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
Case One

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

• 29 y.o. Cauc Man
• ADEM age 5
• ADEM with Bilateral ON age 11
  • Vision worsened with each pred taper
  • Resolved with IVIG
• Rx mycophenolate ages 13 – 27 (“demyelinating illness”)
  • Discontinued 2017 for no clear indication
• August 2018 (age 28): ON OS, both discs pale
  • Rx IVMP, VA improved from 20/125 to 20/30
• MOG IgG positive
MOG Antibody Associated Disorders

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

Myelin Oligodendrocyte Glycoprotein
Myelin Oligodendrocyte Glycoprotein

- Glycoprotein
  - 218 amino acids
- Expressed in oligodendrocytes of mammal CNS
- Biological role is not clear
MOG IgG Antibody

• Animal Models
  • Elicits a demyelinating immune response
  • Mice with T and B cells that target MOG develop an opticospinal form

• Human MOG IgG *in vitro*
  • Leads to oligodendrocyte damage

Immunohistochemical staining of mouse brainstem shows strong immunoreactivity in myelinated neural processes.
MOG IgG Antibody Testing

- Western Blot and ELISA nonspecific
  - Denatured MOG
  - Pediatric ADEM
  - Variable presence in MS
- Cell-based assay more specific
  - Full-length protein
  - Rare in adults with MS
- NMO Spectrum Disorder
  - 30% AQP-4 negative
  - MOG Ab in 25-40% of AQP-4 negative NMOSD
MOG Antibody Associated Disorders

- Phenotype
  - ON 41-63%
  - TM 30%
  - ADEM-like varies based on age
  - Brainstem syndromes (incl. area postrema) up to 30%
  - Many do not fulfill 2015 diagnostic criteria for NMOSD
MOG Antibody Associated Disorders in adults

• Demographics
  • Numbers in series still small
    • Selection bias
  • Mostly white
  • Female = male
  • No associated systemic autoimmunity
    • Recent case report a/w Sjogren’s
MOG Antibody Associated Disorders

• Relapses
  • Monophasic or relapsing
  • Frequency
    • 50% relapse in first two years after presentation
    • 75% relapse by five years

• Titers
  • Higher at time of relapse
  • Up to 50% become antibody negative after relapse
  • Persistent positivity indicates higher risk of relapse
MOG Antibody Associated Disorders

• Disability
  • Outcomes likely better than NMO
    • Severity of relapse may be the same but relapse outcome better than NMO
  • Severe persistent disability in 40-75%
    • Sphincter>cognitive>visual>mobility
  • Disability driven by severity of first attack (70%) and frequency of attacks
  • Progression not described to date
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
Brain MRI

- More brainstem and cerebellar than supratentorial lesions
- Acute enhancement
- Thalamic and cortical lesions common
- Less demarcated and more fuzzy compared to NMO and MS
Myelitis

• Can present along with ON or ADEM
• Severity varies
• Recovery better than NMO
• Persistent sphincter dysfunction
Spine MRI

• 80% longitudinally extensive
  • Rare in MS
• Multiple lesions including conus (75%)
  • Conus involvement uncommon in MS, rare in NMO
• 65% anterior, 30% homogeneous
  • Often confined to grey matter
• 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
  - May show evolution in space and time on MRI but lesions not typical

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 Optic Neuritis
Optic neuritis

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

- The Optic Neuritis Treatment Trial (ONTT)
  - Visual outcome good and same in MS vs. non MS group
    - Steroid treatment has no effect on outcome
  - 15 year risk of MS is 50%
    - 80+% with abnormal MRI
    - 20+% with normal MRI
  - Tests not useful
    - ANA, VDRL, CXR

- 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

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MOG Optic Neuritis

• 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
  • Clinical phenotype

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

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>
<thead>
<tr>
<th></th>
<th>Swelling</th>
<th>Bilateral</th>
<th>MRI</th>
<th>Improve?</th>
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<tr>
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<td>Brain</td>
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<td></td>
<td>Optic Nerve</td>
<td>Optic Chiasm</td>
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<td>MS (n=13)</td>
<td>0</td>
<td>23%</td>
<td>92%</td>
<td>15%</td>
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<tr>
<td>NMO (n=11)</td>
<td>9%</td>
<td>82%</td>
<td>82%</td>
<td>0%</td>
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<tr>
<td>MOG (n=19)</td>
<td>53%</td>
<td>84%</td>
<td>37%</td>
<td>11%</td>
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</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 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)
  - Avg 0.8 relapses per year
  - 10% single episode ON
  - 26% recurrent ON
  - 16% chronic relapsing inflammatory optic neuritis (CRION)
  - 41% other recurrent neurologic symptoms (NMOSD or ADEM)

MOG ON MRI

• Perineural enhancement
MOG ON Mayo Clinic Series

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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 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
MOG Optic neuritis

- Disc swelling common and may be severe
- Often bilateral
- Chronic Relapsing form
- Longitudinally extensive on MRI
- Good outcome
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 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, then 8 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
    • Minority of MS patients have MOG antibodies using CBA
    • Pathological overlap
    • ?Radiological overlap
    • MOG clinical profile is more restricted than MS
  • MOG ON is probably 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
  - Bilateral ON
  - Severe swelling
  - LEON on MRI
- Consider if brain MRI normal or looks like atypical MS
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References


Thank you!