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

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Expert panel

Prof. Said Beydoun

Keck School of Medicine of USC

Los Angeles, CA, USA

Prof. Heinz Wiendl

Department of Neurology

University Hospital Münster

Münster, Germany

Dr Pushpa Narayanaswami

Beth Israel Deaconess Medical Center

Boston, MA, USA

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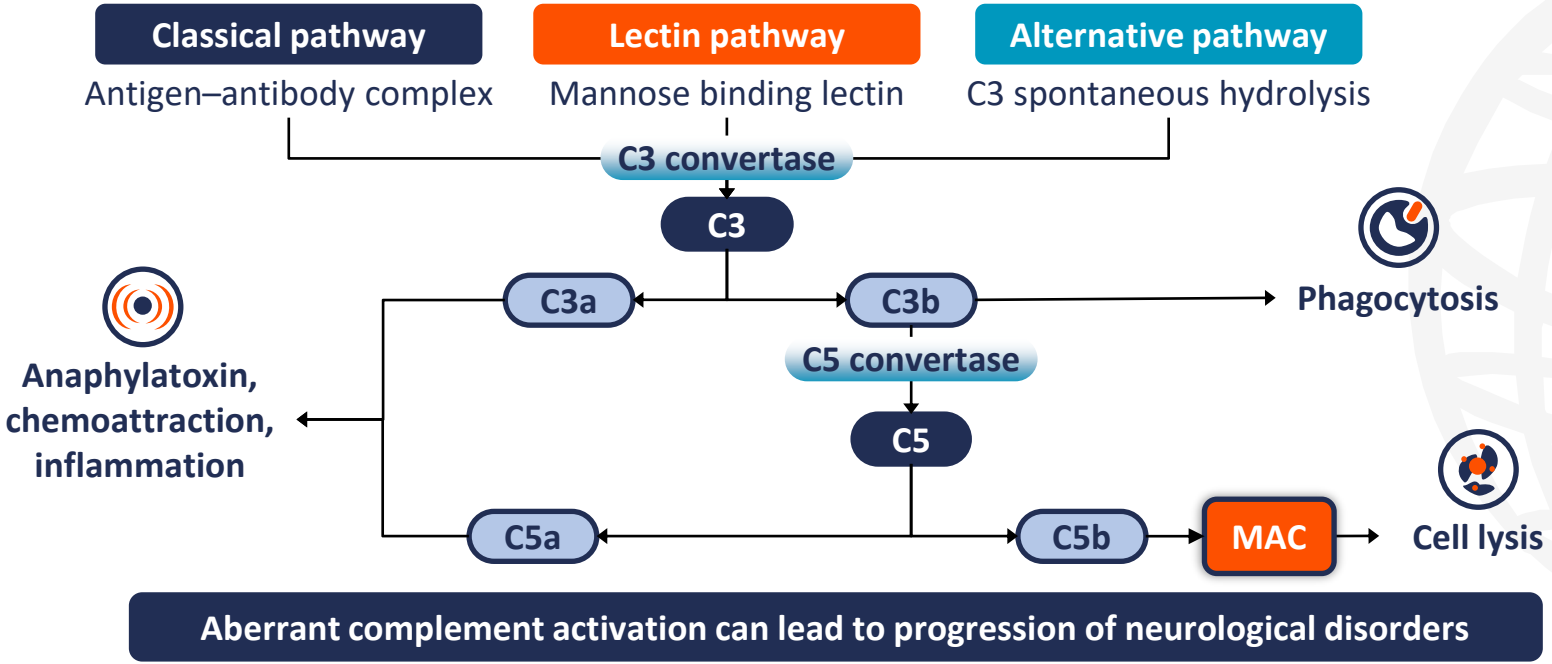
The role of complement in NMOSD and MG pathophysiology

Complement activation is central to the immune response and CNS protection



Adapted from Chen, et al. 2022.

C, serum complement protein; CNS, central nervous system; MAC, membrane attack complex.
Chen Y, et al. *Biomolecules*. 2022;12:337.

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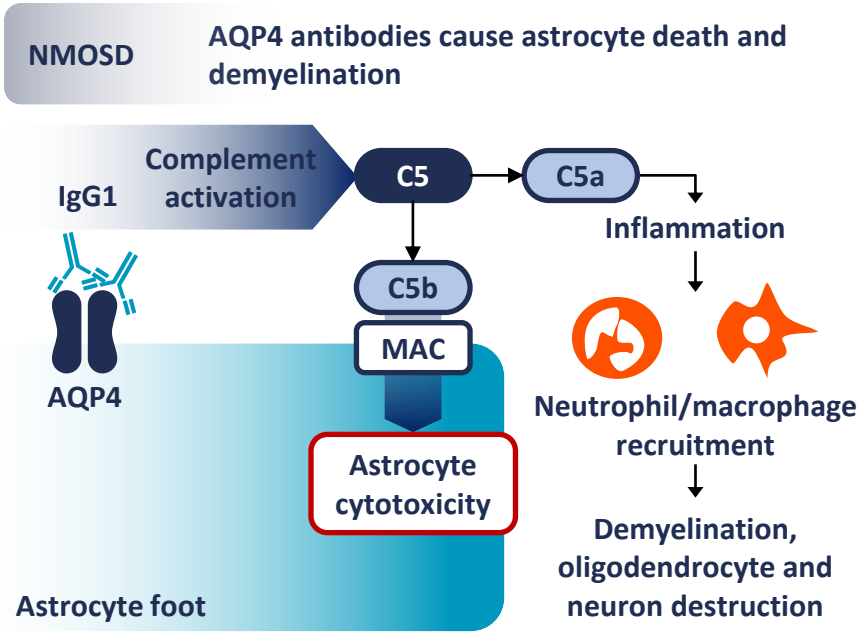
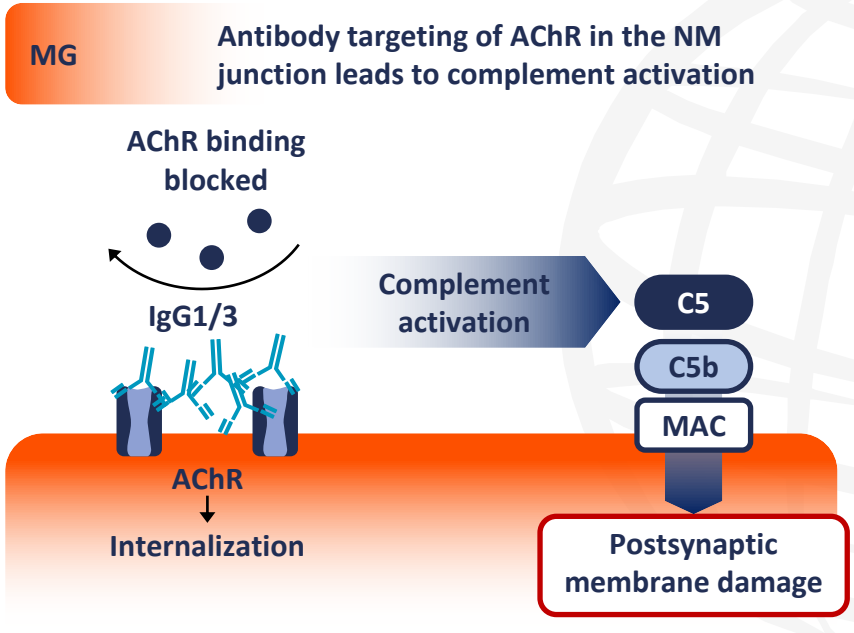
Complement activation is involved in the pathogenesis of both NMOSD and MG



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



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.

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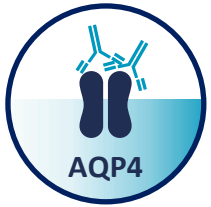
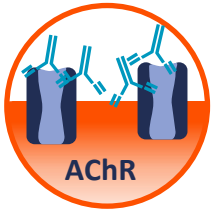
Complement activation as a biomarker in NMOSD and MG

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 attacks[2]
- AQP4-antibody positive patients may be at risk of relapse and require preventative care[3]
- Patients negative for both AQP4 and MOG antibodies termed seronegative NMOSD[4]



MG

- AChR antibodies are **highly specific for MG**[5]
- In AChR-antibody positive MG, IgG1 or IgG3 activate the classical complement pathway[6]
  - MuSK IgG4 antibodies only weakly activate complement; complement-directed therapies are ineffective[6]
- Likelihood of treatment response can vary by antibody type[7]

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-Garcia 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.

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

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Complement-directed therapies in NMOSD and gMG

NMOSD

Eculizumab: mAb C5 inhibitor[1] — **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 inhibitor[4] — **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)

gMG

Eculizumab: mAb C5 inhibitor[1] — **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 inhibitor[5] — **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 inhibitor[9]

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. *N 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/EVIDoa2100066; 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).

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