MOG Antibody Associated Disorders and optic neuritis

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MOG Antibody Associated Disorders

• Take home points
  • MOG is distinct from NMOSD with AQP-4 IgG and MS
  • MOG clinical profile is distinctive and recognizable
  • MOG ON is uncommon but recognizable
MOG Antibody Associated Disorders

- MOG
- MOG antibody
- MOG syndrome
  - Adult
  - Compare to MS, NMO
- MOG optic neuritis
  - Compare to MS, NMO
- Treatment

Myelin Oligodendrocyte Glycoprotein
Myelin Oligodendrocyte Glycoprotein

- Expressed in oligodendrocytes of mammal CNS
- Biological role is not clear
- Historically identified as potential antigenic target in MS
MOG Immunity

• Animal Models
  • MOG IgG Ab elicits a demyelinating immune response
  • Mice with T and B cells that target MOG develop an opticospinal form of EAE
MOG IgG Antibody Testing

- Western Blot and ELISA nonspecific
  - Pediatric ADEM
  - Variable presence in MS
- Cell-based assay more specific
  - Reproducibly rarer in MS
  - Still frequent in pediatric ADEM
- NMO Spectrum Disorder
  - Up to 30% AQP-4 negative
  - MOG Ab in 25-40% of AQP-4 negative NMOSD
- Live cell assay superior to fixed cell assay
  - Mayo Clinic and Oxford labs
NMOSD Diagnostic Criteria

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

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)
MOG IgG Antibody Testing

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  - Variable presence in MS
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  - Rare in adults with MS
- NMO Spectrum Disorder
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MOG Antibody Associated Disorders

- Descriptions limited to case series
- Literature for only about five years
MOG Antibody Associated Disorders

- Phenotype
  - ON 70%
  - TM 40%
  - ADEM mostly in children
  - Brainstem syndromes (incl. area postrema) up to 30%
MOG Antibody Associated Disorders

- Relapses
  - Monophasic
    - 25% after five years
  - Relapses
    - 50% in first two years after presentation
    - 75% by five years
- Titers
  - Higher at time of relapse
  - Up to 50% become antibody negative after relapse
  - Persistent positivity may indicate higher risk of relapse
MOG Antibody Associated Disorders

• Disability
  • Outcomes likely better than NMO
    • Severity of relapse may be the same but outcome better
    • Severe persistent disability in 40-75%
    • Sphincter>cognitive>visual>mobility
  • Disability driven by severity of first attack (70%) and frequency of attacks
  • No progression
MOG Antibody Associated Disorders

- Demographics
  - Numbers in series still small
    - Selection bias
  - Mostly white
  - Female = male
  - No associated systemic autoimmunity
    - Recent case report a/w Sjogren’s
Brain MRI

- May be normal (50%)
- Hemispheric lesions less demarcated and more fuzzy compared to NMO and MS
- Brainstem and cerebellar lesions common
- Thalamic lesions common
- Acute enhancement
Myelitis

- Severity varies
- Recovery better than NMO
- Persistent sphincter dysfunction common
Spine MRI

- 80% longitudinally extensive
  - Rare in MS
- Multiple lesions including conus (75%)
  - Conus involvement uncommon in MS, rare in NMO
- T1
  - Hypointense
  - Usually enhance acutely, but less commonly than NMO and MS
MS Overlap

• 5% of MS patients are MOG-IgG positive
  • Mostly severe, relapsing brainstem and spinal syndromes
  • Poor response to MS DMD; good response to PLEX

CSF

- Pleocytosis 40-50%
  - >50 in 42%
  - Highest reported 306 WBC
  - Lymphocytic predominance
- Elevated protein 33-40%
- OCB rare, Ig index usually normal
  - MOG IgG in CSF in 70% of seropositive subjects
MOG Antibody Associated Disorders

• Histopathologic data is limited (<10)
  • Similar to MS pattern II
    • T cell and macrophage infiltration
    • Complement deposits in macrophages
    • Reactive astrocytes
    • Preservation of mature oligodendrocytes

• Clearly distinct from AQP-4 NMO
  • perivascular complement, loss of AQP-4 expression, astrocytopathy
MOG Optic Neuritis
Optic neuritis

- Clinical characteristics
- Is it isolated or indicative of more widespread neurologic disease?
Optic neuritis

• The Optic Neuritis Treatment Trial (ONTT)
  • 1988-1991
  • Visual outcome good and same in MS vs. non MS group
  • 15 year risk of MS is 50%
    • 80+% with abnormal MRI
    • 20+% with normal MRI

• MS optic neuritis
  • Usually retrobulbar (2/3)
  • Usually unilateral symptoms
NMO optic neuritis

• Generally poor visual outcome
• Longitudinally extensive optic neuritis on MRI
  • > 3 ON segments; >17.6 mm
• Often bilateral; chiasm/tract involved
• Aggressive early treatment w/high dose steroids & PLEX
Short-segment vs. Longitudinally Extensive Optic neuritis

MS

Short-segment increased T2 signal/enhancement

NMO

Longitudinally extensive optic neuritis on MRI
> 3 ON segments; >17.6 mm

NMO optic neuritis

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MOG Optic Neuritis

• Several case series
• Prevalence
• Characteristics
MOG-IgG Optic Neuritis Prevalence

• ONTT Relook
  • Of all ON patients, who has MOG or NMO?
  • Subjects in ONTT were reanalyzed
  • AQP4 and MOG Abs

• Subjects
  • 488 subjects in ONTT (13% had MS)
  • 177 serum samples available
    • Demographics similar to entire cohort

Chen et al. *JAMA Ophthalmol.* 2018;136(4):419-422
MOG-IgG Optic Neuritis Prevalence

• No ONTT subjects were seropositive for AQP4-IgG
• 3/177 seropositive for MOG-IgG (1.7%)
  • Presentation
    • 3/3 disc edema (1/3 in cohort)
      • One “severe”
    • 3/3 had pain on eye movement
    • 3/3 had normal brain MRIs
  • Vision
    • Presenting VA 20/50 – HM
    • Final VA was 20/20 in 3/3
      • 1/3 had a VF defect
  • Outcome
    • 2/3 had recurrent optic neuritis
    • None had or developed MS after 15 years

Chen et al. JAMA Ophthalmol. 2018;136(4):419-422
Optic neuritis

Series of 43 subjects with ON MRI

<table>
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<th>Swelling</th>
<th>Bilateral</th>
<th>MRI</th>
<th>Improve?</th>
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<td>Brain 2011 McDon</td>
<td>Optic Nerve</td>
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<td>MS (n=13)</td>
<td>0</td>
<td>23%</td>
<td>92% 15% Short 5% 0</td>
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<td>NMO (n=11)</td>
<td>9%</td>
<td>82%</td>
<td>82% 0% Long.Ext. 64% 50%</td>
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<tr>
<td>MOG (n=19)</td>
<td>53%</td>
<td>84%</td>
<td>37% 11% Long.Ext. 15% 0</td>
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</tr>
</tbody>
</table>

MOG ON Mayo Clinic Series
largest cohort to date

• 87 ON patients multicenter with + MOG-IgG
• Ages 2-79, 57% female, f/u 2.9 yrs
• Avg nadir VA CF; avg final VA 20/30
  • 6% final VA worse than 20/200
• 86% optic disc edema and pain on EOM
• 37% bilateral
• No difference in visual outcome with IVMP/PLEX/IVIG

MOG ON Mayo Clinic Series

- MRI
  - Optic nerve
    - 82% longitudinally extensive ON
    - 50% perineural enhancement
  - 1/86 had brain MRI “compatible with multiple sclerosis”

- Course (61% treated with immunosuppression)
  - 10% single episode ON
  - 26% recurrent ON
  - 16% chronic relapsing inflammatory optic neuritis (CRION)
  - 41% other recurrent neurologic symptoms (NMOSD or ADEM)
    - Avg 0.8 relapses per year

MOG ON MRI

• Perineural enhancement
MOG ON Mayo Clinic Series

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  • Optic nerve
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Chronic Relapsing Inflammatory ON

- CRION
  - Multiple episodes of idiopathic ON
    - Unilateral or bilateral
    - Corticosteroid-responsive and –dependent
      - Often requires chronic immunosuppression
  - MOG IgG in up to 90%

MOG Optic neuritis - summary

• Disc swelling common and may be severe
• Often bilateral
• Chronic relapsing form
• Longitudinally extensive on MRI
• Good outcome
MOG IgG Associated Disorder Treatment

• Only observational series
  • Relapse treatment
    • IVMP, PLEX, IVIG, cyclophosphamide, lymphocytapheresis
  • Relapse prevention
    • Azathioprine, methotrexate, rituximab, prednisone, mycophenolate, IVIG, MS DMD

• Risk of treatments vs risk of condition of ?morbidity
Treatment
J Chen et al

- Retrospective multicenter chart review, n=68
  - Mostly neuro-ophthalmologists so ON over-represented
- At least six mos treatment, 4.5 yr f/u
- Mycophenolate, azathioprine, rituximab partially effective (62-72% relapsed on Rx)
- **Monthly IVIG markedly effective** (10% relapsed on Rx)
- MS therapies ineffective (but didn’t worsen)

Treatment

• MS DMDs
  • Interferon-beta increased disease activity
  • Mitoxantrone and natalizumab no effect

“Treatment Guidelines”

• Relapses
  • IVMP (#?) followed by oral prednisone (?duration)
  • Consider IVIG or PLEX if unresponsive or recurrent
  • Does time = Vision?
    • H Stiebel-Kalish et al. Does time equal vision in the acute treatment of AQP-4 and MOG optic neuritis? Poster presentation, 45th Annual Meeting of NANOS, Las Vegas, March 2019
      • #9 patients
      • Worse if treatment delayed by > 4 days
Treatment Guidelines

• Maintenance
  • Indication
    • Recurrence or persistent antibody positivity?
  • Duration
    • At least three months to reduce RR?
• Azathioprine, Mycophenolate, Methotrexate, Rituximab, IVIG
• Don’t use MS DMDs
MOG Antibody Associated Disorders

• What do we know?
  • MOG is almost certainly distinct from NMOSD with AQP-4 IgG
  • MOG is probably distinct from MS
  • MOG ON is an uncommon cause of ON
    • a/w disc swelling, bilaterality, CRION, LEON on MRI, good outcome

• Why do we care?
  • MS and NMO are treated differently
  • MOG treatment not yet defined
Proposed Diagnostic Criteria
MOG-IgG-Associated Disorders
(must meet all three criteria)

- Clinical findings: any of the following presentations:
  - ADEM
  - Optic neuritis, including CRION
  - Transverse myelitis (LETM or SSTM)
  - Brain or brainstem syndrome compatible with demyelination
  - Any combination of the above
- Serum positive for MOG-IgG by cell-based assay
- Exclusion of alternative diagnosis

Who gets MOG testing?

- ON
  - in presence of ADEM, TM
  - Bilateral ON
  - Severe swelling
  - LEON on MRI
- Consider if brain MRI normal or looks like atypical MS
Case One

- 34 y.o. healthy AA man
- Feb 2017 bilateral ON to 20/200 OD, 20/50 OS
- Much better with 5 d IVMP, prednisone taper
- Mar 2017 recurrence in OD
- Much better again in OU with IVMP
- Brain and spine MRIs normal
  - Orbital MRI Longitudinally Extensive ON OU
- LP 6 WBC, pro 40, no OCB
- Apr 2018: ON OD, Rx IVMP, good recovery
- Apr 2018: MOG IgG ab positive (1:40)
Case Two

• 29 y.o. Cauc Man
• ADEM age 5, ?Rx
• ADEM with Bilateral ON age 11
  • Vision worsened with each pred Taper
  • Resolved with IVIG
• Rx mycophenolate ages 23 – 27 (“demyelinating illness”)
  • Discontinued 2017 for “no clear indication to treat”
• August 2018 (age 28): ON OS, both discs pale
  • Rx IVMP, VA improved from 20/125 to 20/30
• MOG IgG positive 1:40
References


Thank you!