

The complement system in NMOSD and MG: A target for therapeutic benefit?

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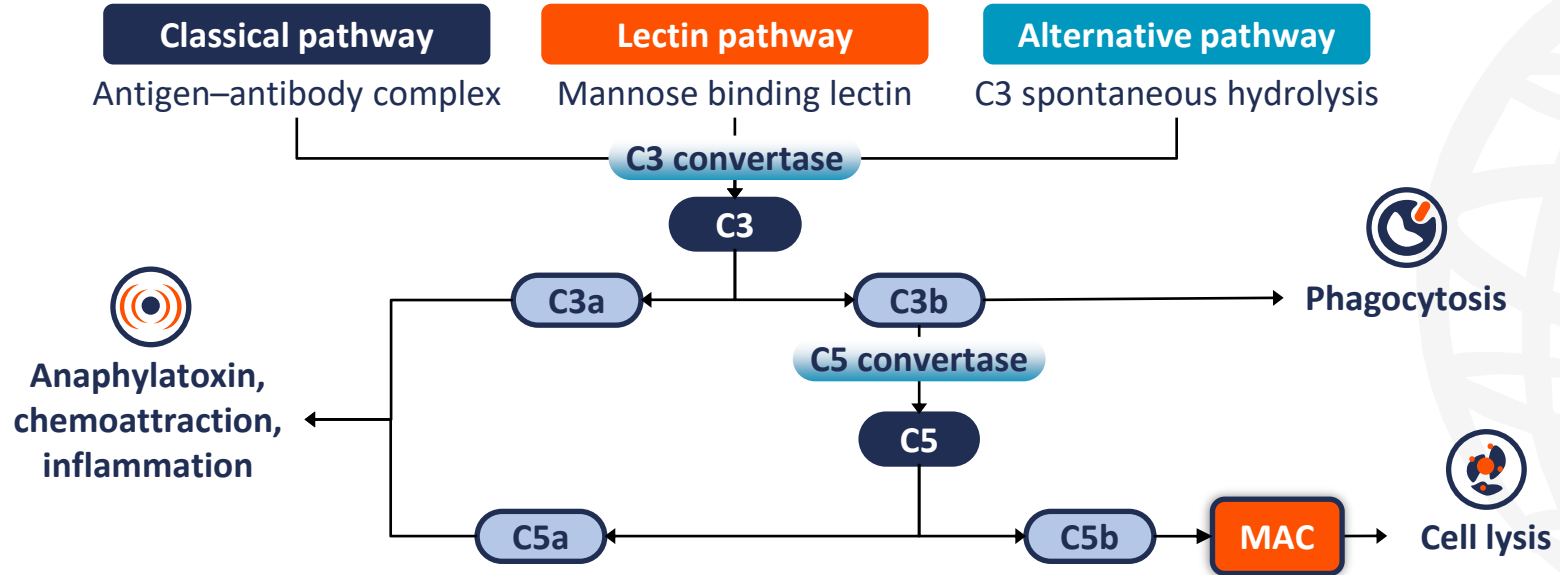
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The role of complement in NMOSD and MG pathophysiology



Complement activation is central to the immune response and CNS protection



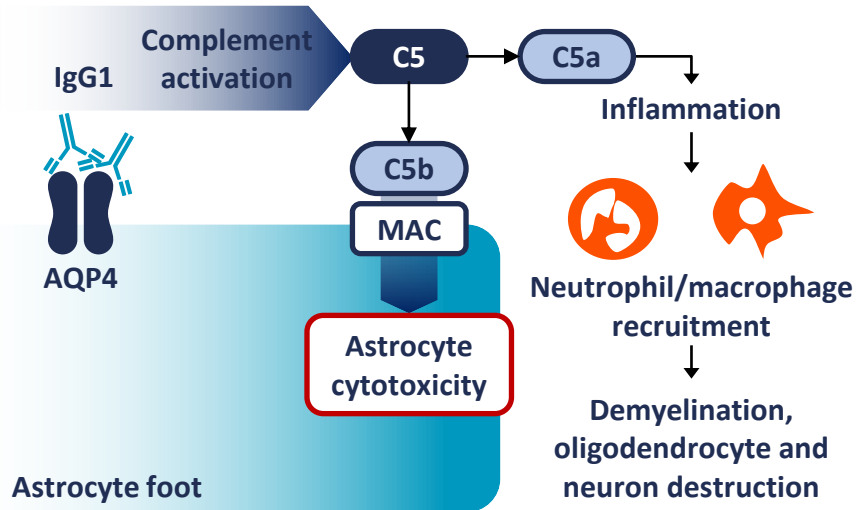
Aberrant complement activation can lead to progression of neurological disorders

Adapted from Chen, et al. 2022.

Complement activation is involved in the pathogenesis of both NMOSD and MG

NMOSD

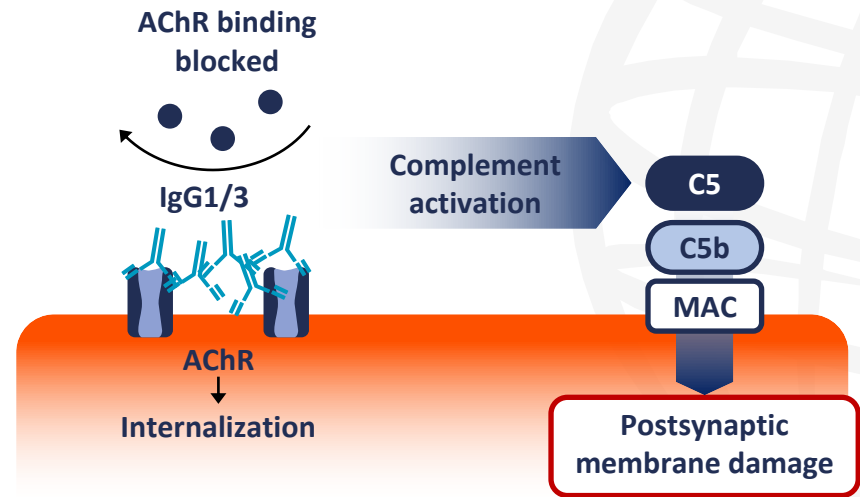
AQP4 antibodies cause astrocyte death and demyelination



Adapted from Dalakas, et al. 2020; Ponleitner, Rommer. 2022.

MG

Antibody targeting of AChR in the NM junction leads to complement activation



Adapted from Dalakas, et al. 2020; Dresser, et al. 2021.

AChR, acetylcholine receptor; AQP4, aquaporin 4; C, serum complement protein; IgG, immunoglobulin G; MAC, membrane attack complex; MG, myasthenia gravis; NM, neuromuscular; NMOSD, neuromyelitis optica spectrum disorder.

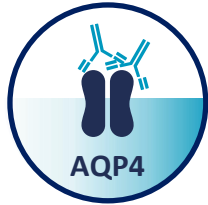
1. Dalakas M, et al. *Nat Rev Neurol.* 2020;16:601–17; 2. Ponleitner M, Rommer PS. *Wien Med Wochenschr.* 2022. doi: 10.1007/s10354-022-00987-2; 3. Dresser L, et al. *J Clin Med.* 2021;10:2235.



Complement activation as a biomarker in NMOSD and MG

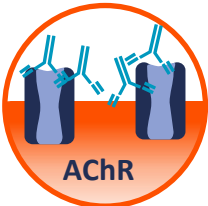


Markers of complement activation in NMOSD and MG



NMOSD

- Serum AQP4 IgG antibodies activate complement and are **highly specific for NMOSD**^{1,2}
- AQP4 antibody titres may correlate with disease course: high antibody serum levels have been associated with attacks²
- AQP4-antibody positive patients may be at risk of relapse and require preventative care³
- Patients negative for both AQP4 and MOG antibodies termed seronegative NMOSD⁴



MG

- AChR antibodies are **highly specific for MG**⁵
- In AChR-antibody positive MG, IgG1 or IgG3 activate the classical complement pathway⁶
 - MuSK IgG4 antibodies only weakly activate complement; complement-directed therapies are ineffective⁶
- Likelihood of treatment response can vary by antibody type⁷

Individual complement components are also showing promise as markers of disease status in both NMOSD and MG^{8,9}

AQP4, aquaporin 4; AChR, acetylcholine receptor; IgG, immunoglobulin G; MG, myasthenia gravis; MOG, myelin oligodendrocyte glycoprotein; MuSK, muscle-specific tyrosine kinase; NMOSD, neuromyelitis optica spectrum disorder.

1. Delgado-García G, et al. *Front Neurol.* 2022;13:966428; 2. Ponleitner M, Rommer PS. *Wien Med Wochenschr.* 2022. doi: 10.1007/s10354-022-00987-2;

3. Wingerchuk DM, et al. *Neurology.* 2015;85:177-89; 4. Dauby S, et al. *Acta Neurol Belg.* 2022;122:135-44; 5. Gilhus NE, Verschuuren JJ. *Lancet Neurol* 2015;14:1023-36;

6. Albazli K, et al. *Front Immunol.* 2020;11:917; 7. Cortés-Vicente E, et al. *Ann Clin Transl Neurol.* 2022;9:122-31; 8. Miyamoto K, et al. *Front Immunol.* 2023;14:1090548;

9. Iacomino N, et al. *Biomedicines.* 2022;10:1360.



Complement as a therapeutic target for the treatment of NMOSD and MG

Complement-directed therapies in NMOSD and gMG

NMOSD

Eculizumab: mAb C5 inhibitor¹ EMA/FDA approved^{1,2*}

PREVENT (NCT01892345):³

- AQP4+ NMOSD: n=96 eculizumab; n=47 placebo
- **94% relapse rate reduction** with eculizumab vs placebo (HR 0.06, 95% CI 0.02–0.2; p<0.001)

Ravulizumab: mAb C5 inhibitor⁴ EMA approved^{5*}

CHAMPION-NMOSD (NCT04201262)⁴

- AQP4+ NMOSD: n=58 ravulizumab; n=47 placebo
- **98.6% relapse rate reduction** with ravulizumab vs placebo (HR 0.014, CI 0.000–0.103; p<0.0001)

C5

C5b

MAC

gMG

Eculizumab: mAb C5 inhibitor¹ EMA/FDA approved^{1,2†}

REGAIN + OLE (NCT02301624)⁶

- AChR+ refractory gMG: n=56 eculizumab; n=61 placebo/eculizumab
- **75% relapse rate reduction** (p<0.0001) from study start
- Functional and QoL improvements sustained over 3 years

Ravulizumab: mAb C5 inhibitor⁵ EMA/FDA approved^{5,7†}

CHAMPION MG (NCT03920293)⁸

- AChR+ gMG: n=86 ravulizumab; n=89 placebo
- **Rapid, sustained ADL improvement** vs placebo (p<0.001)

Zilucoplan: Peptide C5 inhibitor⁹

RAISE (NCT04115293)⁹

- AChR+ gMG: n=86 zilucoplan; n=88 placebo
- **Improved ADL** vs placebo over 12 weeks (p=0.0004)

*Indicated for AQP4+ NMOSD^{1,2,5}; †Indicated for AChR+ gMG^{1,2,5,7}; ‡EMA extended approval granted for treatment of refractory AChR+ gMG in children aged ≥6 years.¹⁰

AChR+, acetylcholine receptor antibody positive; ADL, activities of daily living; AQP4+, aquaporin 4 antibody positive; C, serum complement protein; CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; gMG, generalized myasthenia gravis; HR, hazard ratio; mAb, monoclonal antibody; MAC, membrane attack complex; MG, myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; OLE, open label extension; QoL, quality of life.

1. FDA. Eculizumab PI. Available at: <https://bit.ly/440WZmW> (accessed May 2023); 2. EMA. Eculizumab SmPC. Available at: <https://bit.ly/45f24t5> (accessed May 2023); 3. Pittock SJ, et al. *Engl J Med*. 2019;381:614–25; 4. Pittock SJ, et al. *Ann Neurol*. 2023;93:1053–68; 5. EMA. Ravulizumab SmPC. Available at: <https://bit.ly/45jojhg> (accessed May 2023); 6. Muppidi S, et al. *Muscle Nerve*. 2019;60:14–24; 7. FDA. Ravulizumab PI. Available at: <https://bit.ly/3OJCmHM> (accessed May 2023); 8. Vu T, et al. *NEJM Evid*. 2022;1. doi: 10.1056/EVIDoat2100066; 9. Howard JF Jr, et al. *Lancet Neurol*. 2023;22:395–406; 10. EMA. Soliris. 2023. Available at: <https://bit.ly/3YoSyBg> (accessed July 2023).