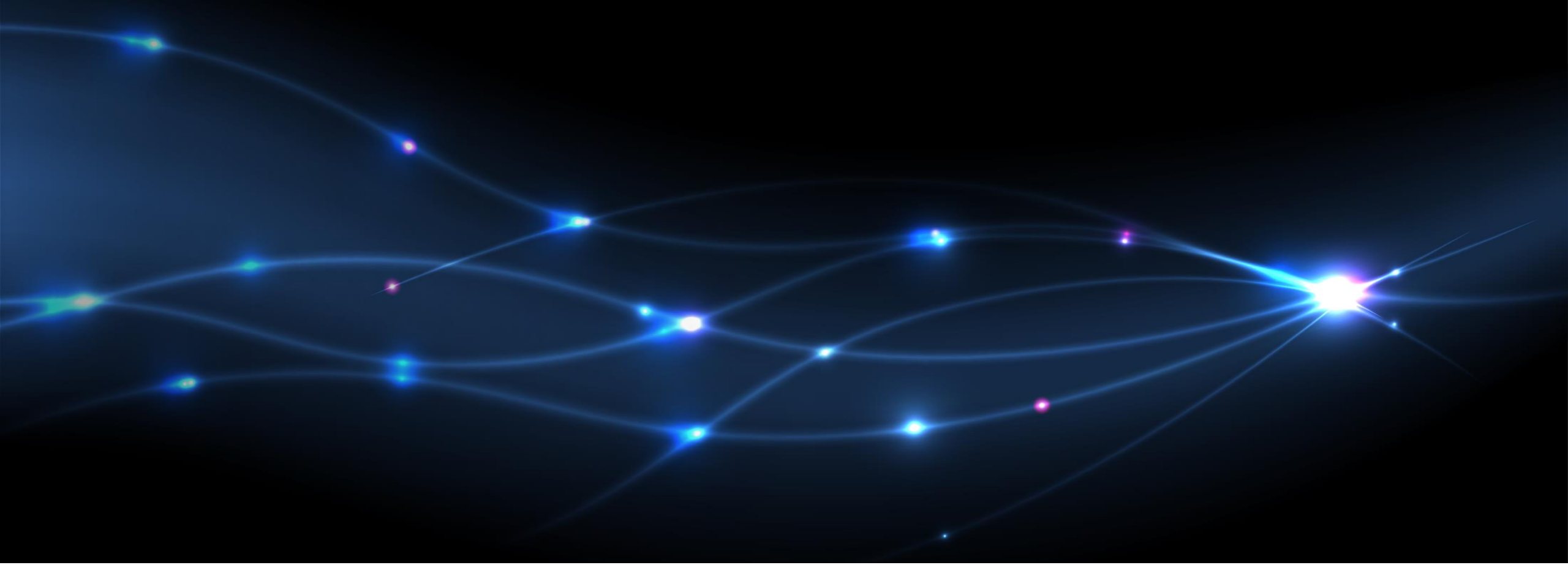


Pathophysiology of NMOSD and the Role of IL-6

Contents & Learning Objectives

AQP4, aquaporin 4; AQP4-IgG, aquaporin-4 immunoglobulin G; IL-6, interleukin-6; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

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**

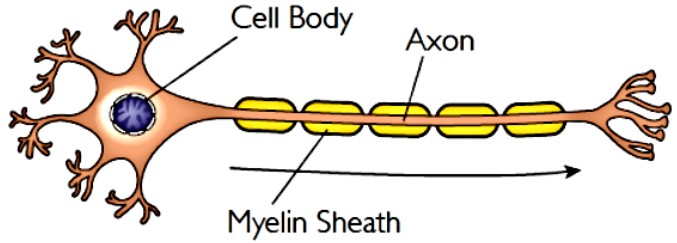
In NMOSD, symptoms are caused by a combination of:

- **Immune-mediated demyelination**[1–3]
- **Damage to axons** in the spinal cord, optic nerve, and brainstem[2,3]
- **Astrocyte death**[3]
- **Rapid loss of oligodendrocytes** and their precursors[1,3]

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

Healthy neuron

Has normal axonal message conduction



Demyelinated neuron

Axonal message can be interrupted or not complete

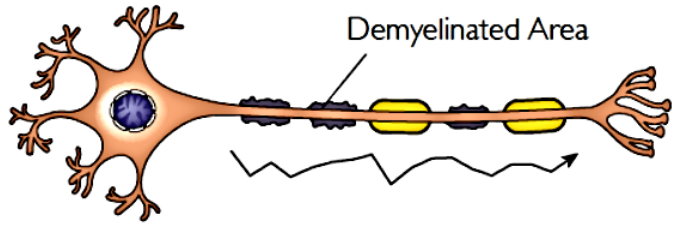
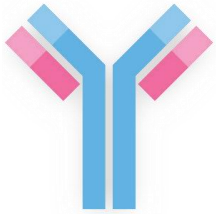


Figure adapted from NMO UK 2012[4]

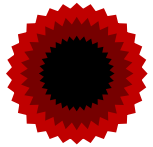
CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorder.

1. Papadopoulos MC, et al. *Nat Rev Neurol* 2014;10:493–506. 2. Wingerchuk DM, et al. *Lancet Neurol* 2007;6:805–815. 3. Wrzos C, et al. *Acta Neuropathol* 2014;127:523–538. 4. NHS NMO UK. Neuromelitis Optica – A Guide to the Condition. 2012. Available at: http://www.nmouk.nhs.uk/wp-content/uploads/2016/12/NMO-A-Guide_Lo-Res-2.pdf. Accessed November 2020.

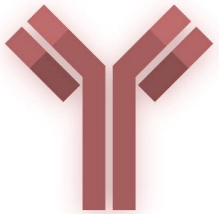
The following three proteins are all associated with NMOSD pathophysiology, and will be covered in this module



AQP4-IgG
A pathogenic autoantibody against aquaporin-4 (AQP4)

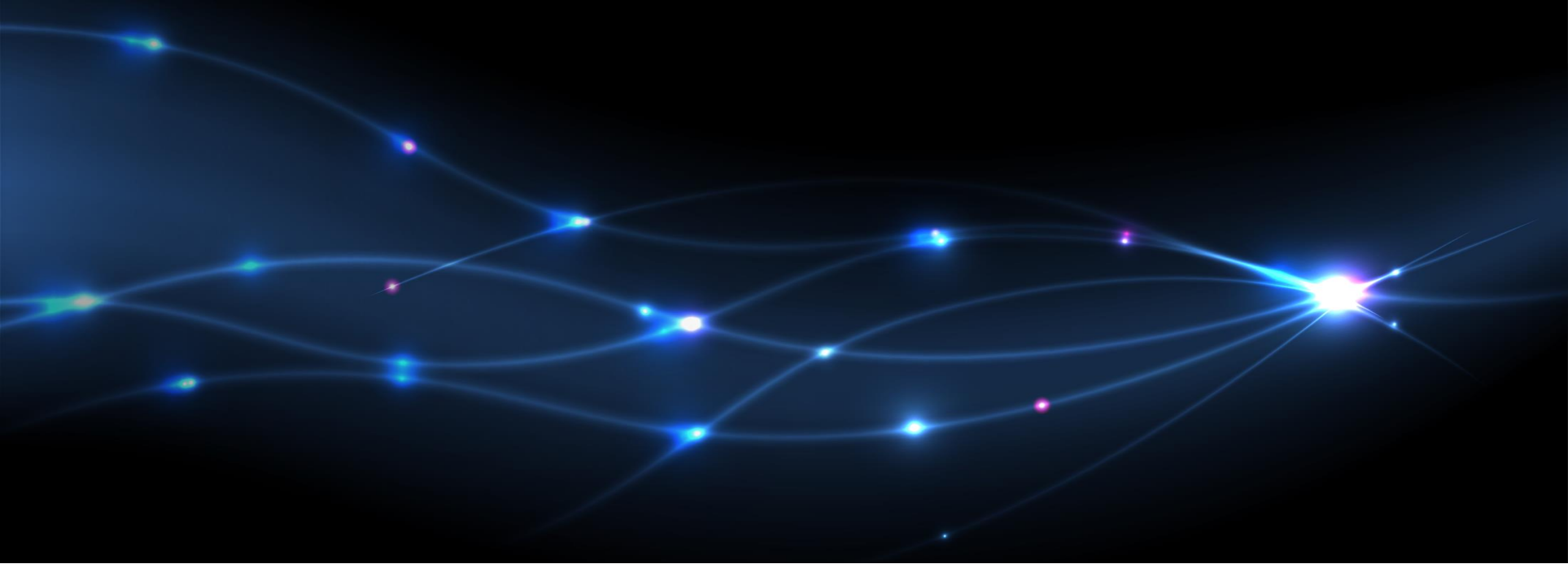


Interleukin-6 (IL-6)
A pleiotropic (i.e. multifunctional) cytokine



MOG-IgG
A pathogenic antibody against myelin oligodendrocyte glycoprotein (MOG)

AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; IL-6, interleukin-6; MOG, myelin oligodendrocyte glycoprotein; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G.



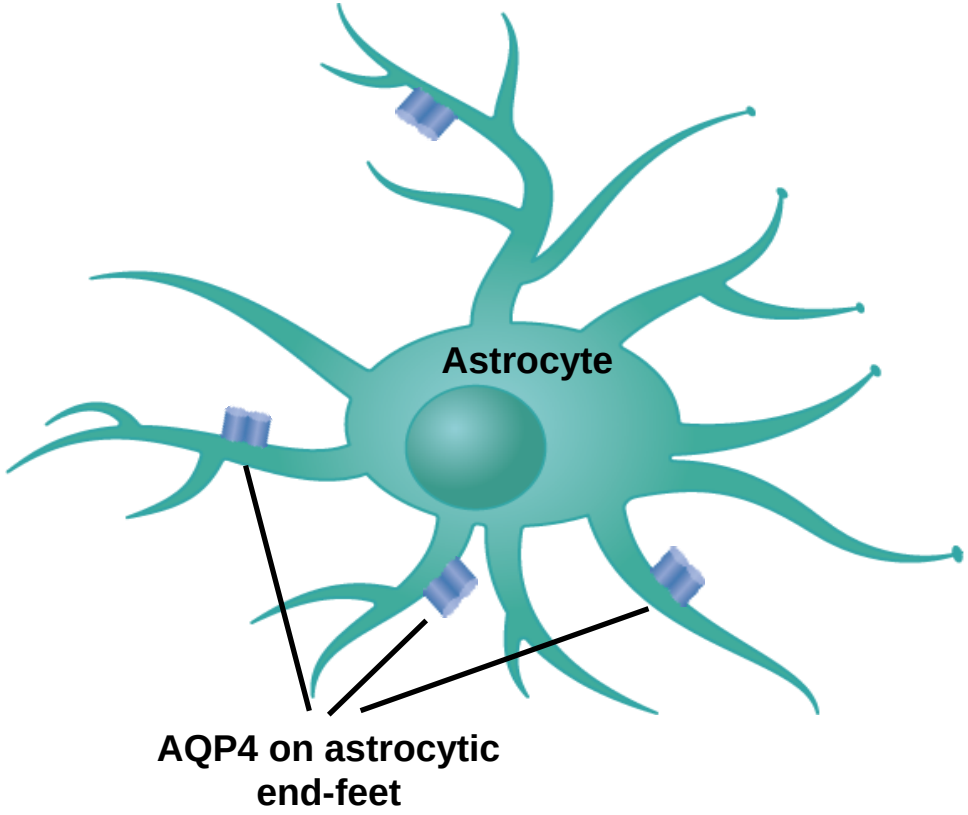
The Role of AQP4-IgG in NMOSD

Aquaporin-4 (AQP4), a water channel protein expressed primarily in the CNS, has an important role in regulating the brain water balance

AQP4 is the most abundant water channel in the CNS[1] and is involved in brain and spinal cord water balance and neuroexcitatory processes[2]

AQP4 is involved in **regulating water balance** in the brain, facilitating high water permeability across the **blood–brain** and **blood–CSF** barriers[2]

AQP4 is **expressed in astrocytes** throughout the CNS, and is **primarily localized on the astrocytic end-feet** surrounding the blood vessels or subarachnoid space[3]



AQP4, aquaporin-4; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid.

1. Jarius S, et al. *Brain Pathol* 2013;23:661–683. 2. Verkman AS. *Annu Rev Med* 2012;63:303–316. 3. Nagelhus EA, et al. *Neuroscience* 2004;129:905–913.

Pathological autoantibodies against AQP4 (AQP4-IgG) are found in at least two-thirds of patients with NMOSD

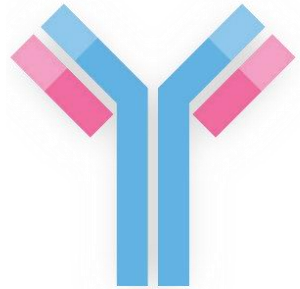
Serum autoantibodies against AQP4, called **AQP4-IgG**, are present in **at least two-thirds** of patients with NMOSD[1]

- Individuals are often categorized based on whether their NMOSD is **AQP4-IgG seropositive** or **AQP4-IgG seronegative**

AQP4-IgG antibodies are **directly pathogenic** and play an important role in mediating the pathophysiology in NMOSD[2,3]

Importantly, **AQP4-IgG** antibodies are **not found** in healthy persons or those with other neurological conditions such as MS[4–6]

AQP4-IgG

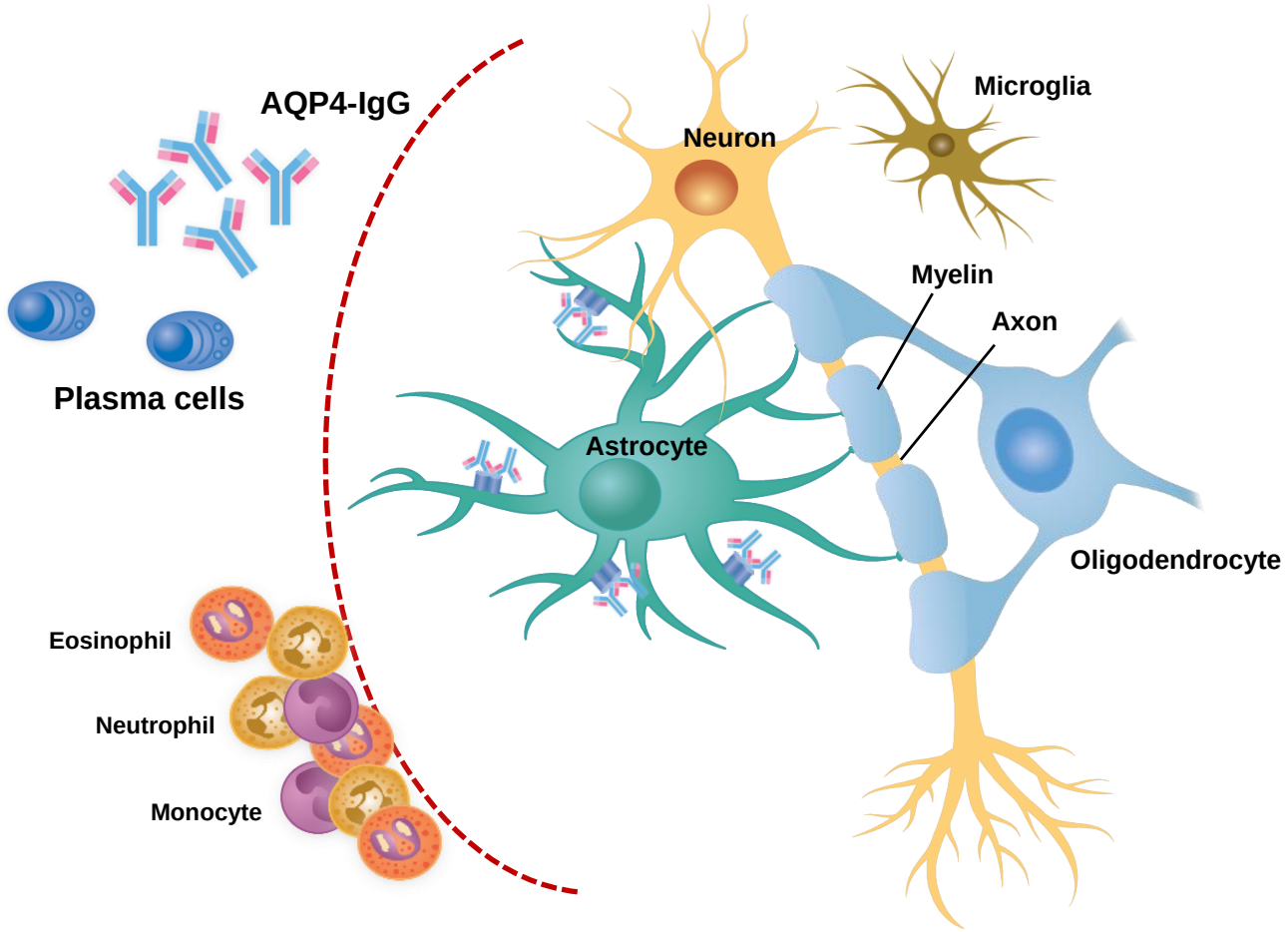


AQP4, aquaporin 4; AQP4-IgG, aquaporin-4 immunoglobulin G; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

1. Wingerchuk DM, et al. *Neurology* 2015;85:177–189; 2. Roemer SF, et al. *Brain* 2007;130:1194–1205. 3. Saadoun S, et al. *Brain* 2010;133:349–361. 4. Jarius S, Wildemann B. *Brain Pathol* 2013;23:661–683. 5. Lennon VA, et al. *Lancet* 2004;364:2106–2112. 6. Chihara N, et al. *Proc Natl Acad Sci* USA 2011;108:3701–3706.

The current hypothesis for AQP4-IgG-seropositive NMOSD pathogenesis involves the binding of AQP4-IgG to AQP4 on astrocyte end-feet[1]

1. Serum AQP4-IgG and plasma cells that produce AQP4-IgG penetrate the CNS
2. AQP4-IgG binds to AQP4 water channels on perivascular astrocyte end-feet
3. AQP4-IgG binding activates the classical complement cascade, resulting in astrocyte death
4. Inflammatory response activated, leading to granulocyte/macrophage infiltration
5. Secondary oligodendrocyte damage, demyelination, and neuronal death occurs



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

1. Papadopoulos MC, et al. *Nat Rev Neurol* 2014;10:493-506.

AQP4-IgG-seropositive patients appear to respond better to NMOSD treatment than seronegative patients[1–3]

Because of the differences in NMOSD pathophysiology, **AQP4-IgG seropositivity can affect disease and treatment outcomes**

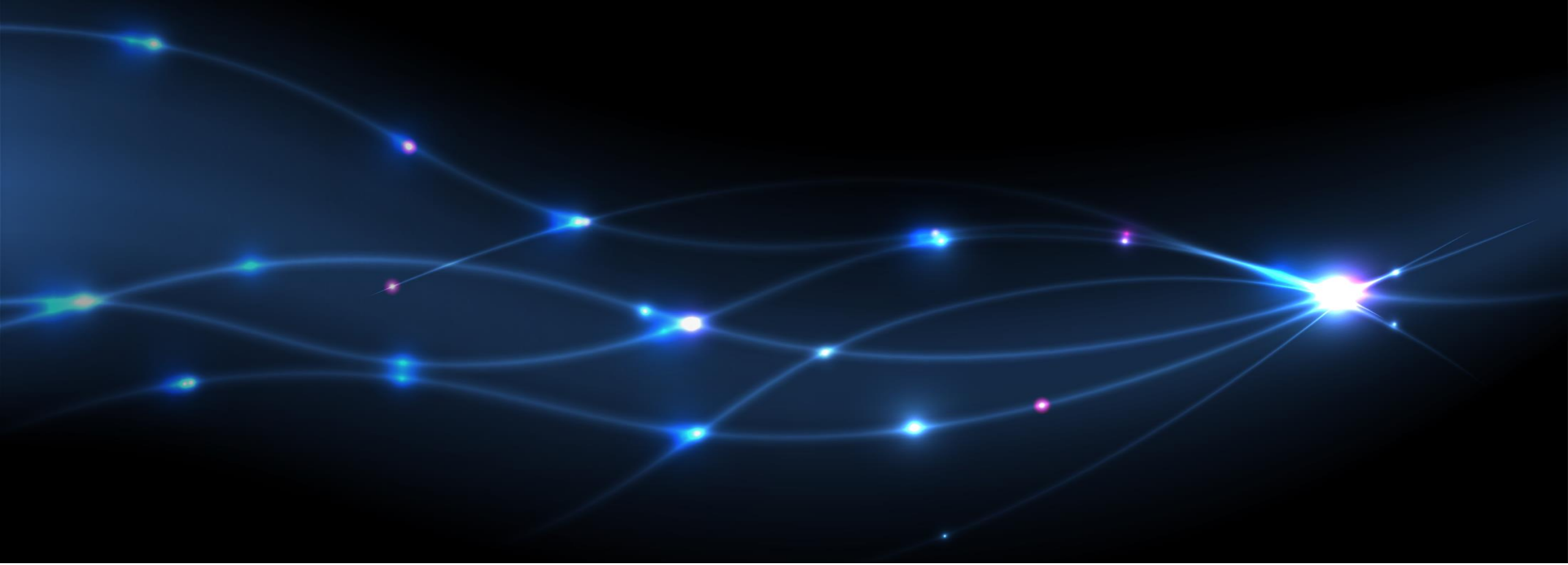
AQP4-IgG-seropositive patients tend to experience a **more severe disease** course than their seronegative counterparts[4–6]

Clinical trials into the latest NMOSD therapies suggest that AQP4-IgG seropositive patients **may respond better to treatment** than seronegative patients[1–3]

- Currently, dedicated NMOSD therapies are **only approved for use in AQP4-IgG seropositive NMOSD**[7–9]

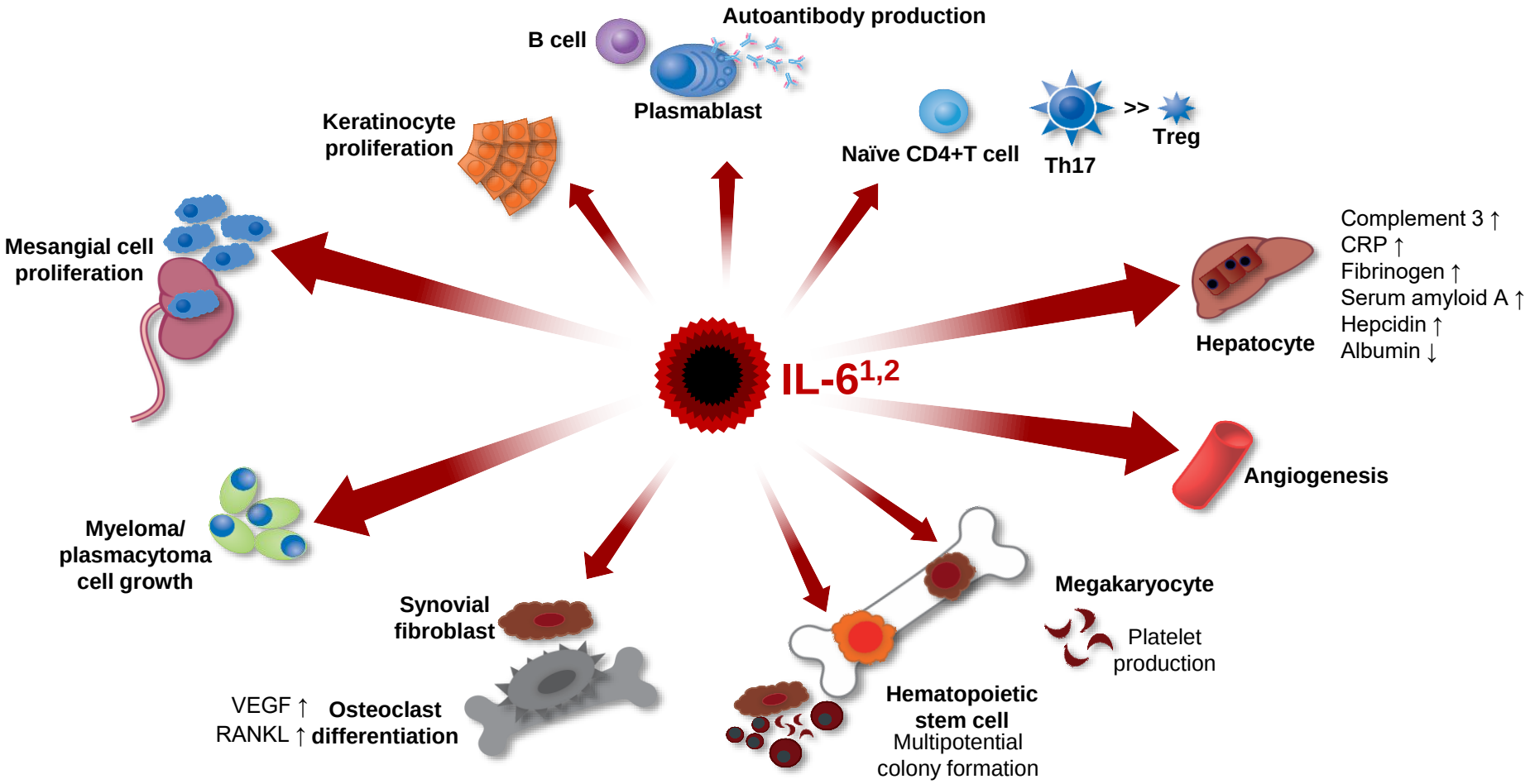
AQP4-IgG, aquaporin-4 immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

1. Sherman E, Han MH. *Curr Treat Options Neurol* 2015;17:48. 2. Jarius S, et al. *J Neuroinflammation* 2012;9:14. 3. Tanaka M, et al. *Eur Neurol* 2009;62:167–170. 4. Cree BAC, et al. *Lancet* 2019;394:1352–1363. 5. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412. 6. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124. 7. US Food and Drug Administration. Available at: Link. Published June 27, 2019. Accessed September 2020. 8. US Food and Drug Administration. Available at: Link. Published August 17, 2020. Accessed September 2020. 9. US Food and Drug Administration. Available at: Link. Published June 11, 2020. Accessed September 2020.



The Role of IL-6 in NMOSD

IL-6 is a soluble, multifunctional cytokine that plays a key role in a variety of cellular biological processes[1–3]



CRP, C-reactive protein; IL-6, interleukin-6; RANKL, receptor activator of nuclear factor kappa-B ligand; Th17, T-helper cell 17; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

1. Tanaka T, Kishimoto T. *Int J Biol Sci* 2012;8:1227–1236. 2. Tanaka T, et al. *Cold Spring Harb Perspect Biol* 2014;6:a016295. 3. Kamimura D, et al. *Rev Physiol Biochem Pharmacol* 2003;149:1–38.

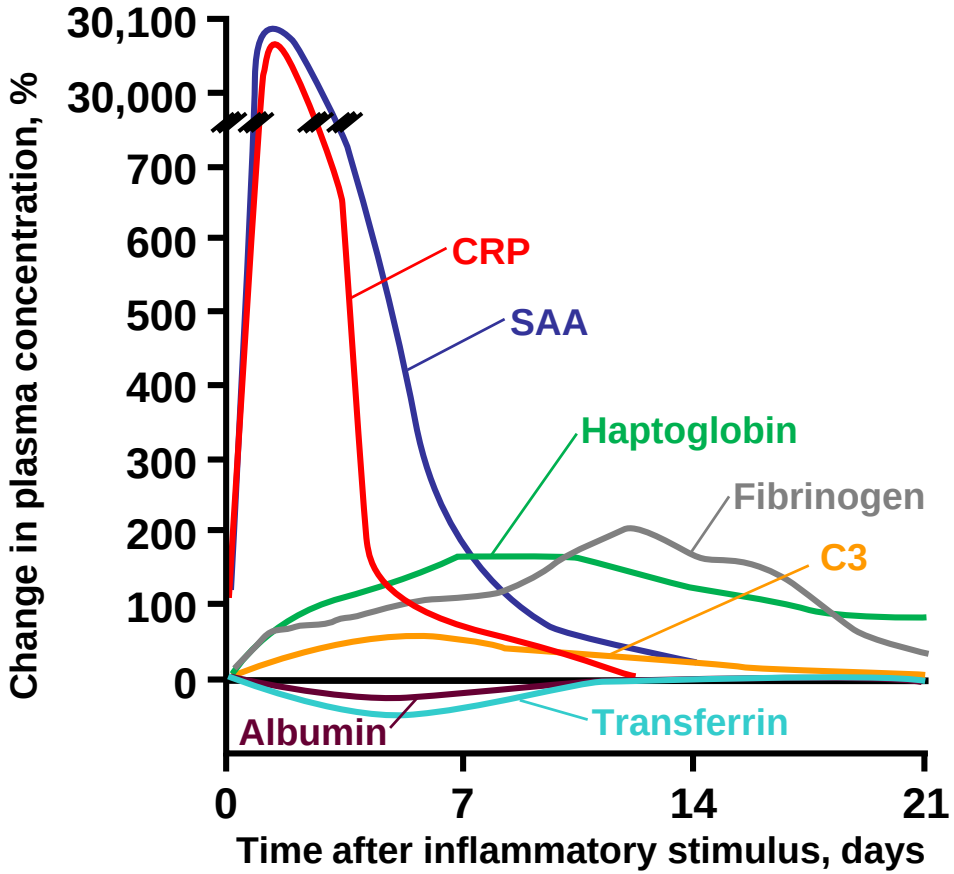
IL-6 receptor signaling plays a key role in mediating the acute-phase response

APPs are proteins that have plasma concentrations that **increase** or **decrease** rapidly in response to inflammation caused by injury or infection

APPs act as inhibitors or mediators of inflammatory processes, and include CRP and SAA

The production of APPs is stimulated by pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6

Changes in plasma APP concentrations are used as a clinical guide to diagnosis and management, as they reflect both the presence and intensity of inflammation



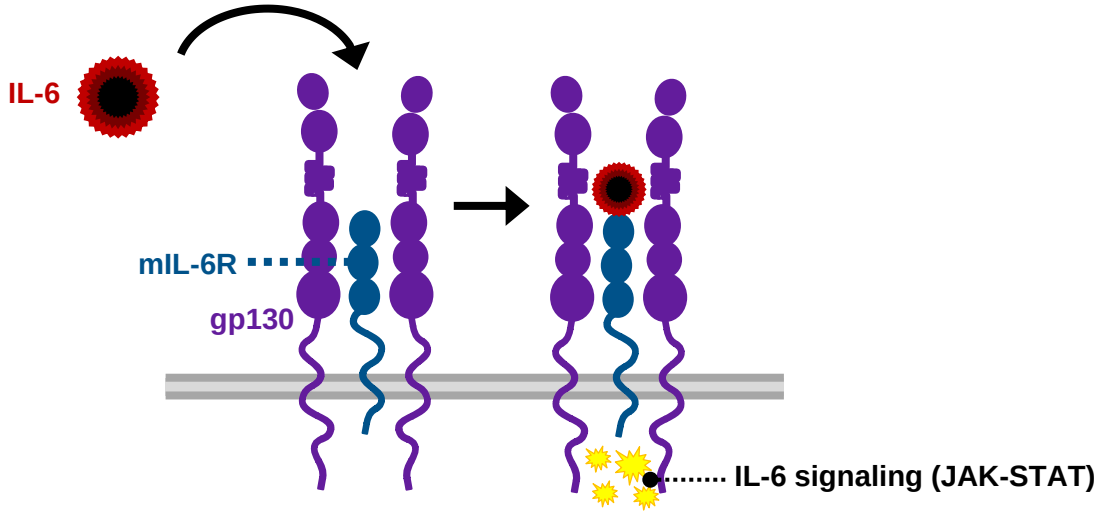
Originally published in Gabay C, Kushner I. N Engl J Med 1999;340:448–454.

APP, acute-phase protein; CRP, C-reactive protein; IL-1/6, interleukin-1/6; SAA, serum amyloid A; TNF-α, tumor necrosis factor-α.
Gabay C, Kushner I. *N Engl J Med* 1999;340:448–454.

IL-6 induces downstream intracellular IL-6R signaling mainly through the JAK-STAT pathway[1,2]

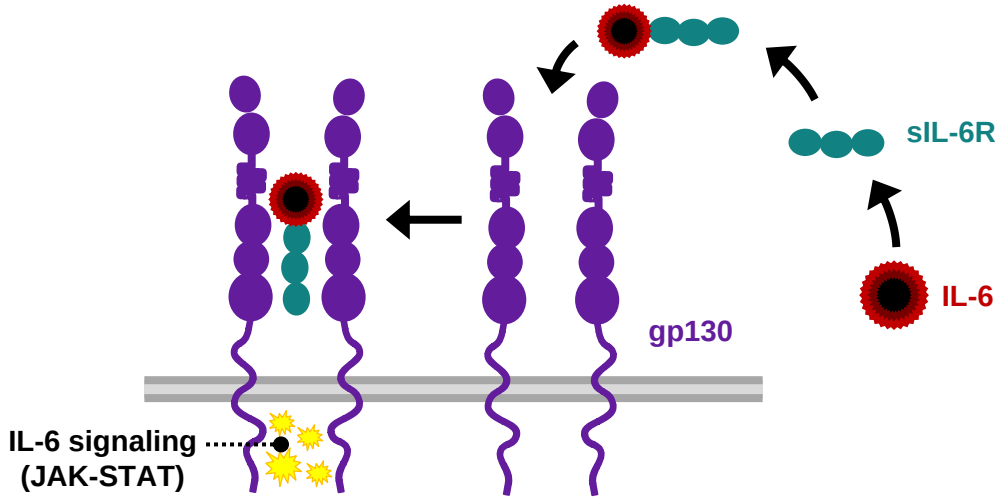
Classic signaling

- In classic signaling, IL-6 binds to the **membrane-bound IL-6R** (**mIL-6R**)
- **Classic signaling can only take place in cells that contain mIL-6R** (hepatocytes, some epithelial cells and certain types of leukocytes)[1,2]
- As **mIL-6R** is not expressed in the central nervous system, classic signaling is unlikely to play a role in NMOSD pathophysiology



Trans-signaling

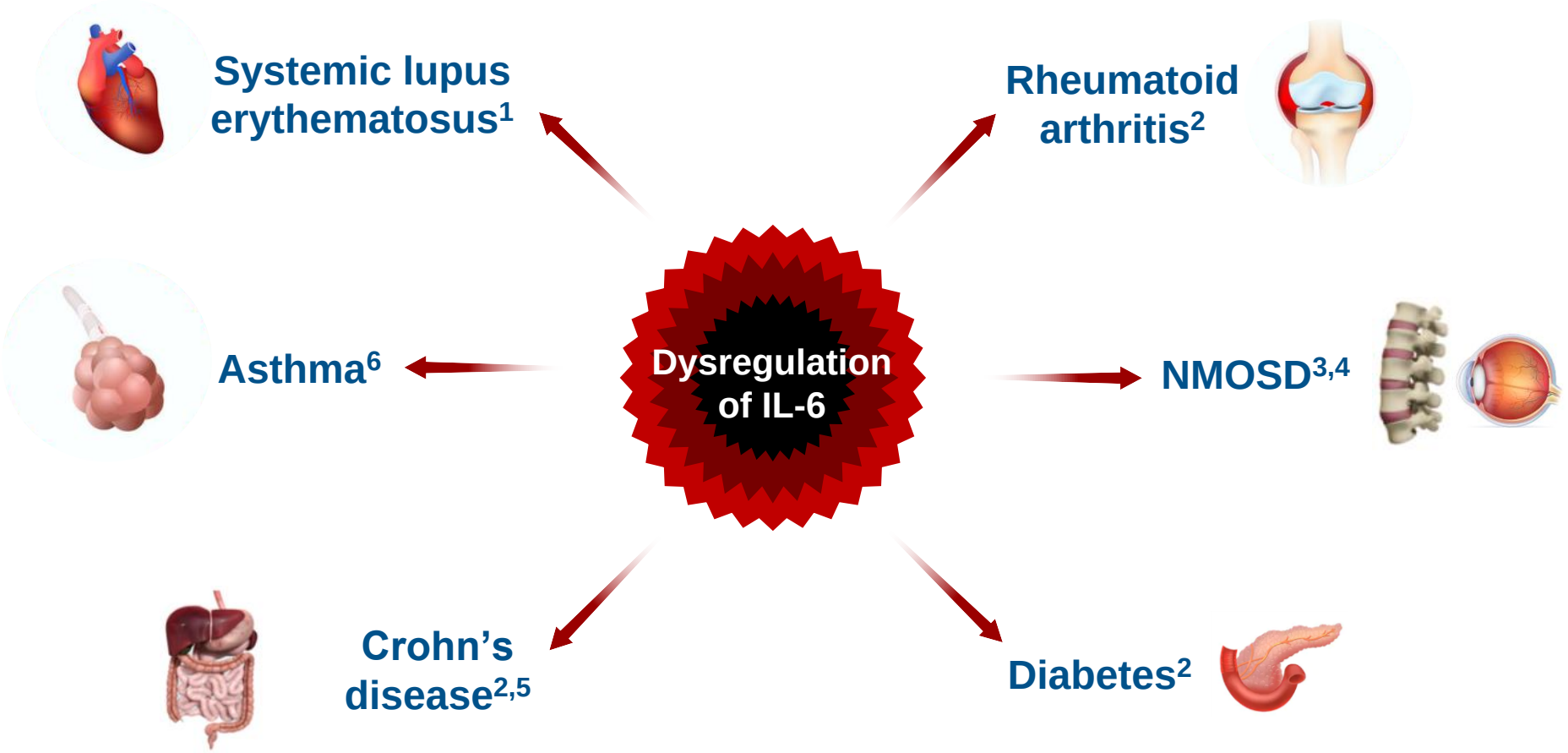
- In trans-signaling, IL-6 binds to **soluble IL-6R** (**sIL-6R**), before forming a membrane complex with **gp130** (a transmembrane glycoprotein essential for IL-6R downstream signaling)
- All cells express **gp130**, so trans-signaling is possible throughout the body, including the central nervous system
- It is likely that the IL-6 signaling associated with NMOSD is trans-signaling[3]



gp, glycoprotein; IL-6, interleukin-6; IL-6R, IL-6 receptor; JAK-STAT, Janus kinase/signal transducer and activator of transcription; mIL-6R, membrane-bound IL-6 receptor; NMOSD, neuromyelitis optica spectrum disorder; sIL-6R, soluble IL-6 receptor.

1. Hunter CA, Jones SA. *Nat Immunol* 2015;16:448–457. 2. Rose-John S. *Int J Biol Sci* 2012;8:1237–1247. 3. Araki M, et al. *Neurology* 2014;82:1302–1306.

Persistent, dysregulated production of IL-6 plays a critical role in the pathogenesis of several chronic autoimmune diseases[1–6]



IL-6, interleukin-6; NMOSD, neuromyelitis optica spectrum disorder.

1. Gottschalk TA, et al. *Front Immunol* 2015;6:550. 2. Maggio M, et al. *J Gerontol A Biol Sci Med Sci* 2006;61:575–584. 3. Içöz S, et al. *Int J Neurosci* 2010;120:71–75. 4. Uzawa A, et al. *Clin Exp NeuroImmunol* 2013;4:167–172.
5. Gabay C. *Arthritis Res Ther* 2006;8(suppl 2):S3. 6. Kamimura D, et al. *Rev Physiol Biochem Pharmacol* 2003;149:1–38.

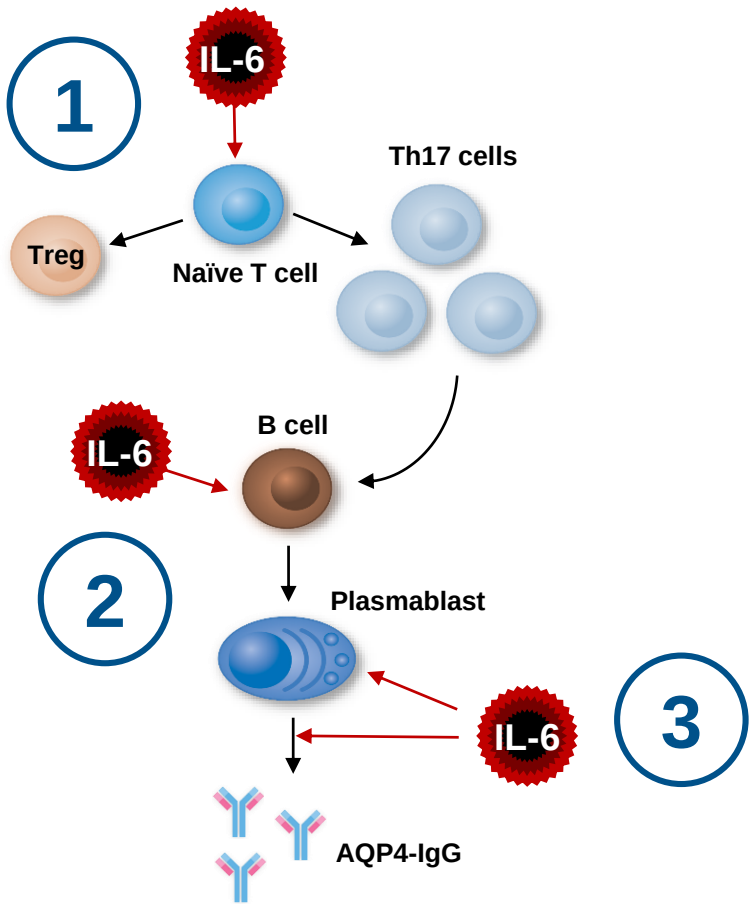
In NMOSD, IL-6 promotes the formation of inflammatory Th17 cells, and stimulates the secretion of pathogenic AQP4-IgG

1. Activation of the autoimmune cascade

1 IL-6 induces **T cell polarization**, shifting the **Treg-Th17 balance** towards an **inflammatory Th17 phenotype**[1]

2 IL-6 stimulates the differentiation of **B cells** into **plasmablasts**, which are the main cells responsible for producing pathogenic **AQP4-IgG**[2–4]

3 IL-6 **promotes the survival** of plasmablasts, as well as **increasing how much AQP4-IgG they secrete**[2–4]



AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; BBB, blood-brain barrier; CDC, complement dependent cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; MAC; membrane attack complex; Treg, regulatory T cell.

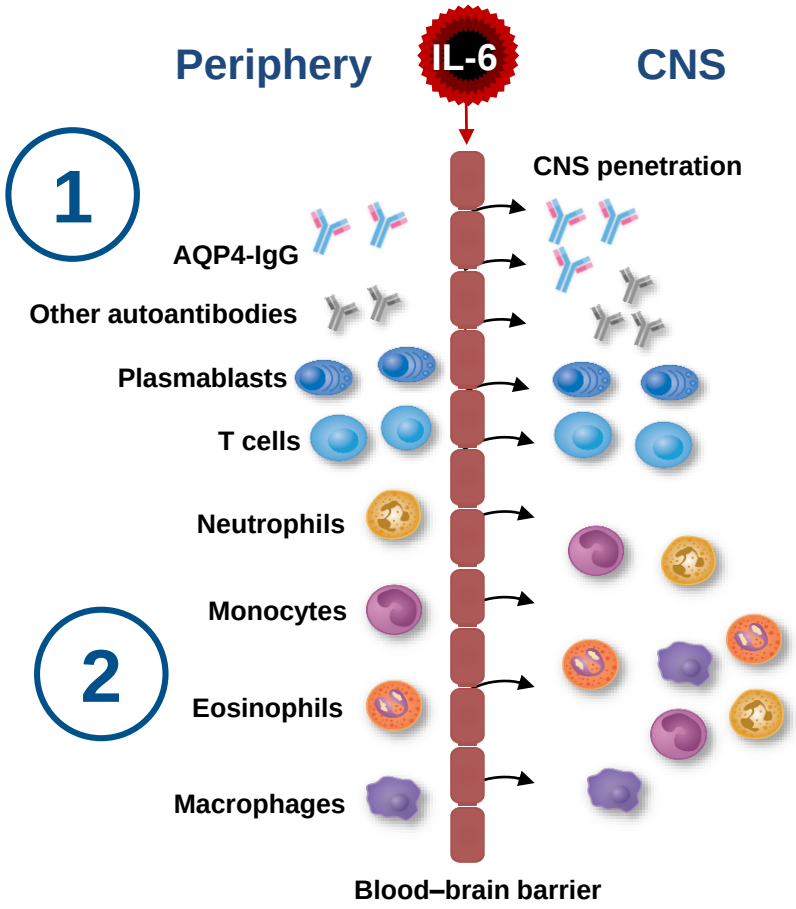
1. Kimura A, Kishimoto T. *Eur J Immunol* 2010;40:1830–5. 2. Kawano MM, et al. *Blood* 1995;85:487–94. 3. Yoshizaki K, et al. *J Immunol* 1984;132:2948–54. 4. Chihara N, et al. *Proc Natl Acad Sci USA* 2011;108:3701–6.

IL-6 disrupts the blood–brain barrier, allowing autoantibodies and pro-inflammatory immune cells into the central nervous system

2. Disruption of the blood–brain barrier

1 IL-6 **increases BBB permeability**, enabling the infiltration of **AQP4-IgG** and **other autoantibodies** into the CNS[1,2]

2 By increasing BBB permeability, IL-6 also allows **pro-inflammatory cells** such as **neutrophils**, **monocytes** and **eosinophils** into the CNS[1–3]



AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; BBB, blood-brain barrier; CDC, complement dependent cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; CNS, central nervous system; IL-6, interleukin-6; MAC; membrane attack complex; Treg, regulatory T cell

1. Takeshita Y, et al. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e311. 2. Traboulsee A, et al. *Lancet Neurology* 2020;19:402-412; 3. Obermeier B, et al. *Nat Med* 2013;19:1584–1596.

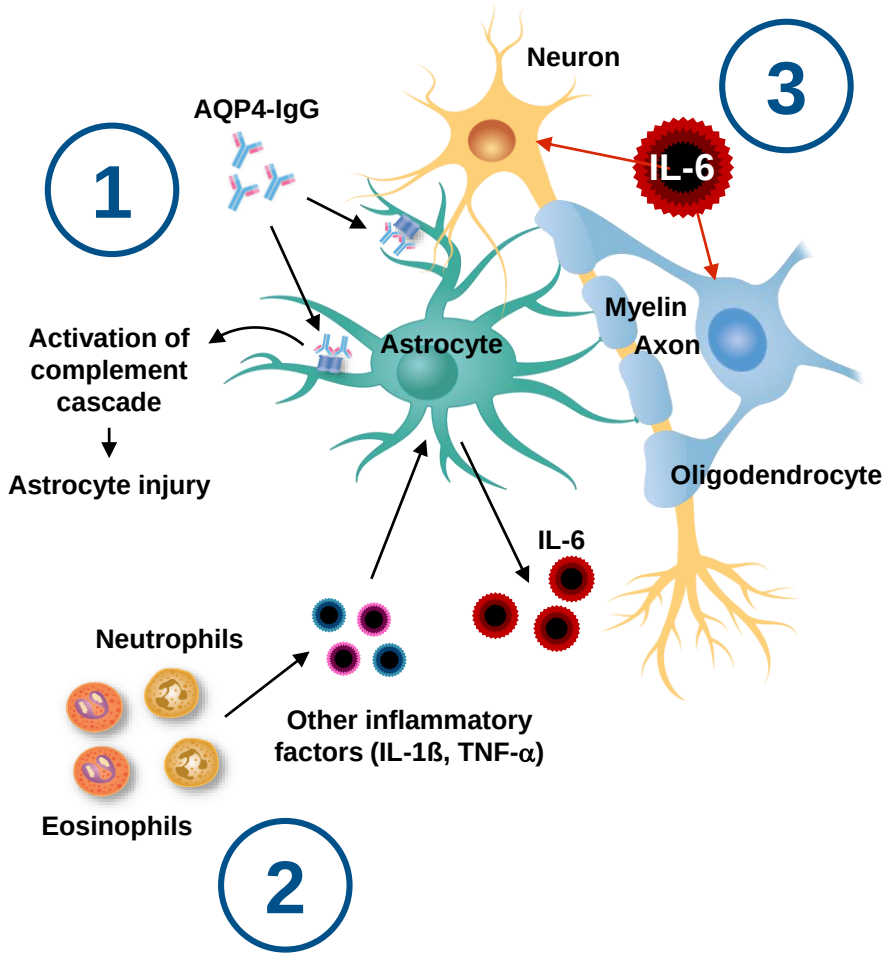
IL-6 contributes indirectly to astrocyte injury, secondary demyelination and neuronal damage

3. Indirect astrocyte injury

1 After entering the CNS, **AQP4-IgG** binds to **AQP4 water channels** on the end-feet of astrocytes – this **activates the complement cascade**, which results in astrocyte injury[1,2]

2 **Granulocytes**, which have entered the CNS through the BBB, release **pro-inflammatory cytokines** (e.g. IL-1β, TNF-α) that cause astrocytes to **secrete more IL-6**, creating a positive feedback loop[1]

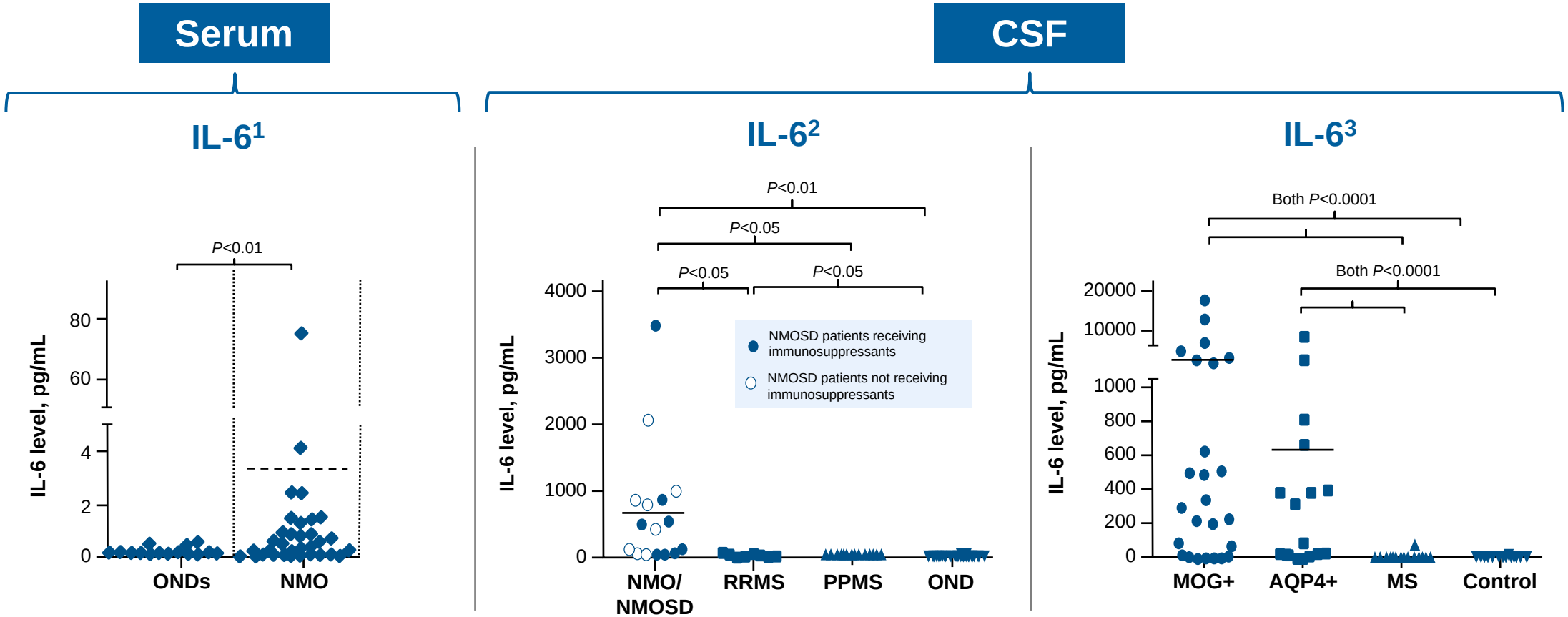
3 Increased IL-6 levels promote **secondary demyelination** and contribute to **oligodendrocyte and axonal damage**, leading to **neuronal death**[1–3]



AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; BBB, blood–brain barrier; CNS, central nervous system; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

1. Erta M, et al. *Int J Biol Sci* 2012;8:1254–1266. 2. Traboulsee A, et al. *Lancet Neurology* 2020;19:402-412. 3. Papadopoulos MC, et al. *Nat Rev Neurol* 2014;10:493–506.

CSF and serum IL-6 concentrations are significantly elevated in patients with active NMOSD, but not in patients with MS

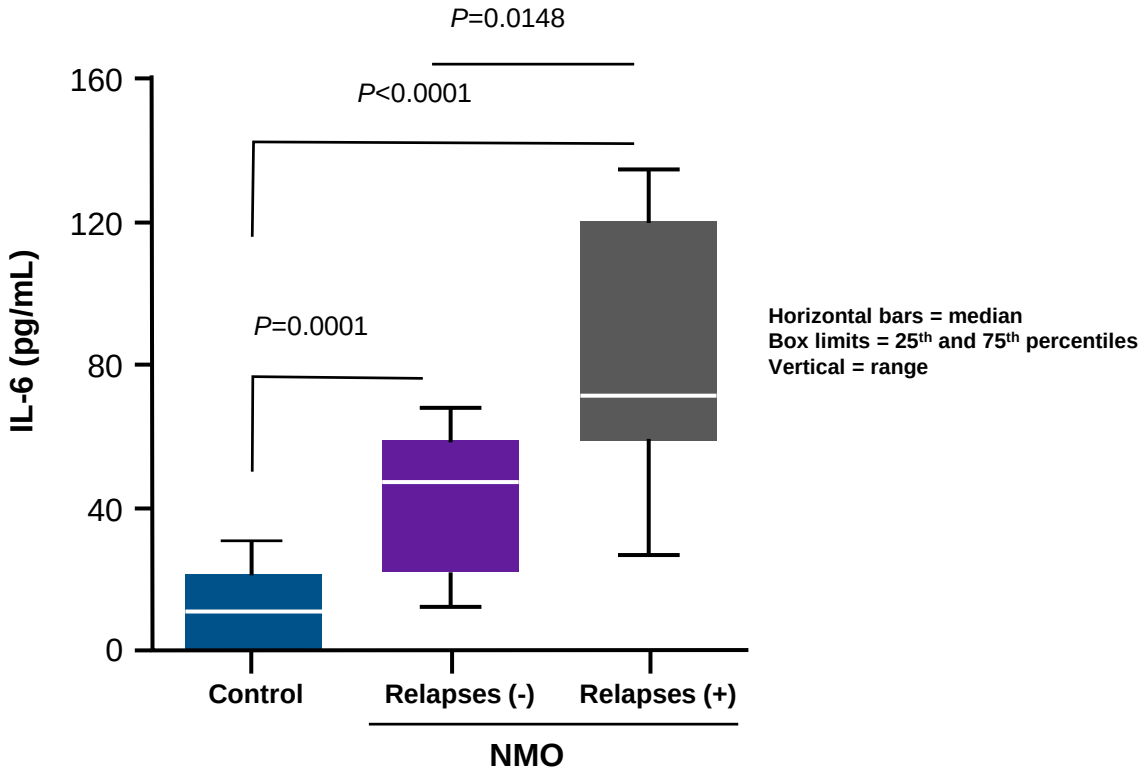


AQP4+, aquaporin-4 immunoglobulin G positive; CSF, cerebrospinal fluid; IL-6, interleukin-6; MS, multiple sclerosis; MOG+, myelin oligodendrocyte glycoprotein immunoglobulin G positive; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; OND(s), (other) non-inflammatory neurological disorders/diseases; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis.

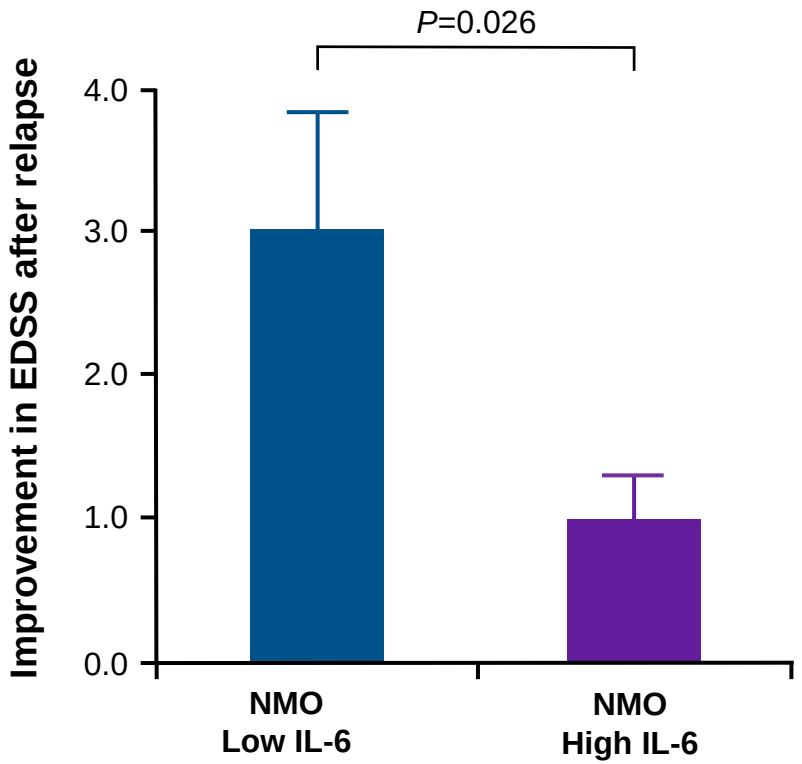
1. Uzawa A, et al. *Mult Scler* 2010;16:1443–1452. 2. Matsushita T, et al. PLoS One 2013;8:e61835. 3. Kaneko K, et al. *J Neurol Neurosurg Psychiatry* 2018;89:927–936.

IL-6 levels appear to correlate with baseline clinical severity and relapse risk in NMOSD, and are elevated in the serum and CSF during relapse[1–3]

Serum IL-6 levels are raised in NMOSD patients during relapse[2]

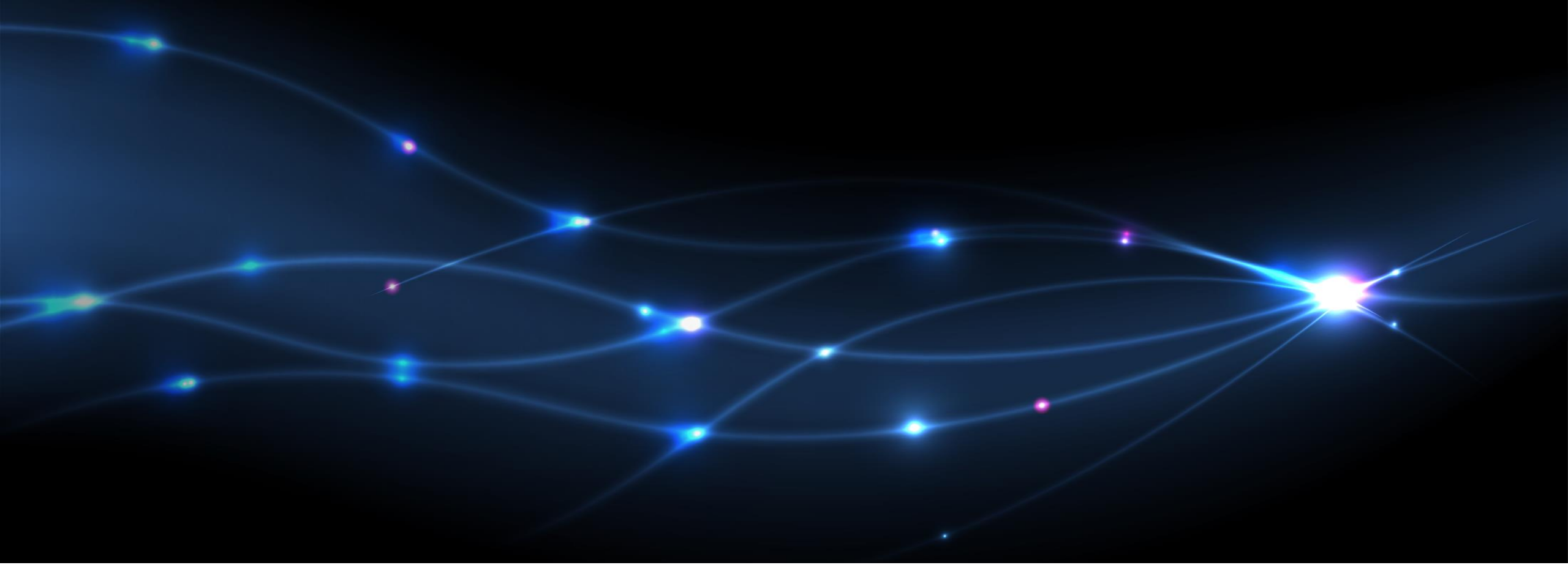


NMO patients with high CSF IL-6 levels experience poorer recovery after relapse (disability measured by EDSS score)[3]



CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IL-6, interleukin-6; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder.

1. Matsushita T, et al. *PLoS One* 2013;8:e61835. 2. Barros PO, et al. *Clin Exp Immunol* 2016;183:480–489. 3. Uzawa A, et al. *J Neurol Neurosurg Psychiatry* 2012;83:339–340.



AQP4-IgG-seronegative NMOSD, and the role of MOG-IgG

Up to one third of patients are AQP4-IgG seronegative, and NMOSD pathophysiology is poorly understood in this population

The existence of seronegative patients with NMOSD indicates that **AQP4-IgG-independent disease mechanisms are involved**[1]

- Disease pathophysiology is poorly understood in this population, so treating seronegative patients is difficult
- Diagnosis of NMOSD also becomes more challenging in the absence AQP4-IgG – criteria require patients to display at least two core clinical characteristics, instead of one core characteristic plus AQP4-IgG serology[2]

MOG

Up to 42% of AQP4-IgG-seronegative patients express **myelin oligodendrocyte glycoprotein (MOG) antibodies**[1], though it is unclear whether these are causative agents or are secondary to tissue damage[3]

Compared to AQP4-IgG-seropositive patients, individuals with NMOSD who are MOG-IgG seropositive show a **more variable** disease course, and are:[4,5]

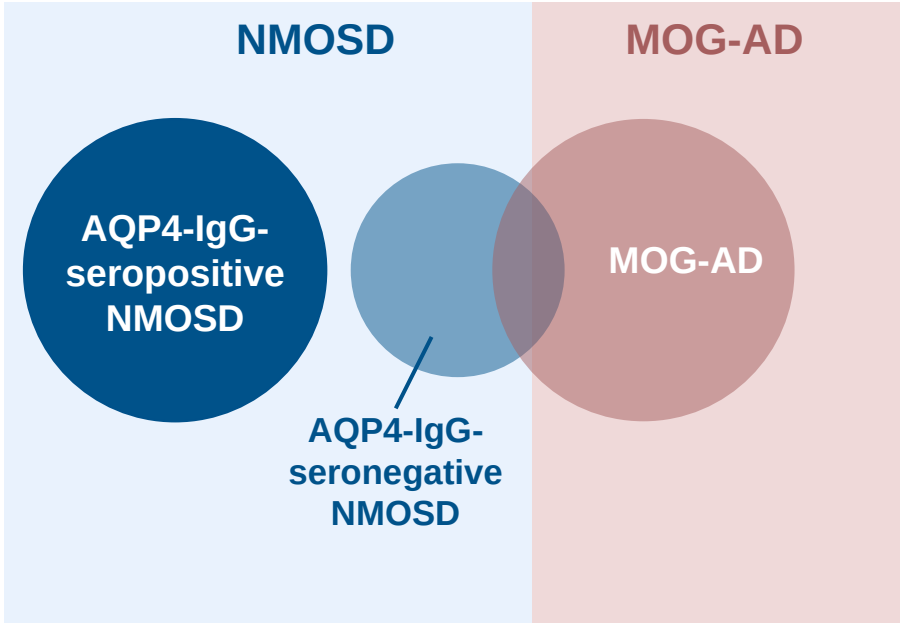
- **Equally likely to be male or female** (AQP4-IgG is more common in females)
- Usually **younger** at the time of disease onset
- More likely to display **isolated optic neuritis** or **myelitis**
- More likely to have **brain involvement**

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

1. Narayan R, et al. *Mult Scler Relat Disord* 2018;25:66–72. 2. Wingerchuk DM, et al. *Neurology* 2015;85:177–89. 3. Fujihara K. *Curr Op Neurol* 2019;32:385–94. 4. de Seze J. *Brain* 2017;140:3069–80. 5. de Seze J. *Curr Opin Neurol* 2019;32:111–4.

The role of MOG-IgG in NMOSD pathogenesis remains unclear

- If a patient tests positive for MOG-IgG, **that does not necessarily mean that they have NMOSD**
- Although a significant proportion of MOG-IgG-seropositive individuals experience the hallmark symptoms of NMOSD,[1–3] **many do not fulfil NMOSD criteria**
  - In a study of 170 MOG-IgG-seropositive patients, only 25% met the criteria for AQP4-IgG-seronegative NMOSD[4]
- Rather than being seen as a subcategory of NMOSD, the latest evidence suggests that MOG-antibody associated disease (MOG-AD) is a **separate condition** that **overlaps** with AQP4-IgG-seronegative NMOSD[5–7] (**Figure**)



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

1. Jarius S, et al. *J Neuroinflammation* 2016;13:279. 2. Ramanathan S, et al. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e40. 3. Kezuka T, et al. J *Neuroophthalmol* 2012;32:107–10. 4. Kunchok A, et al. *JAMA Neurol* 2020:e202743. 5. de Seze J. *Curr Opin Neurol* 2019;32:111–14 6. Jarius S, et al. J *Neuroinflammation* 2018;15:134. 7. Dos Passos GR, et al. *Front Neurol*. 2018;9:217.

MOG-IgG-positive NMOSD patients have significantly fewer subsequent relapses and better outcomes than AQP4-IgG-positive patients

MOG-IgG-positive patients commonly experience **hallmark NMOSD symptoms**, including **impaired ambulation**,[1] **severe visual impairment**[1–3] **and pain**[1]

Clinical feature	AQP4-IgG-positive	Incidence AQP4-IgG-positive vs. MOG-IgG-positive	MOG-IgG-positive
Prevalence in women	87.8–90%*^[4,5]	>	37.5–44%[4,5]
Mean age at disease onset (SD)	44.86 years (14.8)**[5]	>	32.29 years (17.1)[5]
Bilateral ON relapses	24.0–33%[4,5]	<	72.7–75%[4,5]
MRI findings involving conus	18%^[5]	<	75%^[5]
MRI brain lesions deep grey matter	0%†[5]	<	33%†[5]
Lumbar spinal cord lesion location	3.1%[4]	<	66.7%[4]
Attack history			
Single attack in disease history	16.6%‡[4]	<	50.0%[4]
Median number of attacks (range)	4 (1–33)*[4]	>	1.5 (1–3)[4]
Median EDSS (range)	5.8 (1–8.5)*[4]	>	1.5 (0–8)*[4]
Recovery after relapses#	Poorer recovery[4]		Better recovery[4]
Subsequent relapse	40%†[5]	>	0%[5]
Outcomes	Poorer outcome[4,5]		Better outcome[4,5]

Differences were significant – **P*<0.0001[4]; ^*P*=0.02[5]; ***P*=0.05; †*P*=0.03; ‡*P*=0.0031; #Assessed by EDSS and visual acuity.
AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, Expanded Disability Status Scale; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; SD, standard deviation.
1. Jarius S, et al. *J Neuroinflammation* 2016;13:280. 2. Ramanathan S, et al. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e40. 3. Kezuka T, et al. *J Neuroophthalmol* 2012;32:107-110. 4. Sato DK, et al. *Neurology* 2014;82:474-481. 5. Kitley J, et al. *JAMA Neurol* 2014;71:276–283.

Cell-based assays are the preferred choice for AQP4-IgG and MOG-IgG serological testing

AQP4-IgG testing

- Recommended in patients with the following[1]:
  - Recurrent, bilateral or severe optic neuritis
  - Longitudinal, or recurrent transverse myelitis
  - Lumbar MRI spine shows a lesion over >3 vertebrae
  - Poor recovery from MS relapses
- In AQP4-IgG testing, **cell-based assays** are **specific** and **more sensitive** than tissue-based immunofluorescence or ELISA[2,3]
- Assays detecting IgG binding to cells expressing recombinant AQP4 with quantitative flow cytometry detect 77% of AQP4-IgG-seropositive patients[3]

MOG-IgG testing

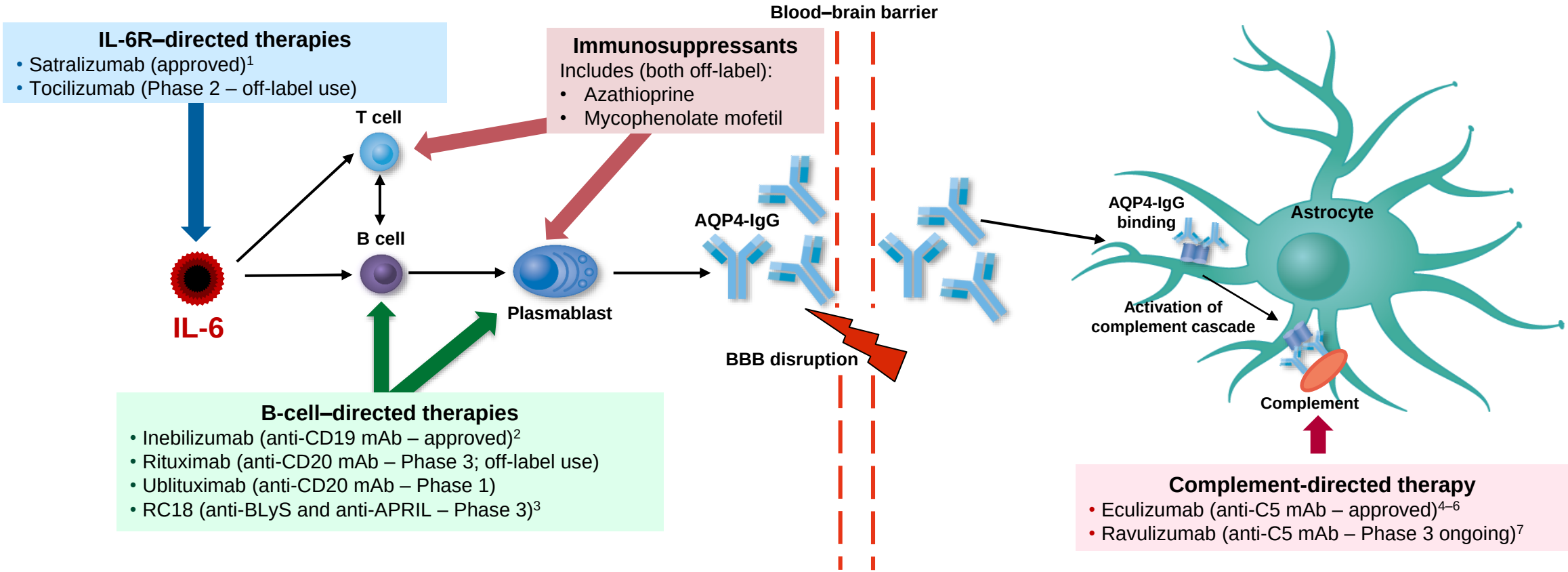
- Recommended in patients with the following[4]:
  - Monophasic or relapsing acute optic neuritis, myelitis, or encephalitis
  - Radiological findings compatible with CNS demyelination
  - MRI/CSF/Histopathology suggestive of acute CNS demyelination of putative autoimmune etiology
- MOG-IgG testing **should not be restricted** to AQP4-IgG-seronegative patients[4]
- A cell-based assay, using full-length human MOG as a target antigen and IgG1-specific antibodies, should be used[4]
- MOG-IgG serum concentrations depend on disease activity, so patients should be re-tested **during an acute attack** if the initial assay was negative[4]

AQP4, aquaporin 4; AQP4-IgG, aquaporin-4 immunoglobulin G; CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; MOG, myelin oligodendrocyte glycoprotein; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis.

1. Aquaporin 4 –antibodies (AQP4). Available at: Link (Accessed September 2020). 2. Fujihara K. *Curr Op Neurol* 2019;32:385–94. 3. Waters PJ, et al. *Neurology* 2012;78:665–71. 4. Jarius S, et al. *J Neuroinflammation* 2018;15:134

Roche

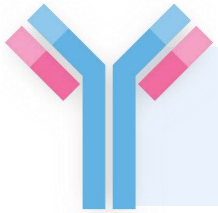
Therapeutic agents for the treatment of NMOSD are designed to affect a number of different targets involved in the disease pathophysiology



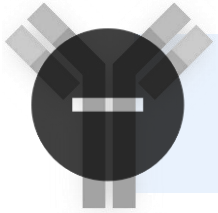
APRIL, A proliferation-inducing ligand (also known as TNFSF13, tumor necrosis factor ligand superfamily member 13); AQP4-IgG, aquaporin-4 IgG immunoglobulin G; BBB, blood–brain barrier; BLyS, B-lymphocyte stimulator; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; mAb, monoclonal antibody; NMOSD, neuromyelitis optica spectrum disorder.

1. Roche. Press Release. Available at: Link. June 29, 2020. Accessed August 2020. 2. Uplizna™ (Inebilizumab) prescribing information. June 2020. 3. Biospace Remegen. Press Release. Available at: Link. Accessed April 2020. 4. Alexion Pharmaceuticals. Available at: Link. Published June 27, 2019. Accessed June 2020. 5. Soliris® (eculizumab) Prescribing Information. June 2019. 6. Alexion Pharmaceuticals. Available at: Link. Published August 27, 2019. Accessed June 2020. 7. Alexion.com. Ravulizumab data release. Available at: Link. Accessed April 2020.

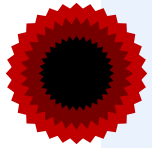
Summary



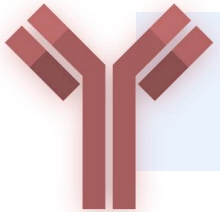
NMOSD is a **complex**, **heterogeneous disease**, with two thirds of patients expressing pathogenic **autoantibodies against AQP4 (AQP4-IgG)**



One third of patients with NMOSD are **AQP4-IgG seronegative;** more research is needed to understand the pathophysiology of disease in these patients



IL-6, a multi-functional cytokine, **plays a critical role in the pathogenesis of NMOSD** by stimulating proinflammatory immune cells, leading to BBB disruption and CNS damage



Antibodies against MOG (**MOG-IgG**) have been identified in patients with NMOSD, but the neurology community is currently trending towards classification as separate disease entity, termed MOG-AD

AQP4-IgG, aquaporin-4 immunoglobulin G; BBB, blood–brain barrier; CNS, central nervous system; IL-6, interleukin-6; MOG, myelin oligodendrocyte glycoprotein; MOG-AD, MOG-antibody associated disease; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.