Neuromyelitis optica spectrum disorder

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Disclosures

- I have no personal financial disclosures.
- We will be discussing off label use of some medications.

Objectives

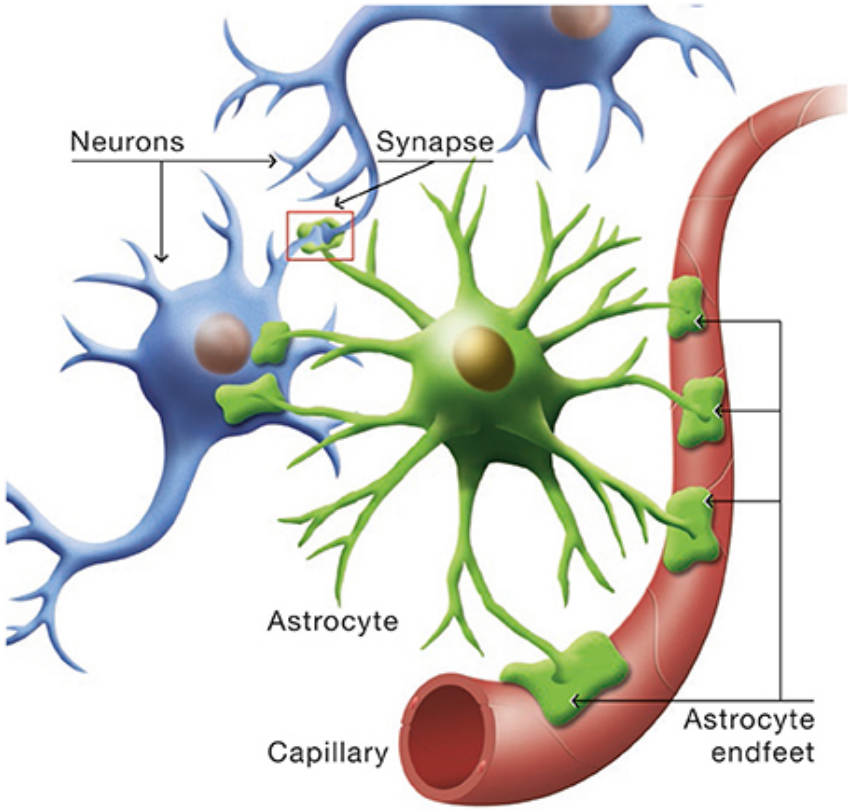
- Epidemiology
- Pathophysiology
- Clinical presentation
- Treatment

Neuromyelitis optica

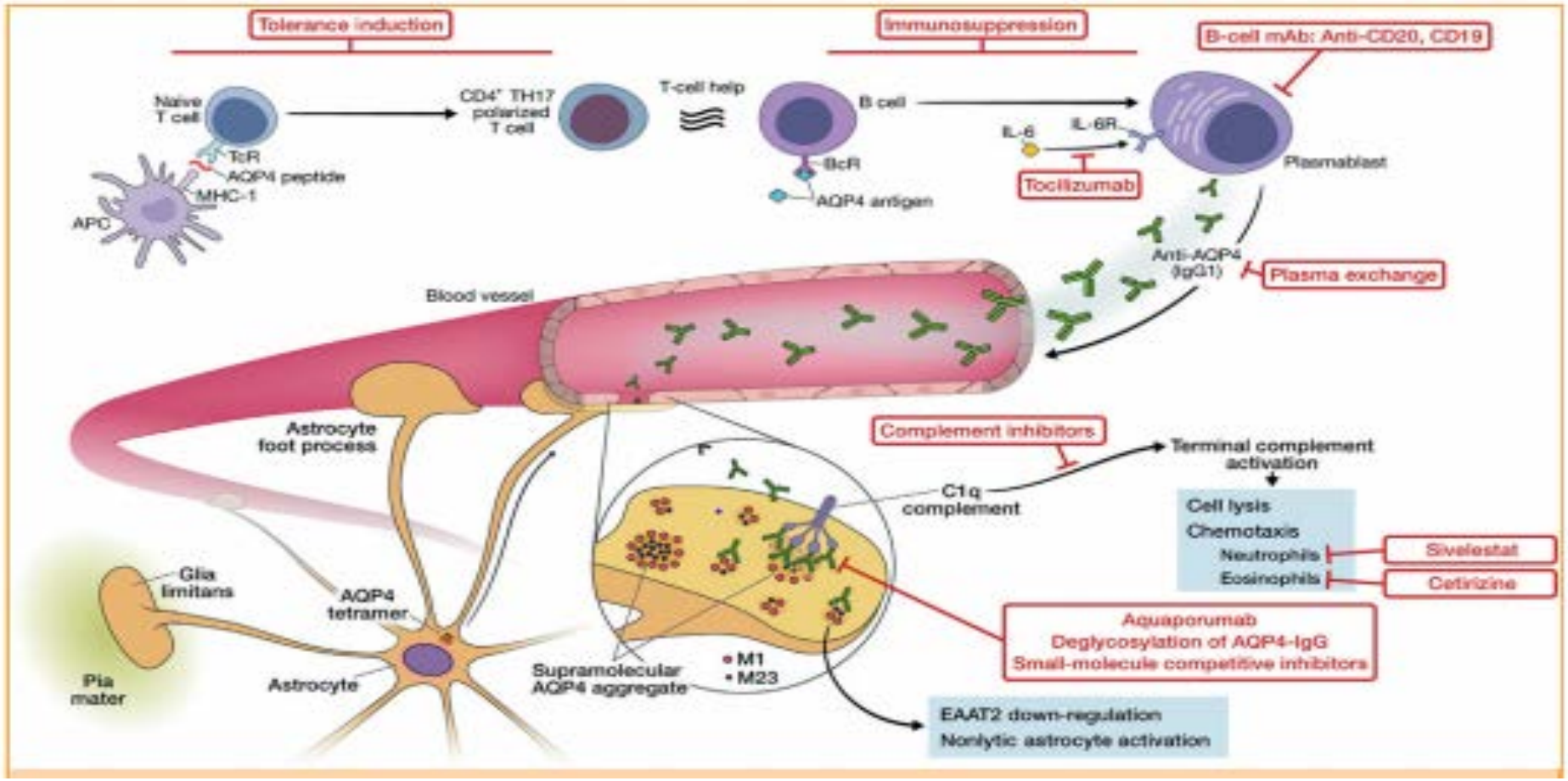
- Classically associated with antibodies against **aquaporin-4 (AQP4) receptors**.
  - Patients may also have no antibodies (seronegative).
- More common in females (8-9:1) [Flanagan et al 2016].
- Can affect all ages, average onset around 40 years old [Etemadifar et al 2015].
- Much lower prevalence in comparison to multiple sclerosis, estimated at **4/100,000** in the United States [Flanagan et al 2016].
  - Higher rates in black patients.
- Commonly associated with other autoimmune diseases such as lupus or Sjogren's.

Neuromyelitis optica (AQP4)

- Inflammatory disorder of the central nervous system affecting primarily the **optic nerves** and **spinal cord**.
  - Caused by antibodies targeting **aquaporin 4 (AQP4) receptors**.
  - AQP4 is a water channel located on astrocyte foot processes.



Neuromyelitis optica (AQP4)



Weinshenker BD and Wingerchuk DM. Neuromyelitis Spectrum Disorders. *Mayo Clin Proc*. April 2017;92(4):663-679

Clinical Presentation

- Dependent on location of attack
  - **Transverse myelitis**: spinal cord lesion can cause paraplegia or quadriplegia, bowel or urinary incontinence, and pain/spasms are common.
  - **Optic neuritis**: typically painful, loss of visual acuity and color vision.
  - **Area postrema syndrome**: lesion in the area postrema (in the brainstem) can cause severe, intractable vomiting.

Clinical Presentation

- If left untreated, further relapses with new lesions can occur.
  - Does not have the same “progressive” course that multiple sclerosis can have.
  - Degree of recovery from an acute relapse tends to be less when compared to a relapse in multiple sclerosis .

Evaluation

- Serum
  - **Aquaporin 4 positive.**
  - Important to rule out other diseases.

- Cerebrospinal fluid (CSF)
  - **High white blood cells** and/or **high protein** in CSF more common than MS.
  - Oligoclonal bands are often negative.
  - Testing for AQP4 antibodies in CSF is not necessary [Majed et al 2016].

Evaluation

- Imaging: MRI
  - Spinal cord imaging classically demonstrates **longitudinally extensive** lesions (**more than 3 spinal cord segments** in length).
  - Lesions can also be seen in the optic nerves if patients present with optic neuritis.
  - Brain is not frequently involved (especially above the brainstem).
    - Pediatric patients are the exception

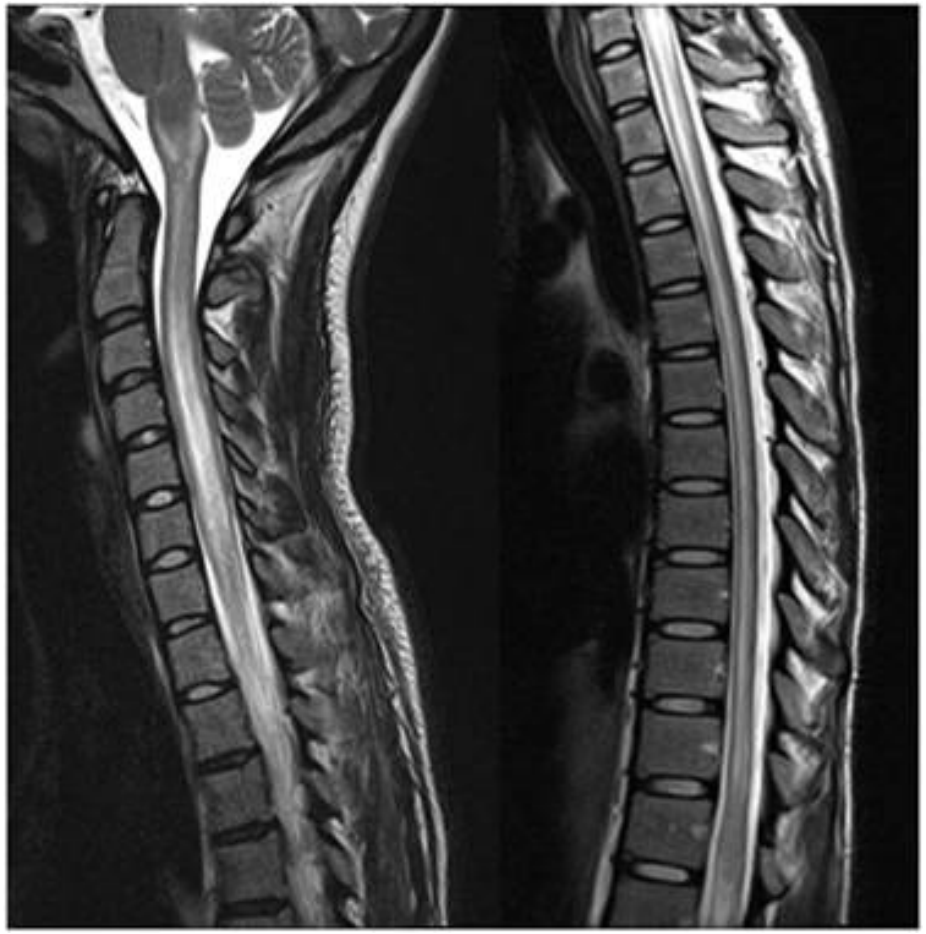


Table 1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.
[a] See table 2 and text discussion on serologic considerations for recommendations regarding interpretation of clinical and serologic testing.

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Wingerchuk Criteria

Wingerchuk DM, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. Jul 2015, 85 (2) 177-189

Acute Therapies

Intravenous steroids

- First line therapy, typically daily for 3-5 days.

Plasmapheresis (PLEX)

- There is benefit in early initiation of PLEX [Bonnan et all 2018].
- Every other day therapy, typically 5-7 therapy sessions.
- Can be done in conjunction with steroids.

Intravenous Immunoglobulin (IVIG)

- Data has not supported that this is as effective in the acute period, although may be used in conjunction with other therapies in patients with severe disability [Li et al 2020].

Long term immunotherapy

- Patients generally **require indefinite immunotherapy** as relapses can occur later in life.
- If patients avoid further relapse, they tend to avoid the progression of disability over time that is seen in multiple sclerosis.
- May need to stay on oral steroids while long term therapy becomes therapeutic.
- Until recently, most immunotherapies for NMO treatment were used off label.

Long term immunotherapy

- Azathioprine, mycophenolate mofetil, methotrexate all have some degree of evidence of benefit [Weinshenker 2017].
- Rituximab (anti-CD20 monoclonal antibody) is widely used off-label.
  - More beneficial than azathioprine [Nikoo et al. 2003].
  - Similar reduction in relapse rates between rituximab and mycophenolate (88.2 to 87.4%, respectively) [Mealy et al. 2014].
- Tocilizumab (anti-IL6 monoclonal) can also be used in refractory cases [Zhang et al 2020].
- Typical DMT for multiple sclerosis including interferons, fingolimod, and natalizumab are ineffective and may be harmful [Weinshenker 2017].

Long term immunotherapy

Solaris (eculizumab) – IV infusion
- Binds complement component C5, prevents formation of C5b-induced membrane attack complex.
- FDA approved, AQP4 seropositive patients.
- Weekly for the first 4 doses, then every other week thereafter.

Uplizna (inebilizumab) – IV infusion
- Anti-CD19 monoclonal antibody.
- FDA approved, AQP4 seropositive patients.
- First, second dose at day 1, 15; then every 26 weeks thereafter.

ENSPRYNG (satralizumab) – SQ injection
- Anti-IL6 monoclonal antibody.
- FDA approved, AQP4 seropositive patients.
- First, second, third dose 2 weeks apart; then every 4 weeks thereafter.

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