in 100,000[1]

1. Hor JY et al. *Front Neurol* 2020;11:501; 2. Guthy Jackson Foundation Patient Resource Guide (Third Edition). Available at: Link. Accessed September 2020.

The majority of patients with NMOSD are diagnosed between 30–40 years of age

- Patients typically present in their 30s,[1–8] but can be diagnosed in old age (12%) and in early childhood (5%).[9] Children are usually diagnosed between 10–14 years of age, although the disease can develop at any stage of childhood[10]

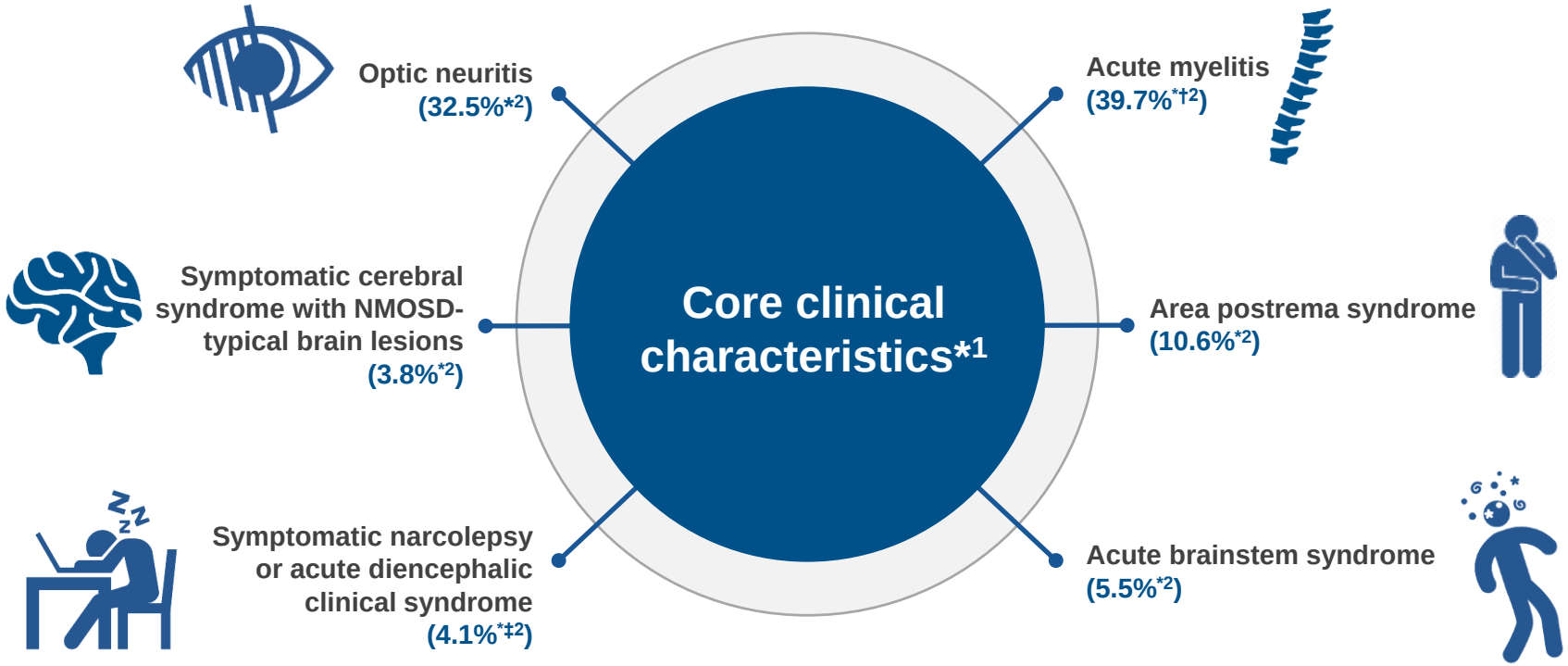


NMOSD, neuromyelitis optica spectrum disorder.

1. Merle H et al. *Opthalmology* 2007;114:810–815; 2. Cabre P et al. *Rev Neurol (Paris)* 2009;165:676–683; 3. Collongues N et al. *Neurology* 2010;74:736–742; 4. Asgari N et al. *Neurology* 2011;76:1589–1595; 5. Altintas O et al. *Neurologist* 2015;20:61–66; 6. Domingos J et al. *Clin Neurol Neurosurg* 2015;134:79–84; 7. Kashipazha D et al. *Iran J Neurol* 2015;14:204–210; 8. Papais-Alvarenga RM et al. *PLoS One* 2015;10:p.e0127757; 9. Quek AML et al. *Arch Neurol* 2012;69:1039–1043; 10. Great Ormond Street Hospital NHS Trust. NMOSD. Available at: Link. Accessed August 2020; 11. Seok JM et al. *J Neurol Sci* 2016;15:209–213.

NMOSD most commonly presents as optic neuritis or transverse myelitis

- Six core NMOSD clinical characteristics have been defined, including optic neuritis and transverse myelitis[1]



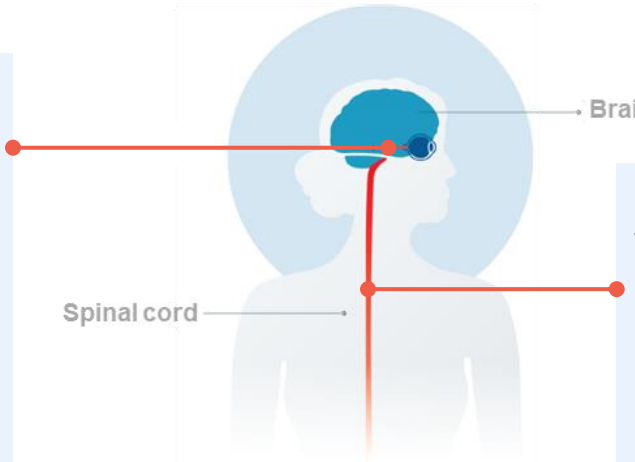
*Study retrospectively evaluated 292 Chinese AQP4-IgG-positive patients diagnosed with NMO/NMOSD based on the 2006 NMO and 2015 NMOSD diagnostic criteria. †As transverse myelitis; ‡With NMOSD-typical diencephalic MRI lesions.
AQP4-IgG, aquaporin-4 immunoglobulin G; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder.
1. Wingerchuk DM et al. *Neurology* 2015;85:177–189; 2. Long Y et al. *Front Neurol* 2017;28;8:62.

Optic neuritis and transverse myelitis associated with NMOSD can cause a wide range of signs and symptoms

- **Characteristic symptoms** include potentially severe motor and sensory impairment, vision loss, fatigue, and pain[1–3]

NMOSD patients with ON can present with:

- Retrobulbar (behind the eye) pain and/or pain on eye movement[4]
- Disturbed color vision, including color desaturation[4]
- Visual impairment that often persists for an extended duration and can be permanent[5–8]
- Acute ON attack-related functional blindness in one or both eyes[4]



NMOSD patients with TM can present with:

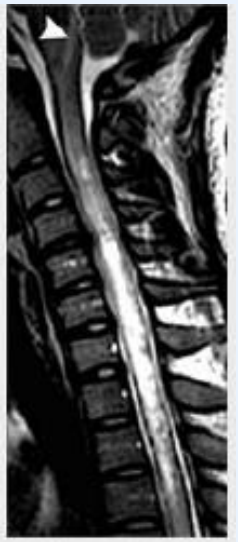
- Leg and/or arm muscle weakness[9]
- Altered limb sensations (pins and needles, numbness)[9]
- Bladder and bowel problems[9]
- Back or limb pain[9]

NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis.

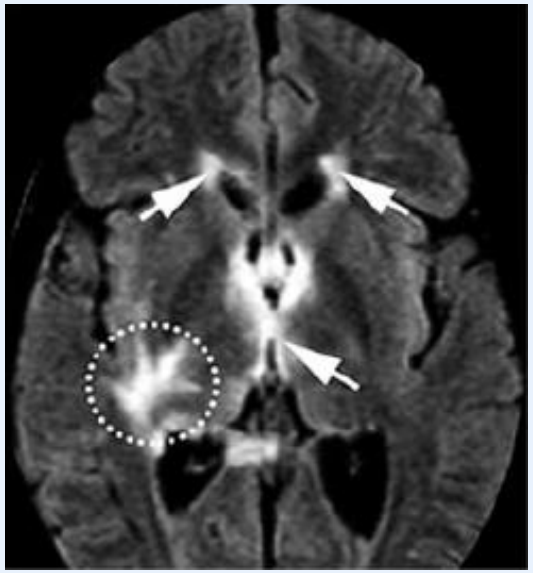
1. SRNA. Available at: Link. Accessed September 2020; 2. Traboulsee A et al. *Lancet Neurology* 2020;19:402–412; 3. Seok JM et al. *PLoS One* 2017;12:e01772303; 4.Jarius S et al. *J Neuroinflammation* 2016;13:280; 5. Seok JM et al. *J Neurol Sci* 2016;368:209–213; 6. Kitley J et al. *Brain* 2012;135:1834–1849; 7. Collongues N et al. *Neurology* 2010;74:736–742; 8. Bizzoco E et al. *J Neurol* 2009;256:1891–1898; 9. NMO UK. Neuromyelitis Optica. A guide to the condition. March 2012. Available at: Link. Accessed August 2020.

In addition to the characteristic symptoms, patients with NMOSD can present with disease-typical MRI features

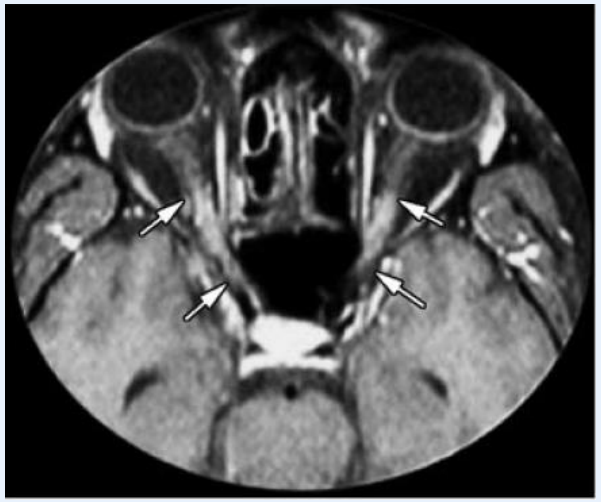
Spinal cord lesions



Brain lesions



Optic nerve lesions



Reproduced from Dutra BG et al. 2018.

MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.

Dutra BG et al. *Radiographics* 2018;38:169–193.

NMOSD shares a number of clinical features with multiple sclerosis, but has a different disease course

- Unlike MS, patients with NMOSD experience an accumulation of neurological disability that is almost exclusively associated with relapses[1,2]
- 5 years after disease onset, neurological disability may be significantly more severe in patients with NMOSD vs MS[2]

	NMOSD	MS
Accumulation of disability with relapses[1,2]	Yes	Yes
Accumulation of disability outside of relapses[1,2]	Rare	Yes
Spontaneous improvement of neurological disability[2]	No	Yes

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

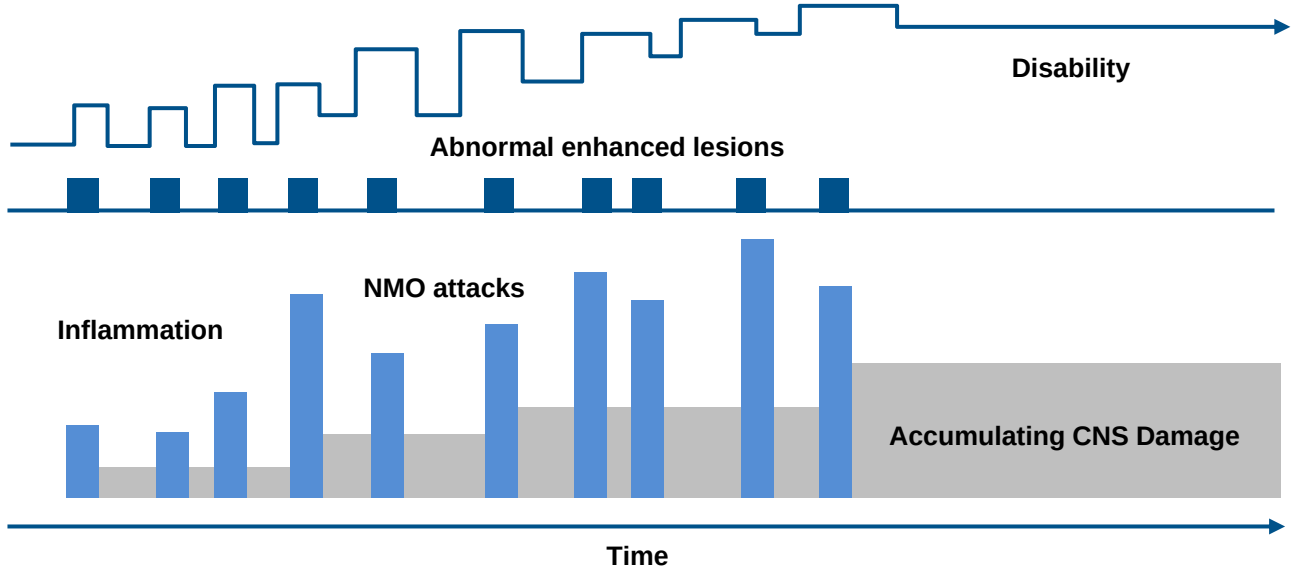
1. Kawachi I et al. *J Neurol Neurosurg Psychiatry* 2017;88:137–145; 2. Akaishi T et al. *Sci Rep* 2020;10:13890.

Patients with NMOSD generally experience a relapsing disease course, with frequent, severe relapses that can directly cause accumulating disability

- Following the first (onset) attack, **up to 90% of patients with NMOSD show an episodic relapsing disease course** – of these, up to 60% relapse within 1 year; 90% within 3 years[1,2]
  - A **relapse** is typically defined as any attack (i.e. worsening of neurological symptoms) that takes place after the first (onset) attack

- **Preventing relapses and reducing the impact of NMOSD-associated symptoms** are, therefore, the foremost disease management priorities[3]

NMOSD disease course[4]



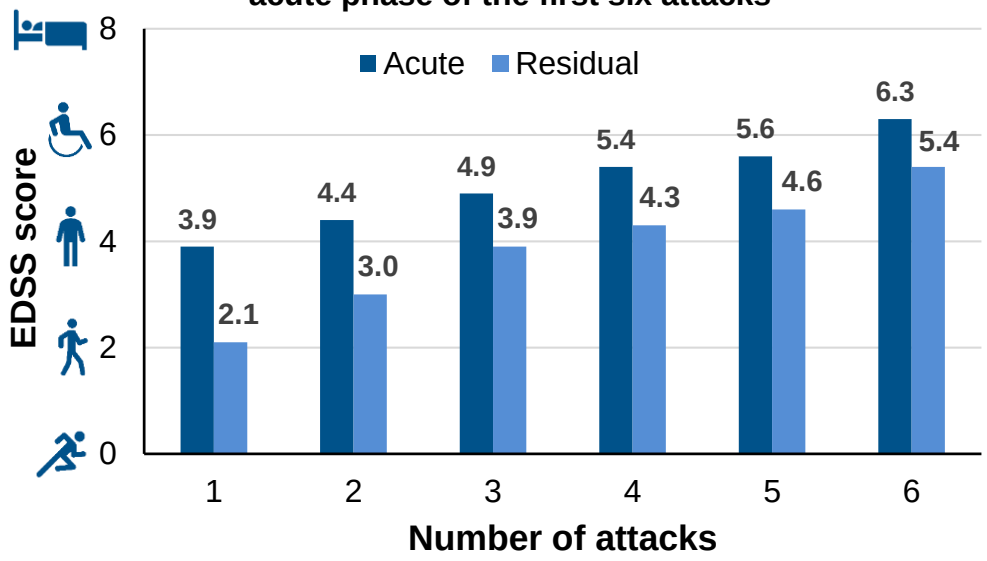
CNS, central nervous system; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder.

1. Kitley J et al. *Brain* 2012;135:1834–1849; 2. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 3. Weinshenker BG et al. *Neurology* 2015;84:1805–1815. 4. Kawachi I et al. *J Neurol Neurosurg Psychiatry* 2017;88:137–145;

A single NMOSD relapse can cause permanent neurological damage and disability

- Most relapses of NMOSD worsen over several days, then improve **slowly**, but often **incompletely**, over weeks or months[1]
- **Successive relapses are associated with accumulating disability,** reflected by increasing EDSS scores, due to the frequency and severity of attacks[1,2]
- Predictors of a worse prognosis include the **number of relapses in the first 2 years** of disease activity, and the **severity of the relapse**[1,4]
  - Relapses that result in an increase in EDSS of ≤2.5 have a nearly **two-fold better chance of complete recovery** compared with those with a severity of ≥3.0[4]

Mean EDSS score during and after the acute phase of the first six attacks[2]



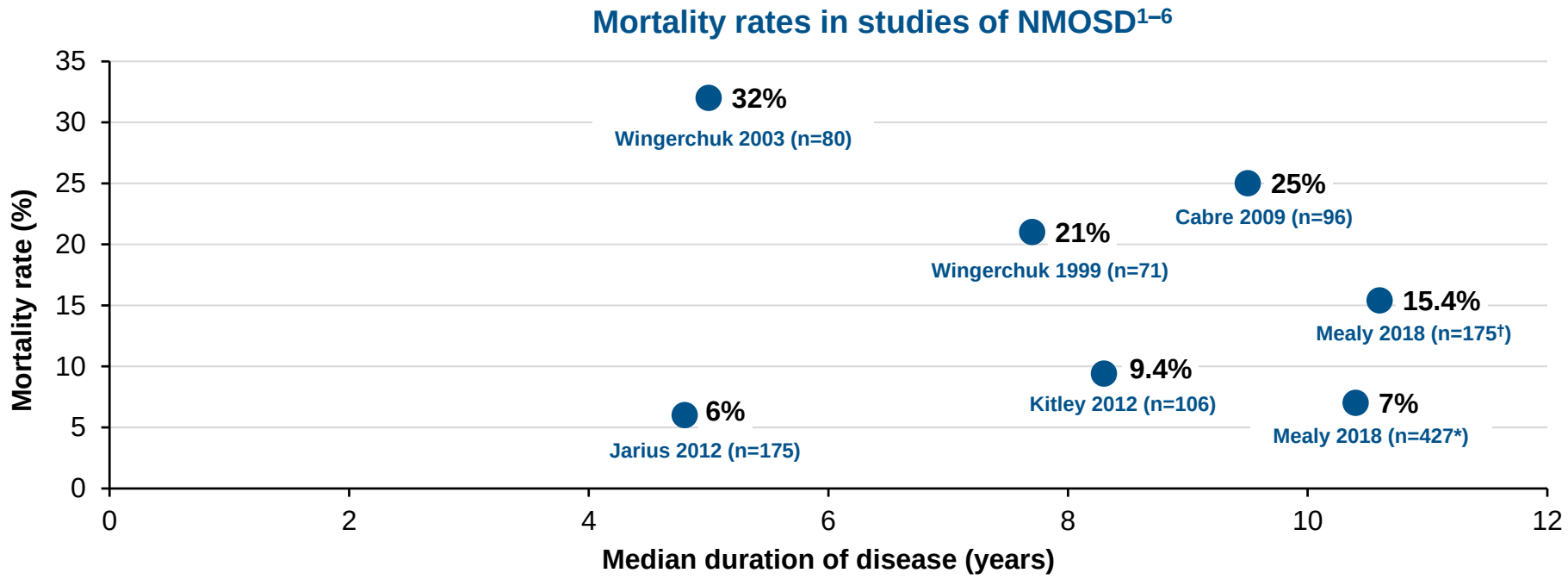
Within **5 years, 50%** of patients with NMOSD require the use of a **wheelchair** and **62%** of patients are **blind**[3]

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

1. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 2. Ghezzi A et al. *J Neurol* 2004;251:47–52; 3. Kessler RA et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e269; 4. Banerjee A et al. *Mult Scler Relat Disord* 2019;28:60–63.

Patients with NMOSD have reduced life expectancy, with death often attributable to a relapse

- As diagnosis and treatment has developed, mortality has been shown in contemporary studies to be **considerably improved** (6–15%)[1–3] versus older landmark studies (21–32%)[4–6]
- However, even with low duration of disease, mortality rates are still a concern[1–6]



*Total study population. †Population with African ancestry
NMOSD, neuromyelitis optica spectrum disorder.

1. Kitley J et al. *Brain* 2012;135:1834–1849; 2. Jarius S et al. *J Neuroinflammation* 2012;9:14; 3. Mealy MA et al. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e468; 4. Wingerchuk DM et al. *Neurology* 1999;53:1107–1114; 5. Wingerchuk DM et al. *Neurology* 2003;60:848–853; 6. Cabre P et al. *J Neurol Neurosurg Psychiatry* 2009;80:1162–1164;

AQP4 autoantibodies are a specific NMOSD disease marker, while the pathophysiology of seronegative disease remains unclear

Over two-thirds of patients have been shown to have detectable **serum antibodies that target AQP4-IgG**, which are highly specific for clinically diagnosed NMOSD[1,2]

This means that **up to one third** of patients with NMOSD are **AQP4-IgG seronegative**[2,3]

The **underlying pathophysiology** of seronegative disease is **heterogenous** and may represent a group of diseases with **similar clinical presentation**, but with **distinct underlying pathophysiologies**[1,4–6]

Some **AQP4-IgG seronegative** patients may have autoantibodies against **MOG-IgG** (discussed in **Module 1.8**),[1,4–6] and are known to have **different clinical outcomes to AQP4-seropositive** NMOSD[1,3,4]

AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorder.

1. Wingerchuk DM et al. *Neurology* 2015;85:177–189; 2. Lennon VA et al. *Lancet* 2004;364:2106–2112; 3. 7. Höftberger R et al. *Mult Scler* 2015;21:866–874; 4. Papadopoulos MC et al. *Nat Rev Neurol* 2014;10:493–506; 5. Reindl M et al. *Nat Rev Neurol* 2013;9:455–461; 6. Mader S et al. *Neuroinflammation* 2011;8:184.

Summary

NMOSD is a rare, debilitating autoimmune disease of the CNS, characterized by inflammatory lesions primarily in the optic nerves and spinal cord[1]

NMOSD exists worldwide with a reported global prevalence of 1.8 per 100,000 people[2]

- Patients typically present with NMOSD in their 30s–40s, but can be diagnosed in old age and in early childhood, and the disease is more common in non-Caucasian women[3,4]

NMOSD commonly presents as ON or TM, causing potentially severe motor and sensory impairment, bladder dysfunction, vision loss, pain, and other debilitating symptoms[1,4–6]

Patients with NMOSD generally experience a relapsing disease course, with frequent, severe relapses that can directly cause accumulating disability[1,7]

- Preventing attacks and reducing symptoms are the foremost disease management priorities in NMOSD[8]

CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis.

1. Wingerchuk DM et al. *Lancet Neurol* 2007;6:805–815; 2. Etemadifar M et al. *Mult Scler Int* 2015;2015:174720; 3. Quek AML et al. *Arch Neurol* 2012;69:1039–1043; 4. Guthy Jackson Foundation Patient Resource Guide (Third Edition). Available at: Link. Accessed September 2020; 5. SRNA. Available at: Link. Accessed August 2020; 6. Traboulsee A et al. *Lancet Neurology* 2020;19:402–412; 7. Ghezzi A et al. *J Neurol* 2004;251:47–52; 8. Weinshenker BG et al. *Neurology* 2015;84:1805–1815.